

**REPORT ON AN INFORMAL MEETING
ASSESSING THE FEASIBILITY OF
INITIATING THE FIRST PHASE II STUDY
OF MOXIDECTIN TABLETS IN SUBJECTS
INFECTED WITH *ONCHOCERCA VOLVULUS***

Accra, Ghana, 5-6 May 2005



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Cover picture: Photomicrograph of *Onchocerca volvulus*, the parasite which causes onchocerciasis (WHO/TDR).

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EXECUTIVE SUMMARY

WHO convened an informal meeting in Accra, Ghana to assess the feasibility of initiating the first study of moxidectin tablets in subjects infected with *Onchocerca volvulus*. The meeting was convened in the context of the post-marketing experiences in the United States of America (USA) with an injectable six month, sustained-release formulation of moxidectin (ProHeart®6) for the prevention of heartworm in dogs.

Participants included three international experts in onchocerciasis control, including two representatives of the Technical Consultative Committee of the African Programme for Onchocerciasis Control, representatives of the Ghana regulatory and ethical review authorities, and the head of the Onchocerciasis Chemotherapy Research Centre in Ghana (the designated principal investigator for the first study of moxidectin tablets in subjects infected with *Onchocerca volvulus*).

WHO/TDR approached Wyeth, the owner of moxidectin, for collaboration for development of orally-administered moxidectin for the treatment and control of onchocerciasis in 1998. This was motivated by data from TDR-sponsored pre-clinical pharmacology studies suggesting that moxidectin might have the potential to be an effective macrofilaricidal or macrofilaria sterilizing agent against *Onchocerca* and review of the pre-clinical toxicology data provided to WHO/TDR by Wyeth's veterinary division Fort Dodge Animal Health suggesting that moxidectin may have the safety profile required for a drug for onchocerciasis control. Development proceeded to the completion of two Wyeth-sponsored Phase I studies of moxidectin administered to healthy volunteers in the United Kingdom in 2001 and Germany in 2003, with subsequent publication of the PK and safety data from the UK study in 2003.¹

Ghana regulatory and ethical clearance, as well as WHO Ethics Committee approval, was then obtained for the first study in subjects infected with *Onchocerca volvulus* (Phase II). However, initiation of this study was put on hold when Wyeth recalled ProHeart®6 from the USA market in September 2004. This recall followed expression of concerns about the safety of ProHeart®6 by the US Food and Drug Administration Center for Veterinary Medicine (FDA-CVM). In January 2005, a US Food and Drug Administration Veterinary Medicine Advisory Committee (FDA-VMAC) recommended against the re-introduction of ProHeart®6 to the USA market without additional data/data analysis being available. The US FDA-CVM has not expressed any concerns about any of the other ProHeart® or moxidectin formulations on the USA market (moxidectin formulations are used in at least four different animal species in the USA). The regulatory authorities of other countries have not expressed any concerns regarding ProHeart®6 or any other moxidectin formulation on their market; there are over 400 such registered moxidectin formulations being sold in 81 countries worldwide.

During the WHO informal meeting, the following data were reviewed and discussed in depth in the context of the draft protocol for the first study of orally-administered moxidectin in subjects infected with *Onchocerca volvulus* (Phase II):

- 1) all data on ProHeart®6 that had been made available to the FDA-VMAC;
- 2) the results of moxidectin toxicology studies;
- 3) the safety data from the two healthy volunteer studies.

Based on these discussions, the participants recommended unanimously:

- The planned first study of moxidectin tablets in subjects infected with *Onchocerca volvulus* (Phase II) should be initiated as soon as possible.

¹ Cotreau MM, Warren S, Ryan JL, Fleckenstein L, Vanapalli SR, Brown KR et al. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003 October;43(10):1108-15

- The protocol should explicitly (rather than implicitly as in the current protocol version) exclude patients with neuro-psychiatric conditions and a history of epilepsy.

- The protocol should include provisions for exclusion of patients with hypotension and appropriate monitoring of vital signs. Both provisions are in the study protocol.
- Women of child-bearing potential should be taking effective contraception despite the fact that there are no suggestions from animal studies that the drug is embryotoxic or teratogenic. This is planned in the protocol.
- The Onchocerciasis Chemotherapy Research Centre in Ghana, where the study is to be performed, is encouraged to provide scientists from onchocerciasis-endemic countries with opportunities to visit and observe the trial of moxidectin. Candidates for such visits should include potential principal investigators for further Phase III studies of moxidectin.

MEETING REPORT

Background and objectives

Pre-clinical pharmacology data show that moxidectin, a macrocyclic lactone, has the potential to be a macrofilaricide and/or a permanently macrofilaria-sterilizing drug. In 1998 WHO/TDR approached the owner of moxidectin (Wyeth) for co-development of a tablet formulation of moxidectin for the treatment and control of onchocerciasis.

The design of the development strategy was based on the available pre-clinical pharmacology and toxicology data, the requirements for a regulatory registration, and the planned post-registration use of moxidectin as a tool for onchocerciasis control programmes.

Moxidectin has been used extensively in veterinary medicine (See Annex II – Meeting documents – sections 4c & d), and pre-clinical safety data available at the time of the decision to initiate development for onchocerciasis supported investigational use of orally-administered moxidectin in humans (see Annex II – Meeting documents – section 2). These data have since been complemented by additional studies on the metabolism of moxidectin in human microsomes, studies on the binding of moxidectin to p-glycoprotein and studies on binding to mammalian receptors (see Annex II – Meeting documents – sections 2, 3, 4c).

Wyeth developed a tablet formulation for human use and conducted two Phase I studies in healthy volunteers in the United Kingdom in 2001 and Germany in 2003. These were to be followed by the first study in subjects infected with *Onchocerca volvulus*, sponsored by WHO/TDR and supported operationally by Wyeth. The study was to be conducted at the Onchocerciasis Chemotherapy Research Centre (OCRC) in Hohoe, Ghana. Regulatory and ethical clearance for the Ghana study was obtained. In 2004, initiation of this study in Ghana was put on hold after the veterinary division of Wyeth, Fort Dodge Animal Health, (Wyeth-FDAH) recalled an injectable sustained-release formulation of moxidectin (ProHeart®6), used for six-month long prevention of heartworm in dogs. The formulation was recalled from the USA market in September 2004 due to safety concerns voiced by the US Food and Drug Administration Center for Veterinary Medicine (FDA-CVM).

Since then additional animal pharmacokinetic studies and mammalian receptor binding studies have been conducted (see Annex 2 – Meeting documents – sections: 3 & 4c). A re-review of the safety data from the two healthy volunteer studies also was conducted by Wyeth medical personnel and the head of the OCRC with regard to any signals that could indicate a potential for adverse events like those of concern to the FDA for ProHeart®6. The results continued to be consistent with a favourable safety profile for moxidectin.

In January 2005, the US FDA Veterinary Medicine Advisory Committee on ProHeart®6 recommended against the re-introduction of ProHeart®6 to the USA market without additional data analyses. Since then the FDA-CVM and Wyeth-FDAH have had numerous interactions. To date, the FDA-CVM has not made a decision on the future of the marketing authorization of ProHeart®6, and ProHeart®6 thus remains off the US market.

This WHO informal meeting was called following a recommendation of the Technical Consultative Committee of the African Programme for Onchocerciasis (APOC TCC) to review and discuss the pertinent data and to make recommendations on:

- whether the study in subjects infected with *Onchocerca volvulus* should be initiated as currently planned;
- in the case of a decision against carrying out the planned study at present, what additional data would be required for further review.

Events and data related to ProHeart®6

ProHeart®6 is a sustained release formulation of moxidectin (in microspheres). It is indicated for the prevention of heartworm in dogs for six months and for the treatment of larval and adult hookworm. The dosing regimen is 0.17 mg/kg, subcutaneously.

ProHeart®6 was launched by Wyeth-FDAH in the US in June 2001, and subsequently in Italy, Canada, Japan, France and other markets. This followed the October 2000 launch of ProHeart®12 in Australia – a formulation like that of ProHeart®6, but containing three times the amount of moxidectin.

In the three years following the ProHeart®6 launch, the US FDA-CVM expressed a series of concerns regarding the number and severity of adverse events (AEs) observed following administration of ProHeart®6 which the FDA-CVM regarded as possibly or probably related to the drug's administration. These concerns resulted in three changes in the ProHeart®6 prescribing information in the USA – in June 2002, November 2002 and July 2003 respectively. In 2004, FDA-CVM requested that Wyeth voluntarily recall the drug from the USA market.

The AEs, which caused the FDA-CVM to request the drug recall were: anaphylaxis/anaphylactoid reactions, convulsions, elevations in serum glutamic pyruvic transaminase, liver lesions, low platelets and immune mediated haemolytic anaemia as well as 485 deaths reported following the administration of ProHeart®6 and regarded as possibly or probably ProHeart®6 related by the FDA-CVM. A major reason for the FDA-CVMs assessment of AEs as possibly or probably related to ProHeart®6 was the temporal relationship between occurrence of AEs and ProHeart®6 administration. Concomitant administration of ProHeart®6 with vaccines and/or other medicines had occurred in between 40% and 68% of these adverse events.

The database maintained and analysed by FDA-CVM and Wyeth-FDAH to assess the safety profile of ProHeart®6 consists of data spontaneously reported to Wyeth-FDAH or to the FDA-CVM from practitioners and the general public alike and thus does not constitute a systematic collection of adverse events (AEs) observed after any administration of ProHeart®6 (or other heartworm preventatives, vaccines or other drugs) from which incidences can be deduced.

US FDA-CVM and Wyeth-FDAH used different systems for assessing the causal relationship between the AEs in that data base and ProHeart®6 administration. The US FDA-CVM used the modified Kramer scoring system for causality assessment.²

Wyeth-FDAH used the assessment system recommended in the approved draft guideline of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). Based on their analysis, Wyeth-FDAH concluded that the majority of adverse events reported were not causally related to ProHeart®6 and reflect the normal range of diseases occurring in the dog population.

In support of their conclusion that ProHeart®6 does not have a worse safety profile than oral heartworm preventatives, Wyeth-FDAH also referred to an epidemiological analysis of the 'Banfield Database'. The Banfield Database is maintained by over 400 veterinary clinics across 42 states in the USA and includes data on adverse events observed during 30 days following treatment in animals treated at these clinics. The Banfield Database records were analysed to assess the relative safety of ProHeart®6 and oral heartworm preventatives, comparing AEs in relation to: 1) ProHeart®6 administered alone or concomitantly with a vaccine, 2) one of two oral heartworm preventatives administered alone or concomitantly with a vaccine, 3) vaccines administered alone. The analysis concluded that ProHeart®6 did not have a safety profile inferior to that of the two oral heartworm preventives.³

² Keller et al., Vet Clin North Am, Food Anim Pract, March 1999,15(1):13-30,
<http://www.fda.gov/cvm/ADEFAQs.htm>

³ Post meeting note: Publication of this study (not available for this meeting) Glickman et al., Intern. J. Appl. Res. Vet. Med, Vol 3, 2005

Wyeth-FDAH furthermore pointed to the fact that other regulatory authorities such as those of Europe, Canada, Japan and Australia did not request Wyeth-FDAH to recall ProHeart®6 or ProHeart®12. As per verbal information from Wyeth-FDAH, these regulatory agencies came to their assessments after examining the data from within their countries and having been sent the USA post-marketing adverse event database with the Wyeth-FDAH analysis.

For more details, see Annex 2 – Meeting documents – section 4.

Discussion of data on ProHeart®6

On the basis of the documentation and presentations provided for the January 2005 FDA VMAC meeting on ProHeart®6, the data and events relating to ProHeart®6 were discussed to address the following questions:

- Given these divergent views from the US FD-CVM, on one hand, and the other national regulatory bodies and Wyeth-FDAH on the other, and the fact that these data relate to an injectable sustained-release formulation of moxidectin, while the planned study in humans will use a tablet, is there a scientific rationale for NOT proceeding with the initiation of the first study of moxidectin in patients with onchocerciasis?
- If so, what is this rationale, and what additional data should be provided or which additional data analyses are needed, to reconsider the decision against initiation of this study?

The AE reporting rates and system of veterinary post marketing pharmacovigilance in the USA compared to those in other countries and national regulatory authorities and the impact of those different systems on regulatory conclusions were discussed. The differences in causality assessment procedures between the FDA-CVM and Wyeth-FDAH and other regulatory authorities made direct comparison of the different assessments difficult. Information on the analyses performed by, and the rationale for the decision of the other regulatory agencies to allow continued marketing of ProHeart®6 or ProHeart®12 in their countries, would have been helpful, but was not available.

The high incidence of convulsions/seizures (0.2 per 10 000 doses sold) and anaphylactic reactions (1.1 per 10 000 doses sold) associated with administration of ProHeart®6 was regarded with particular concern in the context of the objectives of this meeting. (There are no records of ProHeart®6 doses administered in the USA. Wyeth-FDAH estimates that at least 2 of 3 doses sold were actually administered). Temporal relation between AEs and ProHeart®6 drug administration can indicate some form of causality. The concomitant administration of other drugs and vaccines, however, makes causality assessment very difficult. The possibility was raised that dogs with convulsions/seizures after ProHeart®6 administration may have had convulsions/seizures previously. The overall lack of adequate information on the relevant medical history of animals in which AEs were reported was noted as a constraint for causality assessment.

An analysis of the correlation between the frequency of AEs and the rate of transmission of heartworm may give some insight into the mechanism of the possible causal relationship between ProHeart®6 and the observed AEs. Furthermore, a case-control study could yield some answers on pathogenesis and causal relationship.

It was noted that similar AEs were not reported in association with oral administration of ProHeart® tablets. Some 846 379 oral ProHeart® doses have been sold in the USA since 1998. Approximately 65 million such oral doses have been sold globally since 1993 – with around 80% of those doses sold in Japan, Australia and Italy.

This indicates that any causal relationship between ProHeart®6 and observed AEs may be related to the formulation of injectable ProHeart®6 (residual solvents? microspheres?) rather than inherent physico-chemical properties of moxidectin. It was noted that the FDA-CVM has not expressed any concerns about the safety of formulations of moxidectin other than ProHeart®6.

Since the planned study in subjects infected with *Onchocerca volvulus* will use an oral tablet, not ProHeart®6, the ProHeart®6 data were not regarded as providing a scientific rationale for further postponement or cancellation of the planned study.

Data from pre-clinical studies of orally-administered moxidectin

The majority of the safety data on orally-administered moxidectin was acquired in studies undertaken for the registration of different moxidectin formulations for treatment of companion or food animals. This safety data was then supplemented by studies on metabolism in human microsomes, and studies on the potential for drug-drug interaction at the cytochrome P450 enzyme system in human mitochondria and P-glycoprotein. Other recent studies provide more data on the pharmacokinetics of moxidectin in two animal species administered moxidectin orally at the No Toxic Effect Level (NTEL) determined in previous toxicology studies, and data on binding of moxidectin to 64 mammalian receptors. The main findings include:

- Metabolism: metabolism of moxidectin is minimal in both animal and human microsomes and the metabolic profile in different animal species, including rabbits and dogs is very similar. The metabolic profile in rats and humans is identical in liver microsomes and the rat thus appears to be a valid toxicological model.
- There is very little potential for clinically relevant drug-drug interactions involving moxidectin as the drug is a weak inhibitor of CYP1A2 and CYP2C9 (IC₅₀ 459 µM and 145 µM). It does not inhibit other cytochrome P450 enzymes.
- Moxidectin is a weak inhibitor of P-glycoprotein and potential interactions with other p-glycoprotein substrates, e.g. HIV protease inhibitors, though unlikely, have to be individually evaluated.
- Tissue distribution: Moxidectin has the longest half life in fat (11.5 days in rats).
- Excretion: Moxidectin is readily absorbed after oral administration. Some 88-96% of the dose administered is excreted via faeces in rats.
- The half life of the drug in rats is 22-45 hours.
- At the NTEs in 4 week, 13 week and 1 year studies in dogs and in 4 and 13 week studies in rats the exposure of the animals was several tens to hundreds times higher than the exposure in healthy human volunteers (Phase 1), who received a dose 4 times higher than the maximum dose planned for the study in subjects infected with *Onchocerca volvulus*. Dose limiting toxicities were primarily neurological in nature (hypersensitivity to touch, tremors, ataxia, lethargy, anorexia, salivation, piloerection, aggressive behaviour, loss of righting reflex).
- Carcinogenicity – no moxidectin-related target-organ toxicity or tumourigenicity.
- Genotoxicity – in vitro and in vivo negative.
- Reproductive toxicity – the conclusion of both the US FDA-CVM and the European Agency for the Evaluation of Medicines is that moxidectin is not a developmental toxicant. In the three generation diet reproductive toxicology study, the NTEL was 0.4 mg/kg/day resulting in minimum exposure substantially higher than that in humans administered the maximum dose currently planned for evaluation in subjects infected with *Onchocerca volvulus*.
- Moxidectin does not significantly bind to 64 mammalian receptors.

For more details, see Annex II – Meeting documents – sections 2, 4 c.

Safety data from the two Phase I healthy volunteer studies in the UK and Germany

There have been two studies of orally administered moxidectin in human volunteers so far in the United Kingdom (2001) and Germany (2003). These include:

- The First-in-Man (FIM) study: A single ascending dose, placebo controlled, double masked, safety, tolerability and pharmacokinetic study of orally administered moxidectin in 37 healthy male subjects, ages 18-45 years and weight ≥ 50 kg, of whom 31 received orally liquid moxidectin at doses between 3 mg and 36 mg.
- A study of the relative bioavailability of a tablet and a liquid formulation of moxidectin in 58 male healthy volunteers, ages 20-45 years, weight ≥ 50 kg, of whom 29 received a single dose of 10 mg of liquid moxidectin orally and 29 received a single dose of 10 mg of moxidectin in the tablet formulation.

The FIM study showed moxidectin to be safe and very well tolerated. No clinically significant dose-related adverse events were observed at doses up to 4 times the highest dose planned in the first study in subjects infected with *Onchocerca volvulus*. The data from the relative bioavailability study confirm the data from the FIM study.

Review of the safety data from the FIM study and the relative bioavailability study (with special focus on signals for adverse events like those of concern to the FDA-CVM following ProHeart[®]6 administration in dogs, as well as the dose-limiting toxicities in the animal toxicology studies (neurological toxicity), showed no allergic reactions to moxidectin, anaphylaxis, convulsions, ECG abnormalities, or clinically important and sustained haematological or liver test abnormalities. There were no dose related neuro-psychiatric adverse events. One of 29 subjects who received 10 mg of liquid moxidectin developed an allergy (pollinosis) unrelated to moxidectin 144 days after administration of moxidectin.

The only adverse event of potential significance in the context of use of moxidectin in subjects infected with *Onchocerca volvulus* was Grade 1 hypotension in one subject 8 hours after receiving 36 mg moxidectin orally after a high fat breakfast. The hypotension resolved without treatment (pre-dose value: 130/68, 8 hrs post moxidectin administration 97/34, 12 hrs post moxidectin administration 130/67).

For more details see Annex II – Meeting documents – section 2.

Discussion of safety data from pre-clinical studies and clinical trials in humans

Based on these data, the following questions were discussed as a basis for making recommendations:

- Do these results provide any reasons why a study in subjects infected with *Onchocerca volvulus* should not be initiated?
 - If yes: What are these reasons and what additional data or additional data analyses are required prior to the decision to initiate this study?
- Do the results of the two studies in healthy volunteers provide particular safety concerns that need to be addressed in the study protocol?
 - If yes: What additional measures should be taken during the study in subjects infected with *Onchocerca volvulus* to ensure appropriate patient monitoring so that necessary medical responses can be instituted in a timely manner?

The discussion resulted in the following conclusions:

- The pre-clinical studies suggest that moxidectin has the potential to have a good safety profile in humans. The available data support the further development of moxidectin for human use.
- The data from the pre-clinical and the clinical studies do not provide any reason why a study in subjects infected with *Onchocerca volvulus* should not be initiated.

- Special attention should be paid in the design and conduct of the study to carefully monitor and record neurological adverse events and hypotension.

Protocol for the planned study of orally administered moxidectin in subjects infected with *Onchocerca volvulus*

The study is planned to be conducted at the Onchocerciasis Chemotherapy Research Centre (OCRC) in Hohoe, Ghana. The OCRC has a long history of conducting clinical trials in subjects infected with *Onchocerca volvulus*.

The study is a double blind, ivermectin controlled, single dose study that will enrol a total of 192 males and females in groups of 16 by ascending dose (2 mg, 4 mg, 8 mg) and ascending severity of infection (1-<10 microfilaria/mg skin (mf/mg) with 0 microfilaria in the eyes, 10-20 mf/mg with ≤10 mf in both eyes, >20 mf/mg without upper limit for the number of microfilaria in the eyes).

The objectives of the study are to determine:

- safety and tolerability of a single dose in subjects with *Onchocerca volvulus* infection (primary objective);
- dose(s) that effectively eliminate(s) microfilariae and prevent their return to the skin via skin microfilarial loads at days 8, 30, 60, 90, 180 and at 12 and 18 months after treatment;
- viability and fertility of adult worms at 18 months post treatment via histopathological assessment;
- pharmacokinetics in male and female adults via serum concentrations over 6 months.

The doses planned are between around 25 µg/kg and 200 µg/kg depending on dose group and subject weight. Doses/kg in healthy volunteers were between 38 µg/kg and 720 µg/kg.

Eligible subjects will be adults 18-60 years infected with *Onchocerca volvulus* but otherwise healthy as judged by the principal investigator (PI) on the basis of physical examination (including neurological exam), ECG, laboratory data and medical history. The list of 17 exclusion criteria includes pregnancy, orthostatic hypotension and co-incidental infection with *Loa loa*. Pregnant or breastfeeding women are not eligible for the study, women of childbearing potential have to be on medically accepted methods of birth control (prior or provided during the study).

Subjects will be hospitalized for 18 days after drug administration during which time they will be extensively evaluated including physical examination (including neurological exams), AEs, vital signs (several times per day), ECGs, ocular examinations (including colour fundus photography and fluorescein angiograms), serum chemistry, haematology (including prothrombin times) and urinalysis.

The same examinations will be conducted at each follow up visit during the outpatient period (30 days, 2, 3, 6, 12, 18 months post drug administration) with the exception of colour fundus photography and fluorescein angiograms which will be performed at 6, 12 and 18 months follow up only in individuals with visual function deficits, and ECGs.

The decision to move to the next cohort within the same dose group will be made by the PI based on the safety data obtained during the first 30 days post drug administration in the previous cohort(s). The PI will inform the sponsors of his decision, who can put the trial on hold/discontinue the trial if they do not agree with that decision.

The decision to move to the next higher dose will be based on unanimous agreement of the PI (blinded), personnel involved in the trial at the sponsors (blinded) and an unblinded team of three clinical experts (Clinical Expert Review Team).

For more details see Annex II – Meeting documents – section 5.

Discussion of the protocol for the planned clinical study

The protocol design and conduct were discussed to answer the following questions as a basis for recommendations:

Given all the data reviewed and discussed up to now:

- Is there any reason why this study should not be initiated?
 - If there is/are, what are these reasons?
- Is there any reason why the study should not be conducted as planned?
 - What is the reason/are the reasons?
 - What should be changed in the protocol?

It was concluded that there is no reason not to initiate this study as soon as possible. The recommendations regarding the study protocol and conduct are provided further below.

Final committee observations

Considering the evidence available and the nature of the microfilarial disease burden, the meeting participants agreed on the following:

- Infections caused by *Onchocerca volvulus* remain a significant cause of morbidity in several countries in Africa.
- The only recommended agent for treatment and control of onchocerciasis is ivermectin.
- There is a huge pressure on the use of ivermectin and this is compounded by reports of suboptimal response to ivermectin in some individuals.
- There is no alternative to ivermectin in development other than moxidectin.
- From the pharmaceutical point of view ProHeart®6 and moxidectin tablets are different drug products. The differences in the number of AEs reported to Wyeth-FDAH and FDA-CVM with respect to ProHeart® tablets as compared to ProHeart®6 point to the formulation rather than the drug substance as the basis for any possible or probable causal relationship between ProHeart®6 and the reported AEs. This conclusion is supported by the fact that the FDA-CVM asked the company to recall ProHeart®6 but not any other formulation of moxidectin.
- The formulation for human use is a tablet which is thus unlikely to be associated with AEs reported after ProHeart®6 administration.
- Data from animal toxicology studies indicate the safety of orally-administered moxidectin.
- Clinical studies in 89 healthy subjects who received moxidectin in doses between 3 and 36 mg showed moxidectin to have the potential for a good safety profile with no serious or severe adverse events recorded.
- The Ghana Food and Drug Board has very thoroughly reviewed the clinical trial exemption application, the data on ProHeart®6 as well as the protocol for the planned Phase II study in subjects infected with *Onchocerca volvulus* and is convinced that the protocol is well designed and that there are enough guarantees for the protection of subjects and for carrying out the trial in line with ICH guidelines.
- The Clinical Expert Review Team and the monitoring of the trial by the Ghana Ethical Committee guarantee patient welfare and protection.
- The Onchocerciasis Research Centre in Hohoe, Ghana has the capacity to carry out the trial in line with the provisions of the protocol.

COMMITTEE RECOMMENDATIONS

The meeting participants recommended unanimously:

- The planned Phase II study of moxidectin tablets in subjects infected with *Onchocerca volvulus* should be initiated as soon as possible.
- The protocol should explicitly (rather than implicitly as in the current protocol version) exclude patients with neuro-psychiatric conditions and a history of epilepsy.
- The protocol should include provisions for exclusion of patients with hypotension and appropriate monitoring of vital signs. Both provisions are in the current study protocol.
- Women of child-bearing potential should be taking effective contraception despite the fact that there are no suggestions from animal studies that the drug is embryotoxic or teratogenic. This is planned in the protocol.
- The OCRC in Ghana is encouraged to give scientists from onchocerciasis-endemic countries the opportunity to visit and observe the trial of moxidectin. Candidates for such visits should include potential principal investigators for further Phase III studies of moxidectin.

ANNEX 1 – LIST OF PARTICIPANTS

Ghana – Regulatory and Ethical Review Officials

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Dr Harry OPATA, WHO Country Office Ghana, Disease Prevention and Control, PO Box M.B.142, Accra, GHANA.

ANNEX 2 - MEETING DOCUMENTS

Documents provided to participants ahead of the meeting

1. Draft agenda
Introduction, background, objectives of the meeting
2. a. Investigator brochure, April 2004 and
b. IB safety attachment
3. Summary of safety relevant animal and human data generated since April 2004 and source documents:
 - a. Wyeth review of safety data from human volunteer studies, November 2004:
Alain Patat, Moxidectin human safety evaluation of studies 100 and 101
 - b. Report on moxidectin pharmacokinetics after of a single dose of 10 mg of liquid or tablet formulation
4. Summary of data related to ProHeart[®]6 and source documents
 - a. FDA-CVM briefing package for FDA Veterinary Medicines Advisory Committee (FDA VMAC)
 - b. FDA-CVM presentations at FDA VMAC (2 documents)
 - c. Fort Dodge Animal Health (FDAH) briefing package for FDA VMAC
 - d. FDAH presentations at FDA VMAC (3 documents)
5. Protocol for OCRC study in patients with onchocerciasis
6. Link of OCRC study in patients with onchocerciasis to other clinical studies

ANNEX 3 - ABBREVIATIONS

AE	Adverse event
APOC TCC	African Programme for Onchocerciasis Control Technical Consultative Committee
EMA	European Agency for the Evaluation of Medicinal Products
FDA-CVM	US Food and Drug Administration Center for Veterinary Medicine
FDA-VMAC	US Food and Drug Administration Veterinary Medicine Advisory Committee
FDAH	Fort Dodge Animal Health, a Wyeth company
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals
NTEL	No Toxic Effect Level
OCRC	Onchocerciasis Chemotherapy Research Centre, Hohoe, Ghana
PI	Principal Investigator
US	United States of America
V ICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
WHO/TDR	Special Programme for Research and Training in Tropical Diseases sponsored by UNICEF/UNDP/WORLD BANK/WHO

**Special Programme for Research & Training
in Tropical Diseases (TDR) sponsored by**
UNICEF / UNDP / World Bank / WHO



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**World Health Organization
UNICEF/UNDP/Worldbank/WHO Special Programme for Research and
Training in Tropical Diseases**

INFORMAL MEETING ON MOXIDECTIN

WHO, ACCRA, 5-6 MAY 2005

Agenda

Thursday, 5 May 2005

9:30 - 9:45	Welcome	Drs. George and Kuesel
9:45 - 10:15	Introductions	All
10:15 - 10:45	Background and Objectives of the meeting	Dr. Awadzi
10:45 - 11:15	Coffee break	
11:15 - 12:30	Review of animal safety data on moxidectin (Presentation and discussion)	Dr. Kuesel
12:30- 13:30	Lunch	
13:30 - 14:30	Events and data related to Proheart 6 (Presentation and discussion)	Dr. Kuesel
15:00 - 15:45	Review of safety data from the 2 human volunteer studies (Presentation and discussion)	Dr. Awadzi
15:45 - 16:00	Coffee Break	
16:00 - 16:20	Review of safety data from the 2 human volunteer studies (Discussion continued)	All
16:20 - 17:30	Overview of protocol for first study of moxidectin in patients with onchocerciasis including provisions for safety (Presentation and discussion)	Dr. Awadzi



Friday, 6 May 2005

9:00 - 10:30

Discussion:

All

1. Given the current data on the safety of
moxidectin - should the study in patients with
onchocerciasis go ahead as planned?

YES

NO

2. If NO

what additional data should be obtained to review
the decision to go ahead with the study?

10:30 - 11:00

Coffee Break

11:00 - 12:30

Discussion continued

12:30 - 14:00

Lunch

14:00 - 16:00

Discussion continued

16:00 - 16:30

Coffee Break

16:30 - 17:30

Review of Rapporteur's notes

Closing remarks



World Health Organization
UNICEF/UNDP/Worldbank/WHO Special Programme for Research and
Training in Tropical Diseases

INFORMAL MEETING ON MOXIDECTIN

ACCRA, 5-6 MAY 2005

Introduction

1 Background and guide to briefing package documents with further information

Based on the promising results of a number of *in vitro* and *in vivo* studies in models of onchocerciasis within the WHO/TDR research program supported by APOC, WHO/TDR asked the manufacturer of moxidectin (Fort Dodge Animal Health, a Wyeth company) for collaboration in the development of moxidectin for the treatment and control of onchocerciasis.

The Wyeth-WHO/TDR development team designed and started to implement a development strategy and plan. The table below provides an overview of the major elements of this plan.

Activity	Primary responsibility	Comments, relevant section of briefing package
Pre-clinical pharmacology studies	WHO/TDR	Completed
Animal toxicology data to support the conduct of studies in humans	Wyeth	Completed (data package that supports animal registrations) See briefing package section 2a, 2b
Additional pre-clinical drug safety and metabolism studies required for registration	Wyeth	80% completed
Development of a tablet suitable for control program use	Wyeth	Completed (long term stability studies ongoing)
Studies in human volunteers for safety and for qualification of tablet	Wyeth	Completed See briefing package section 2a, 2b
Discussion of development strategy with regulatory agencies	WHO/TDR, Wyeth	Completed
First study in onchocerciasis patients (OCRC study)	WHO/TDR	Protocol completed (see briefing package section 5, 6) Regulatory/EC approval INITIATION PUT ON HOLD
Additional studies in patients	WHO/TDR	
Regulatory submissions	Wyeth	
Community effectiveness studies	WHO/TDR	



The initiation of the first study in patients was put on hold when the manufacturer of moxidectin voluntarily recalled Proheart 6, an injectable, sustained release formulation of moxidectin for the 6 month long prevention of heartworm in dogs.

Proheart6 is one of several different formulations of moxidectin for the treatment and prevention of parasites in companion and food animals¹.

The recall of Proheart6 followed concerns about the safety of Proheart6 expressed by the United States Food and Drug Administration Veterinary Division (FDA VM) about the safety of Proheart 6.

The recall prompted:

- Review of the data that had caused FDA concern by the regulatory agencies in Canada, Japan, Europe and Australia. All agencies confirmed the marketing authorization in their countries for Proheart (in Canada, Japan, Europe) and Proheart 12 (in Australia).
- Wyeth review of the safety data from the two previously completed human volunteer studies with special emphasis on looking for signals of safety issues the FDA was concerned about with Proheart6. The review concluded that there is no scientific reason not to proceed to further clinical studies (see briefing package section 3a)
- Conduct of additional *in vitro* safety pharmacology and pharmacokinetic studies in dogs and rats. The results relevant for the assessment of the safety of moxidectin in dogs and humans were:
 - Moxidectin does not significantly inhibit the binding of appropriate radio-ligands to any of 64 mammalian receptors, indicating a lack of binding activity of moxidectin (see briefing package section 3).
 - Administration of 1.1 mg/kg/day moxidectin daily for 1 year does not result in any toxicologically significant findings. The exposure is several hundred times the exposure after two doses of Proheart6 given two months apart (see briefing package, section 4, 4c, 4d)
 - Moxidectin exposure in dogs administered 1.1 mg/kg/day moxidectin daily for 6 months results in an exposure several hundred times higher than that found in human volunteers after a single oral tablet dose of 10 mg. The highest dose planned for the study in patients with onchocerciasis is 8 mg (see briefing package section 3, 3b).
- Review of the Proheart 6 safety data by an FDA VM advisory committee.
 - FDA presented their analysis of the data base of adverse events provided to FDA by Fort Dodge. FDA concluded that their decision to ask Fort Dodge to recall was correct. (see briefing package section 4, 4a, 4b).
 - Fort Dodge presented their analysis of the same data base, the results of the review of a large amount of these data by external experts, the animal toxicology and kinetic study data, the results of an epidemiological analysis including >700 thousand administrations of Proheart 6, and > 400 thousand administrations of two oral heartworm preventatives. Fort Dodge and the

¹ Other formulations include: oral tablets for heartworm prevention in dogs, an oral gel for deworming of horses, a pour-on formulation for cattle, oral formulation for sheep, Proheart12 - an injectable, sustained release formulation of moxidectin for the 12 month long protection of dogs against heartworm in Australia containing 3 times the dose of moxidectin as Proheart6.



external experts concluded that there is no scientific rationale for keeping Proheart6 off the US market (see briefing package 4, 4c, 4d).

- The Advisory committee voted 8:7 that the data presented on Proheart6 should not result in the immediate return on the US market (see briefing package section 4).
- As a consequence of the mixed signal from the advisory committee, the FDA is now having discussions with Fort Dodge (see briefing package section 4).

2 Objectives of the informal meeting

The animal toxicology data package, which far exceeds that usually available at the time a drug candidate for human use enters the first study in patients, as well as the data available from the two human volunteer studies conducted to date with a liquid formulation of moxidectin and the tablet formulation developed for use in patients with onchocerciasis by Wyeth, support the conclusions that moxidectin is a drug candidate suitable for evaluation in patients.

This conclusion is further supported by

- the new data generated by Fort Dodge Animal Health in collaboration with Wyeth Research, in particular the data on the lack of significant binding of moxidectin to 64 mammalian receptors
- the data on the exposure during the long term animal toxicology studies in dogs and rats at doses which did not result in any significant toxicological findings as compared to the exposure in humans after a single dose of moxidectin in the dose range to be evaluated in patients with onchocerciasis.
- The formulation of Proheart6 is different from that of any other formulation of moxidectin, including that of the tablet developed for human use. Not even the FDA did voice any concerns regarding the safety of any of the other formulations of moxidectin on the market in the US.

Thus it is not clear why the events surrounding Proheart6 should have any relevance for the decision to initiate the first study in patients with onchocerciasis:

The protocol for the first study in patients with onchocerciasis has been designed taking into account the results of the studies in human volunteers as well as the experience with the administration of ivermectin to patients with onchocerciasis.

To date, the review of the data has only involved persons directly or indirectly connected with Wyeth Research. The aim of this meeting is to seek the opinion of the guardians of drug safety in the country where the study is to be performed, assisted by other knowledgeable scientists. The participants of this meeting are asked to critically examine the data presented relative to the protocol designed and to provide recommendations as to whether

1. The study in patients with onchocerciasis should be initiated as planned
2. If NO, what additional data should be obtained prior to a review of the decision to initiate the study.

WYETH
INVESTIGATOR'S BROCHURE

MOXIDECTIN
[WAY-204148]

This brochure is intended to acquaint clinical investigators with such scientific data as are currently available for **Moxidectin**.

As new data become available, they will be incorporated into this brochure, and the revised brochure will be forwarded to investigators. The investigator is asked to contact the ***Clinical Research and Development Department of Wyeth Research*** regarding any questions that may arise concerning this compound.

This brochure is a confidential communication of Wyeth Research and the World Health Organization (WHO), and the brochure and its contents are the property of Wyeth Research and the WHO. The recipient of the brochure agrees that no unpublished information contained herein will be duplicated, copied, published, disseminated, or in any way distributed without prior written approval from Wyeth Research and WHO. However, this document may be disclosed to appropriate institutional review boards and ethics committees or duly authorized representatives of international regulatory authorities under the condition that they maintain confidentiality.

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Moxidectin
[WAY-204148]

Investigator's Brochure
April 2004

The following personnel are responsible for the scientific content of the **Moxidectin** Investigator's Brochure.

**CHEMICAL AND PHARMACEUTICAL
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Senior Vice President, Chemical and Pharmaceutical
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Magid Abou-Gharbia, PhD
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NONCLINICAL PHARMACOLOGY

Frank S. Walsh, PhD
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Date

Time (24-hr) & Time Zone

Frank S. Walsh 4/28/04 12:00 EST

NONCLINICAL PHARMACOLOGY

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For Research and Training in Tropical Disease
WORLD HEALTH ORGANIZATION

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Janis Lazdins-Held 30.4.04 14:00 GENEVA SWITZERLAND

DRUG SAFETY AND METABOLISM

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Senior Vice President, Drug Safety and Metabolism

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30 APR 2004

1055 ET

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Thorir Bjornsson, PhD

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Thorir S. Bjornsson

28 Apr-04

16:15 EST

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Senior Vice President, Global Safety Surveillance and
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Maureen Caulfield

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1500 EDT

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28 Apr 04

09:00 GMT-5

Time Zones: CET = Central European Time; EST = Eastern Standard Time; EDT = Eastern Daylight Time;
GMT = Greenwich Mean Time

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1. SUMMARY

Onchocerciasis is a parasitic disease caused by the nematode *Onchocerca volvulus*, which is transmitted to humans by the bite of the black fly. Onchocerciasis is endemic in 37 countries, including Yemen, 30 countries in sub-Saharan Africa, and 6 in the Americas. Approximately 18 million people are afflicted with the disease. Moxidectin, a macrocyclic lactone drug derived from the actinomycete *Streptomyces cyanogriseus*, was developed by Fort Dodge Animal Health as a veterinary product, and is registered worldwide (including the United States) for the prevention of canine heartworm and for the treatment of parasites in cattle, sheep, and horses. It is now being developed in collaboration with the World Health Organization (WHO) as a treatment for humans with onchocerciasis.

1.1 Nonclinical Studies

After oral administration in rats, moxidectin was absorbed at a moderate rate, with a mean time to peak concentration (t_{max}) of 4.8 hours. The bioavailability of moxidectin was moderate at 19% and the apparent terminal half-life ($t_{1/2}$) was long (22.9 to 44.6 hours). After intravenous (IV) administration in rats, the clearance of moxidectin was low and the steady-state volume of distribution (Vd_{ss}) was high, indicating that the compound is widely distributed to tissues.

In rats, the major site of distribution of moxidectin was fat. The $t_{1/2}$ in fat was 11.5 days. Moxidectin represented the major component of total radioactivity in tissues and feces, and was largely eliminated through feces (60% to 91% of the recovered dose over 7 days).

There were no differences between rat and human liver microsomes in the metabolites detected. Four (4) moxidectin-related peaks were detected in the presence of cofactors and were characterized by liquid chromatography/tandem mass spectrometry (LC/MS/MS) as apparent hydroxylations at the C-4-methyl, C6-C19, C-28-methyl, and C-14 methyl positions.

In human liver microsomes, there was no inhibition of cytochrome P450 (CYP) 2A6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4 activity at the highest substrate concentration

used (100 μ M) and weak inhibition of CYP1A2 and CYP2C9 activity (extrapolated concentration at which there is 50% inhibition [IC_{50}] values of 459 and 145 μ M, respectively). Based on plasma concentrations in humans and these IC_{50} values, clinical metabolic drug-drug interactions for all the CYPs tested are unlikely to occur.

In single-dose toxicity studies of mice and rats given moxidectin by oral gavage, the median lethal dosage (LD_{50}) values were 118 mg/kg in male mice, 42 to 78 mg/kg in female mice, and 122 and 97 mg/kg in male and female rats, respectively.

Repeat-dose toxicity was evaluated in oral (diet) studies of mice (4 weeks), rats (4 and 13 weeks), and dogs (4 and 13 weeks and 1 year) and in oral (diet) carcinogenicity studies of mice and rats (2 years). Results of the repeat-dose studies indicate that moxidectin was well tolerated with no toxicologic effects at calculated dosages of up to 6.9 mg/kg/day for 4 weeks in mice, 3.9 mg/kg/day for 13 weeks in rats, or 1.1 mg/kg/day for 1 year in dogs. Moxidectin was not carcinogenic in mice or rats.

Reproductive toxicity was evaluated in developmental oral gavage studies of rats and rabbits and in pilot and definitive multigeneration diet studies. Maternal toxicity was evident at doses of 10 mg/kg/day or more in the rat developmental study, at doses of 125 ppm (calculated dosage averaging between 10.9 and 12.0 mg/kg/day) in the rat pilot multigeneration study, and at doses of at least 5 mg/kg/day in the rabbit developmental study; toxicity consisted primarily of decreased body weight and/or food consumption. At maternally toxic dosages (≥ 10 mg/kg/day) in the rat developmental study only, there were statistically significant increases in the number of fetuses with malformations and/or variations, largely reflective of increases in cleft palate and reversible delays in ossification. Although there were no fetal alterations in the other 3 studies, there was decreased fetal and/or pup survival at doses of 10 mg/kg/day in the rabbit developmental study and at doses of at least 10 ppm (calculated maternal dosage of ≥ 0.8 mg/kg/day) in the rat pilot 1-generation and 3-generation studies. The reproductive no-toxicologic-effect levels (NTEs) were 5 mg/kg/day in both the rat and rabbit developmental studies and at 5 ppm (0.4 mg/kg/day) in the rat 3-generation study.

Moxidectin was not genotoxic in a battery of in vitro and in vivo assays.

In conclusion, the results of nonclinical studies support clinical trials for the oral administration of moxidectin in the treatment of onchocerciasis.

1.2 Clinical Studies

The first-in-man (FIM) study (protocol 3110A1-100-EU) investigated the effects of single doses of 3 mg to 36 mg of moxidectin in healthy subjects. This randomized, placebo-controlled, sequential, ascending, single-dose study was designed to evaluate safety and tolerability and to provide an initial assessment of the pharmacokinetics of a liquid formulation of moxidectin. A total of 37 subjects in this study were treated with single doses of 3 mg to 36 mg (approximately 50 µg/kg to 600 µg/kg). Subjects were randomly assigned to placebo, 3-mg fasting, 9-mg fasting, 9-mg fed, 18-mg fasting, 36-mg fed, and 36-mg fasting groups.

The pharmacokinetic data obtained from the 3- to 36-mg dose groups showed that the $t_{1/2}$ ranged from 19.9 to 37.4 days. Rapid absorption was seen in all dose groups ($t_{max} = 0.1$ to 0.2 days). The results of the comparison of t_{max} between fasting and fed groups suggested that high-fat food may delay the absorption of moxidectin. Monotonic trend analysis evaluated maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$) and confirmed that moxidectin displayed linear, dose-proportional pharmacokinetics within the dose range studied. The distribution of moxidectin was extensive, as indicated by large mean values in the apparent volume of distribution during the terminal phase (V_d/F) with all dose groups evaluated, which was not unexpected in light of the lipophilic nature of moxidectin. The $t_{1/2}$ of moxidectin was long and no statistically significant differences were found between the means of the different dose groups.

There was no significant relationship between the overall number of adverse events (AEs) and the dose of moxidectin administered in the FIM study. No serious AEs, grade 4 AEs (according to the recommendations of the WHO for grading acute and subacute toxic effects), or deaths occurred during the study. The only grade 3 AE was enteritis (resulting

from food poisoning) in the 36-mg moxidectin fasting group; the investigator did not consider this event to be related to the test article. There were no clinically significant changes in vital signs, physical examination findings, or electrocardiograms (ECGs). Overall, moxidectin appeared to be safe at the doses evaluated.

The safety of moxidectin was confirmed in a further study (protocol 3110A1-101-EU) in healthy subjects who received 10 mg of moxidectin either as the liquid formulation used in the FIM study or as tablets. A total of 58 healthy male subjects participated in this open-label, randomized, single-dose, parallel-design study. The mean age of the subjects (32 years, range 20 to 45 years) and weight (81 kg, range 57 kg to 107 kg) were similar for those receiving the tablet formulation (n = 29) and those receiving the liquid formulation (n = 29).

Each subject received 1 orally administered dose of moxidectin, either as five 2-mg tablets or as a 10-mg liquid. In both cases moxidectin was administered under fasting conditions. All subjects participated in the study for approximately 7 months. Participation included a screening evaluation within 3 weeks before test article administration, a 3-day inpatient period, and a 180-day follow-up period.

During this study there were no serious AEs and no subjects discontinued the study as a result of an AE. A total of 36 (62.1%) subjects had treatment-emergent AEs (TEAEs) during the study, with the same number and percentage of subjects (18; 62.1% in each group) reporting TEAEs in both the moxidectin liquid and tablet groups. The most commonly reported TEAEs (reported by $\geq 5\%$ of subjects) were flu syndrome (17.2% and 20.7% in the liquid and tablet groups, respectively), headache (17.2% and 13.8% in the liquid and tablet groups, respectively), infection (13.8% and 6.9% in the liquid and tablet groups, respectively), diarrhea (10.3% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group).

All TEAEs that were reported during the study were mild to moderate in intensity, and none were considered to be related to treatment. No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory tests during the study.

The data from the clinical studies of moxidectin in normal subjects (study protocols 3110A1-100-EU and 3110A1-101-EU) suggest that progression to a safety and tolerability study in subjects with different degrees of severity of infection with *Onchocerca volvulus* is warranted.

2. INTRODUCTION

Moxidectin is a macrocyclic lactone drug that is derived from the actinomycete *Streptomyces cyanogriseus*. A veterinary product manufactured by Fort Dodge Animal Health, moxidectin is licensed and marketed worldwide as an anthelmintic agent for use in cattle, sheep, swine, horses, and dogs. It is now being developed in collaboration with the WHO as a treatment for humans with onchocerciasis (river blindness), a disease caused by infection with the tissue filarial nematode *Onchocerca volvulus*. The ultimate goal of the WHO in developing moxidectin is to eliminate onchocerciasis as a disease of public health and socioeconomic importance through the vigorous efforts of programs such as the African Programme for Onchocerciasis Control.

Onchocerciasis is endemic in 37 countries, including Yemen, 30 countries in sub-Saharan Africa, and 6 in the Americas. Approximately 18 million people are afflicted with the disease, which is transmitted from person to person through the bite of the black fly of the genus *Simulium*. Each adult female nematode, which can live for an average of 11 years but up to 18 years in the human body, produces millions of microfilariae that migrate through the skin, eyes, and lymph nodes. The microfilariae are the main cause of the clinical manifestations of onchocerciasis, which include severe dermatitis, depigmentation and atrophy of the skin, lymphadenitis, and elephantiasis. Visual impairment leading to blindness, however, is the severest manifestation of onchocerciasis. These manifestations have serious social and economic consequences that justify the vigorous efforts being made to control the disease.

Current strategies to control the disease include killing the larvae of the black fly vector with insecticides and treating infected populations with the macrocyclic lactone drug ivermectin (Mectizan). Ivermectin is a microfilaricide that must be administered at least once per year to reduce the microfilarial load. Eradication of onchocerciasis, however, is unlikely to occur

with these measures alone. It is widely recognized that a macrofilaricide, which can affect the motility and viability of adult forms of the nematode, is needed to prevent reaccumulation of larval forms of the nematode in the skin.

Moxidectin has some substantial differences from ivermectin. In vitro and in vivo animal studies have shown that moxidectin has a longer $t_{1/2}$ than ivermectin and a larger volume of distribution.¹ Moxidectin was found to be 2 to 10 times more potent than ivermectin on a dose-per-kilogram basis.^{2,3,4} Moxidectin was also found to reduce the motility and viability of adult worms in vitro and in vivo.⁵ Although structurally related to ivermectin, moxidectin is considerably more lipophilic and is therefore expected to have a longer duration of action than ivermectin after oral administration in humans.⁶ Animal data indicate that moxidectin is highly lipophilic, residing primarily in fatty tissue. Moxidectin has a long $t_{1/2}$, approximately 19.9 to 37.4 days in humans.

The exact mechanism of action of moxidectin is still under investigation. However, studies indicate that moxidectin binds to glutamate-gated chloride channels in the neurons and muscle cells of parasites. Binding to the ion channel results in hyperpolarization of the nerve and muscle fibers, leading to paralysis and death of the parasitic organism. Specificity of moxidectin for the parasite versus the mammalian host results from this compound having low affinity for mammalian chloride channels. An additional action of moxidectin is its activity at the γ -aminobutyric acid (GABA)-A receptor complex.

Results of these preclinical evaluations have suggested that orally administered moxidectin may be a useful treatment for onchocerciasis. Moxidectin, however, has not yet been administered as a treatment for individuals with onchocerciasis. The first clinical study of moxidectin examined the safety, tolerability, and pharmacokinetics of single ascending doses from 3 mg to 36 mg of moxidectin liquid orally administered to healthy male subjects. Because future clinical trials will be conducted with a tablet formulation of moxidectin, another study involving healthy, male subjects compared the relative bioavailability of tablet and liquid formulations of moxidectin at the 10-mg dose strength. The data from these clinical studies in normal subjects (protocols 3110A1-100-EU and 3110A1-101-EU)

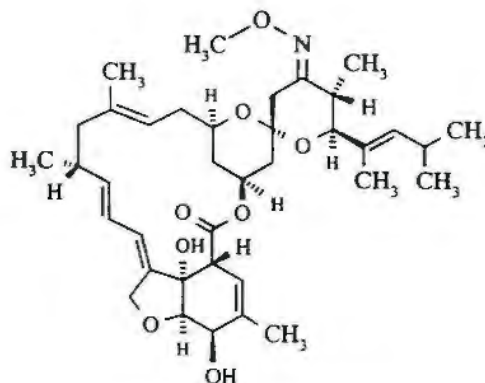
suggest that progression to a safety and tolerability study of subjects with different degrees of severity of infection with *Onchocerca volvulus* is warranted.

3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Molecular Structure and Chemical Name

Chemical Name: (2a*E*,4*E*,5'*R*,6*R*,6'*S*,8*E*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-[(*E*)-1,3-dimethyl-1-butenyl]-5',6,6',7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5',6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-4',17(3'*H*)-dione 4'-(*E*)-(O-methyloxime)

Molecular Structure:



Moxidectin, CL-301423

3.2 Physical, Chemical, and Pharmaceutical Properties

Table 3.2A lists the physical, chemical, and pharmaceutical properties of moxidectin.

TABLE 3.2A. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES OF MOXIDECTIN

Formula	C ₃₇ H ₅₃ NO ₈
Molecular weight	639.82
Appearance	White to pale yellow powder
Solubility in water and aqueous vehicles	Slightly soluble in water (0.51 mg/L); solubility not affected by change in pH. Readily soluble in organic solvents such as methylene chloride, diethyl ether, ethanol, acetonitrile, ethyl acetate, propylene glycol and benzyl alcohol.
Melting point (range)	145°C to 154°C
Dosage form	Tablet in capsule

3.3 Formulation

The formulations to be used in clinical studies are shown in Table 3.3.A.

TABLE 3.3.A. CLINICAL TRIAL FORMULATIONS

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In addition, commercially available ivermectin 3-mg tablets are overencapsulated with an inert ingredient powder (consisting of microcrystalline cellulose, sodium starch glycolate, anhydrous lactose, and magnesium stearate) in No. 0 hydroxypropyl methylcellulose or hypromellose (HPMC) capsules.

3.4 Storage and Handling

All clinical trial material should be stored at room temperature (up to 30°C) with protection from light.

4. NONCLINICAL STUDIES

4.1 Introduction

Moxidectin is an approved veterinary product (worldwide) that is now under development for use by the WHO for the treatment of human onchocerciasis. It is anticipated that moxidectin will be administered clinically as a single oral dose with the possibility of retreatment at 12-month intervals. The metabolism and toxicologic potential of various formulations of moxidectin were evaluated during its global development as an antiparasite treatment for veterinary use. Summaries of those studies considered relevant to the proposed clinical development are included in this Investigator's Brochure, as well as summaries of more recent studies specifically conducted to support human use (metabolic profiles in rat and human liver microsomes and CYP inhibition in human liver microsomes). Tabular summaries of nonclinical pharmacology studies are presented in Appendix 2.

4.2 Nonclinical Pharmacology

A series of physiologic function tests was used to demonstrate the activity of moxidectin.⁷ These studies indicated that moxidectin had activity at the GABA-A complex. Activity of milbemycin compounds has also been associated with glutamate-gated chloride channels.⁸ The multidrug transporter P-glycoprotein has been implicated in the mechanism of resistance to macrocyclic lactones.⁹ However, moxidectin has been shown to control parasites that are resistant to other macrocyclic lactones as well as benzimidazoles,^{10,11} suggesting a different mechanism or susceptibility to resistance. A different binding activity has been demonstrated for a GABA-gated chloride ion channel between ivermectin and moxidectin.¹²

Various in vitro and in vivo studies in mice, jirds, dogs, and cattle have evaluated the activity of moxidectin against several *Onchocerca* species and *Brugia pahangi*.^{2,3,4,5,13} In in vitro test systems, the effects of moxidectin and ivermectin were evaluated against

microfilariae from *O. volvulus* and *O. lienalis* in 7-day motility assays; both drugs had comparable effects on the motility of both organisms.² In addition, the effects of ivermectin, moxidectin, doramectin, and milbemycin oxime against *O. volvulus* and *O. gutturosa* male adult worms (macrofilaria) were examined using in vitro motility assays. Macrofilaria motility was significantly reduced by all 4 compounds at 2 hours, followed by a steady decline up to 120 hours. At the end of the study, the mean percentage reductions in worm motility for ivermectin, moxidectin, doramectin, and milbemycin oxime were 86%, 93%, 93%, and 74%, respectively.⁵

In vivo studies in CBA/Ca mice experimentally infected with *O. lienalis* consistently showed that, when moxidectin was given in a single subcutaneous or oral dose or in 5 subcutaneous doses, it was more efficacious in clearing microfilariae compared with ivermectin. Moxidectin administered as a single subcutaneous dose was also found to have more persistent microfilaricidal activity compared with ivermectin when given up to 28 days before infection to mice inoculated with *O. lienalis*. Moreover, in mice infected with *O. volvulus*, a single dose of moxidectin was more effective in reducing microfilarial burden compared with ivermectin.^{2,5}

Investigation of Guadali cattle in Cameroon addressed the effect of moxidectin and ivermectin on preventing infection of *O. ochengi* third- and fourth-stage larvae in naive calves under very high natural challenge (infection) conditions. Ivermectin (150 µg/kg) or moxidectin (200 µg/kg) was subcutaneously administered monthly or at 3-month intervals. At the end of the study, 11 of 14 control animals had nodules (total number of nodules = 110). Animals treated with ivermectin once every month had no nodules, but 2 of 10 animals treated with ivermectin every 3 months had nodules (total number of nodules = 2). In moxidectin-treated animals, no nodules were found in animals treated monthly or once every 3 months.^{3,4}

The activity of moxidectin against *B. pahangi* was evaluated in jird and dog models. In the jird model, the effect of moxidectin, ivermectin, and doramectin on microfilariae and macrofilariae was determined. Moxidectin induced a rapid reduction in microfilariae, with none detectable after day 224. Ivermectin and doramectin treatment resulted in a gradual

reduction in microfilariae through day 336; however, most jirds still had a few microfilariae remaining. Treatment of jirds with moxidectin resulted in more than 90% killing of microfilariae, whereas ivermectin and doramectin had no effect on macrofilarial burden.¹⁴

In the beagle dog model, moxidectin at doses of 250 µg/kg or 1000 µg/kg was given 1, 3, 6, or 12 times over a 12-month period to dogs experimentally infected with *B. pahangi*. After the first dose of moxidectin, the microfilariae count for all of the treated dogs gradually declined from pretreatment levels during the first 2 weeks after treatment. By 3 months, the microfilariae counts were suppressed 90% or more from pretreatment levels. The microfilariae counts remained suppressed to the end of the study at 12 months, with only 3 of the 78 moxidectin-treated dogs not clearing microfilariae.¹³ The same study also evaluated the effect of moxidectin on macrofilaria. At 6 months after the first dose, dogs treated with moxidectin at 250 µg/kg for 3 or 6 doses had 77% and 92% fewer worms, respectively, than controls. At 12 months after the first dose, dogs given 1 or more doses of moxidectin at either 250 µg/kg or 1000 µg/kg had at least 92% fewer worms than controls, with only 6 of 48 treated dogs having live adult worms at necropsy. The worm recoveries from all of the moxidectin-treated animals were significantly less ($p < 0.05$) than the recoveries for the controls, but there was no significant difference among the worm recoveries for the different moxidectin treatments.

The results of this study were confirmed in another study in the beagle dog model in which beagles were given a single oral dose of 250 µg/kg moxidectin or ivermectin 4 months after infection with *B. pahangi*.^{13, 14} At 333 days posttreatment microfilaria counts were significantly reduced relative to untreated controls in moxidectin-treated but not ivermectin-treated dogs. One (1) of 8 untreated controls and 1 of 8 ivermectin-treated dogs had no microfilaria, whereas 6 of 8 moxidectin-treated dogs were without microfilaria and 2 of 8 had microfilaria levels of 1 per 20 µL blood or lower. Upon necropsy at 334 days posttreatment, live macrofilaria were detected in 5 of 8 controls and in 4 of 8 ivermectin-treated dogs, but in only 1 of 8 moxidectin-treated dogs. These data show that a single dose of oral moxidectin of 250 µg/kg can result in long-term reduction of microfilaria, clearance of microfilaria, and impede macrofilaria viability. The limitations of the beagle model (high percentage of self cure > 6 months) preclude more definitive conclusions.

In conclusion, moxidectin is a potent microfilaricidal agent. The suppression of microfilariae is independent of the dosage or the number of treatments and, in the dog model, the effect is sustained for at least 1 year. Furthermore, moxidectin was also effective against *B. pahangi* macrofilaria.¹³

4.3 Pharmacokinetics and Product Metabolism in Animals

The metabolism studies summarized in this document include single-dose pharmacokinetics in rats and dogs, tissue distribution in rats, metabolic profile in rat and human liver microsomes, CYP inhibition in human liver microsomes, and excretion in rats.

4.3.1 Absorption and Pharmacokinetics

4.3.1.1 Rat, Single-Dose

The pharmacokinetics of moxidectin were evaluated after a single oral gavage or IV dosage of 0.2 mg/kg of ¹⁴C-moxidectin as part of an absorption, distribution, metabolism, and excretion study in rats.¹⁵ For oral administration, rats (5 males and 4 females) received moxidectin in a vehicle of corn oil; controls (1 male and 1 female) received vehicle only. For IV administration, rats (5 males and 5 females) received moxidectin in a vehicle of rat plasma containing 10% ethanol; the control (1 male) received vehicle only. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 120, and 168 hours after dosing for determination of concentrations in whole blood. Data from the 168-hour time point were not used due to possible contamination of the samples.

The pharmacokinetic parameters of total radioactivity (as equivalents [eq] of moxidectin) are provided in Table 4.3.1.1.A. C_{max} values were reached 4.8 hours after oral dosing. Based on area under the concentration-versus-time curve (AUC) values, the absorption was 19%. Based on calculated apparent terminal $t_{1/2}$ values, elimination appeared to be more rapid with oral than with IV administration; however, this may have been affected by the blood sampling time points used for calculation of the $t_{1/2}$. When $t_{1/2}$ values were calculated using the 24 to 48 hour time points, no difference in $t_{1/2}$ values was observed between oral and IV doses. After IV administration, body clearance ranged from 15.9 to 39.0 mL/h in males and

14.8 to 28.1 mL/h in females, and the $V_{d_{ss}}$ ranged from 1864 to 2610 mL in males and 1350 mL to 2589 mL in females. There were no sex-related differences after either route of administration.

TABLE 4.3.1.1.A. MEAN ($\pm$ SD) PHARMACOKINETIC PARAMETERS OF TOTAL RADIOACTIVITY IN RATS AFTER ORAL GAVAGE OR IV ADMINISTRATION OF A SINGLE

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4.3.1.2 Dogs

Moxidectin concentrations following oral administration in dogs were examined in 2 studies. As part of a 3-year study of moxidectin sustained release (SR) injectable, 4 male beagle dogs were administered 2 doses of approximately 90 μ g/kg in tablet form separated by 2 months.¹⁶ Blood samples for determination of serum concentrations were collected at 1, 3, 5, 7, 10, 14, 21, and 56 days after the first dose and at 8, 16, and 24 hours after the second dose.

Following the first dose, serum concentrations declined over time from 11 ng/mL to 1.6 ng/mL at day 21, and were undetectable at day 56 (N = 2). The lower limit of detection was 0.5 ng/mL for a 2-mL sample. The highest observed serum concentration (apparent

$C_{\max}$; 19.4 ng/mL) was seen at the earliest sampling time point (8 hours after second dose). Using data from the 2 doses, the minimum estimate of $AUC_{0-\infty}$ was 2515 ng•h/mL and the apparent $t_{1/2}$ was 8.1 days (194 hours).

In a second exploratory study, groups of 3 female beagle dogs received a single dose of 100 μ g ^{3} H-moxidectin (calculated dosage of 10 μ g/kg) in 1 liquid formulation or 1 of 4 different tablet formulations.¹⁷ Blood was collected for determination of radioactivity concentrations at 0, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dose administration. ^{3} H-moxidectin was rapidly absorbed and concentrations of total radioactivity in blood peaked at 2 hours. The maximum concentrations ranged from 3.7 to 6.1 ng eq/mL. Concentrations decreased over time, with none detected at 96 hours except in 1 tablet formulation in which 96 hour concentrations ranged from 0.6 to 0.9 ng eq/mL. The following pharmacokinetic parameters were obtained for the liquid formulation: $C_{\max}$ = 4.60 ng eq/mL, $t_{\max}$ = 2 hours, $AUC_{0-\infty}$ = 176 ng eq•h/mL, and $t_{1/2}$ = 101 hours. Similar values were obtained for the tablet dosage formulations.

4.3.2 Tissue Distribution

4.3.2.1 Rats

Tissue distribution was evaluated as part of an absorption, distribution, metabolism, and excretion study in rats.¹⁵ Rats received ^{14} C-moxidectin in corn oil by oral gavage at a dosage of 1.5 mg/kg once daily for 7 days. Groups of 3 males and 3 females were sacrificed at 6, 24, 72, 120, and 168 hours after the last dose for collection of tissue samples (liver, kidney, muscle, and fat).

Fat contained the highest concentration of radioactivity (Table 4.3.2.1.A). Radioactivity in tissue samples was higher in females than in males at all time points. The $t_{1/2}$ values of total radioactivity (average for males and females combined) in tissues were: liver, 2.4 days; kidney, 2.4 days; muscle, 3.9 days; and fat, 11.5 days.

TABLE 4.3.2.1.A. TOTAL ^{14}C RESIDUES IN TISSUES FROM RATS
ADMINISTERED 1.5 mg/kg OF ^{14}C -MOXIDECTIN ONCE DAILY FOR 7 DAYS

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4.3.3 Metabolism

Moxidectin was initially developed as a veterinary drug and to support this use, an in vitro/in vivo metabolism study was conducted in rats. For the current development of moxidectin for use in humans, an in vitro metabolism study was conducted in rat and human liver microsomes. Because the studies were conducted during different time frames and by different groups, the designations for the various metabolites differ. These designations are cross-referenced in Table 4.3.3.A. For those metabolites with 2 different designations, the designation given in the earlier study (in vivo rat metabolism study) will be used.

TABLE 4.3.3.A. DESIGNATIONS FOR MOXIDECTIN METABOLITES
DETECTED IN VITRO AND IN VIVO

**REDACTED COMMERCIALY
SENSITIVE PROPRIETARY DATA**

4.3.3.1 In Vitro Metabolism

4.3.3.1.1 Metabolic Profile in Rat and Human Liver Microsomes

The metabolism of moxidectin was investigated in liver microsomes pooled from male Sprague-Dawley (S-D) rats and from men and women.¹⁸ In the presence of reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) and uridine diphosphate-glucuronic acid (UDPGA), moxidectin was minimally metabolized in both rat and human liver microsomes ($t_{1/2} > 60$ minutes), suggesting that the metabolic clearance of moxidectin is likely to be low in both species. This finding was consistent with the results of an in vivo study with rats (section 4.3.3.2.1).

There were no differences between rat and human liver microsomes in the metabolites detected. Four (4) moxidectin-related peaks (M VI, M2, M IV, and M II)^a were detected in the presence of cofactors (NADPH and UDPGA) and were characterized by LC/MS/MS as apparent hydroxylations at the C-4-methyl, C6-C19, C-28-methyl, and C-14 methyl positions. Metabolites M VI, M IV, and MII were detected in minor quantities relative to the parent compound in the livers and feces of rats in the in vivo study (section 4.3.3.2.1). The proposed in vitro metabolic pathway in rats and humans is presented in Figure 4.3.3.1.1.A.

^a In this study report the following designations were used for metabolites: M VI was M1, M IV was M3, and M II was M4.

FIGURE 4.3.3.1.A. PROPOSED METABOLIC PATHWAYS OF MOXIDECTIN IN LIVER
MICROSOMES FROM RATS AND HUMANS

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SENSITIVE PROPRIETARY DATA**

4.3.3.1.2 Cytochrome P450 Inhibition in Human Liver Microsomes

The potential for moxidectin to inhibit the activity of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was evaluated in human liver microsomes at moxidectin concentrations ranging from 0.1 to 100 μM .¹⁹ Moxidectin was a weak inhibitor of CYP1A2 and CYP2C9, with extrapolated IC_{50} values of 459 μM and 145 μM , respectively. There was no inhibition of the other CYP enzymes examined. In humans, the mean C_{max} after an 18-mg oral dose was 141 ng/mL (0.2 μM). Therefore, it is unlikely that clinical drug-drug interactions involving these CYP enzymes would occur.

4.3.3.2 In Vivo Metabolism

4.3.3.2.1 Rats

The metabolic profile of moxidectin was examined as part of an absorption, distribution, metabolism, and excretion study with rats.¹⁵ The profiles were determined for urine, feces, and tissue (liver, kidney, muscle, and fat) samples from rats administered ^{14}C -moxidectin by oral gavage at a single dosage of 1.5 or 12 mg/kg or at a dosage of 1.5 mg/kg once daily for 7 days. Because radioactivity concentrations were low in tissues and/or the supply of tissues was limited, the metabolic profile was also determined in vitro in rat liver microsomes.

The metabolite profiles in liver (in vitro and in vivo), kidney, muscle, and fat were qualitatively similar. Moxidectin was identified as the only major ^{14}C component in the tissues and feces at 24 hours after dosing. Only a small amount of moxidectin was observed in urine. Five (5) metabolites (M I, M II, M III, M IV, and M VI) were identified in liver and feces. A sixth minor metabolite (M V) was also identified in feces. The metabolites were identified as C-14 hydroxymethyl moxidectin (M II), the O-demethylated derivative of C-14 hydroxymethyl moxidectin (M I), C-24 hydroxymethyl moxidectin (M III), C-4 hydroxymethyl moxidectin (M VI), a moxidectin derivative hydroxylated on the side chain at either the C-26 methyl group or the C-28 methine group (M IV), and the 23-keto derivative (M V). Most of these metabolites are mono-oxygenated derivatives, indicating that hydroxylation is the principal route of metabolism in rats. The metabolic transformation of moxidectin is depicted in Figure 4.3.3.2.1A and Table 4.3.3.2.1A.

FIGURE 4.3.3.2.1A. THE METABOLIC TRANSFORMATION OF MOXIDECTIN IN RATS

**REDACTED COMMERCIALY
SENSITIVE PROPRIETARY DATA**

4.3.4 Excretion

4.3.4.1 Rats

In a preliminary mass balance study, rats (2/sex) received 1.5 mg/kg of ^{14}C -labeled moxidectin as a single oral dose in corn oil.²⁰ Total feces, urine, and respired carbon dioxide were collected through 72 after dose administration. Cages were rinsed at the end of the study and all samples were assayed for total ^{14}C content. Total recovery of the administered radioactivity ranged from 92% to 95%. The primary route of excretion of radioactivity was in feces, accounting for 88% to 96% of the administered dose. Urine accounted for less than 1%. No radioactivity was detected in the respired air, demonstrating that carbon dioxide was not a product of the metabolism of moxidectin.

In a second study, male and female rats (5/sex/group) received ^{14}C -labeled moxidectin as a single oral dosage (1.5 or 12 mg/kg) or a daily oral dosage (1.5 mg/kg) for 7 days.¹⁵ Total excreta and tissues were collected at intervals up to 7 days after dose administration. Feces was the primary route of excretion, accounting for 60% to 91% of the radioactivity for all rats after 7 days. Less than 2% of the dose was eliminated in the urine.

4.4 Toxicology

Toxicity was evaluated in mice, rats, and dogs. Single-dose toxicity was evaluated in oral gavage, intraperitoneal (IP), and subcutaneous (SC) studies with mice and rats and in a dermal study with rabbits. Repeat-dose toxicity was evaluated in 4-week diet studies with mice, rats, and dogs; 13-week diet studies with rats and dogs; and a 1-year diet study with dogs. Carcinogenic potential was evaluated in 2-year diet studies with mice and rats. Reproductive toxicity was evaluated in oral gavage developmental toxicity studies with rats and rabbits and in pilot and definitive 3-generation oral diet studies with rats. Genotoxic potential was evaluated in a battery of in vitro and in vivo assays.

4.4.1 Single-Dose Studies

The single-dose toxicity of moxidectin was evaluated in oral gavage, IP, and SC studies of mice and rats and in a dermal study of rabbits.^{21,22,23,24,25,26,27,28,29} Animals were observed for 2 weeks after the single dose for signs of toxicity. The LD_{50} values are presented in Table 4.4.1A. Study findings for the oral studies of male and female mice and rats are summarized below.

TABLE 4.4.1A. SINGLE-DOSE TOXICITY STUDIES WITH MOXIDECTIN

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SENSITIVE PROPRIETARY DATA**

4.4.1.1 Oral

4.4.1.1.1 Mice

There were 3 studies conducted in mice. In 1 study (A90-45.01), mice (5 sex/group) received dosages of 15, 30, 60, 120 (females only), or 240 mg/kg. In 2 studies (A91-44 and A91-43), female mice (5/group) received dosages of 30, 60, or 120 mg/kg. Dosages were administered as a corn oil dispersion.

In study A90-45.01, mortality occurred in 1 female at a dose of 30 mg/kg, 1 female at a dose of 60 mg/kg, 4 females at doses of 120 mg/kg, and 5 males and 5 females at doses of 240 mg/kg. In study A91-44, mortality occurred in 1 female at a dose of 30 mg/kg, 3 females at doses of 60 mg/kg, and 5 females at doses of 120 mg/kg. In study A91-43, mortality occurred in 5 females at doses of 60 mg/kg and 4 females at doses of 120 mg/kg. With the exception of the accidental death of 1 female at a dose of 60 mg/kg in study A90-45.01 (not included in calculation of the LD₅₀), all deaths in these 3 studies occurred between 8 and 24 hours after dose administration.

In study A90-45.01, decreased activity was observed at doses of 15, 30, and 60 mg/kg. Females in the 60 mg/kg-dose group showed an average weight loss of 2.1 grams; other treated groups that survived to the end of the study showed weight gains of 0.4 to 5 grams. In the 2 studies of females, decreased activity, tremors, ataxia, prostration, and diuresis were observed in at least 1 of the 2 studies of females at dosages as low as 60 mg/kg. In the 3 studies, the clinical observations generally occurred during the first 24 hours after dosing and recovery of surviving animals was generally complete within 3 to 4 days after dosing and there were no macroscopic findings.

4.4.1.1.2 Rats

Rats (5 sex/group) received oral dosages of 75, 150, or 300 mg/kg. Mortality occurred in 1 female at a dose of 75 mg/kg, 4 males and 5 females in the 150-mg/kg group, and 5 males and 5 females in the 300-mg/kg group. All deaths occurred between 8 and 24 hours after dose administration. Clinical observations were hypersensitivity to touch and sound, epistaxis, and diarrhea at doses of 75 mg/kg; decreased activity, prostration, and decreased respiration at dose of 75 mg/kg or more; tremors at doses of 75 mg/kg and 300 mg/kg; and chromodacryorrhea at doses of 300 mg/kg. Macroscopic findings in rats that died were congested liver at doses of 75 mg/kg or more; and congested kidney and/or lung at dose of 150 mg/kg or more. There were no macroscopic findings in surviving rats.

4.4.1.2 Intraperitoneal

4.4.1.2.1 Mice

Mice (5 sex/group) received IP dosages of 40, 80, 160, or 320 (females only) mg/kg. Mortality occurred in 1 female at doses of 40 mg/kg, 2 males and 3 females at doses of 80 mg/kg, 5 males and 3 females at doses of 160 mg/kg, and 5 females at doses of 320 mg/kg. Most deaths (17 of 19) occurred between 8 hours and 3 days after dose administration. Clinical observations were decreased activity at doses of 80 mg/kg or more, epistaxis at doses of 80 mg/kg, tremors at doses of 160 mg/kg or more, coma at doses of 160 mg/kg, and loss of righting reflex at doses of 320 mg/kg. In surviving animals, recovery was generally complete within 5 days. Body-weight gains were somewhat decreased at the end of the study. There were no compound-related macroscopic findings.

4.4.1.2.2 Rats

Rats (5 sex/group) received IP dosages of 160, 320, or 640 mg/kg. Mortality occurred in 1 male and 1 female at doses of 160 mg/kg, 2 males and 2 females at doses of 320 mg/kg, and 3 males and 4 females at doses of 640 mg/kg. Deaths occurred between 2 and 12 days after dose administration. Clinical observations were decreased activity, prostration, anorexia, and epistaxis at doses of 160 mg/kg or more and chromodacryorrhea at doses of 160 mg/kg. In surviving animals, recovery was generally complete within 4 days. Body-weight gains were somewhat decreased at the end of the study. In animals that died, necropsy findings were evidence of salivation, diuresis and/or epistaxis; test material attached to abdominal organs; congested liver; hemorrhagic lung; hemorrhagic intestine; and gas-filled intestinal tract. In surviving animals, the only necropsy finding was test material attached to abdominal organs.

4.4.1.3 Subcutaneous

4.4.1.3.1 Mice

Mice (5/sex/group except there were 4 males in the low dosage group) received SC dosages of 80, 160, or 320 mg/kg. Mortality occurred in 3 males and 4 females at doses of

320 mg/kg. All deaths occurred between 8 hours and 2 days after dose administration. Clinical observations were decreased activity and tremors at doses of 320 mg/kg. In surviving animals, recovery was generally complete within 3 days. Small nodules containing a yellow exudate were observed at the injection site.

4.4.1.3.2 Rats

Rats (5 males and 5 females) received a SC dosage of 640 mg/kg. There were no deaths or compound-related clinical observations. Body-weight gains were somewhat decreased by the end of the study. Ulceration or nodules filled with yellow-green exudate were observed at the injection site.

4.4.1.4 Dermal

4.4.1.4.1 Rabbits

Rabbits (5 males and 5 females) received a dermal application of 2000 mg/kg to intact skin. There were no deaths or compound-related effects.

4.4.2 Repeat-Dose Studies

Repeat-dose oral (diet) toxicity was evaluated in 4-week studies with mice, rats, and dogs; 13-week studies with rats and dogs, and a 1-year study with dogs. Summaries of these studies are provided in the following sections.

4.4.2.1 Mice

4.4.2.1.1 Four-Week Oral (Diet) Study

Moxidectin was given to groups of mice (5/sex/group) for 1 month in the diet at concentrations of 0, 33.7, 75, 100, 125, or 150 ppm.³⁰ The calculated dosages for 33.7, 75, 100, and 125 ppm were 6.9, 17.7, 23.2, and 24.1 mg/kg/day, respectively; due to high mortality, a value could not be calculated for the 150-ppm group. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, organ weights, and macroscopic and microscopic examinations.

Mortality occurred in 1 of 10 mice at doses of 75 ppm, 8 of 10 mice at doses of 100 ppm, 9 of 10 mice at doses of 125 ppm, and 10 of 10 mice at doses of 150 ppm; the deaths occurred during the first 14 days of the study. Microscopic examination did not reveal the causes of death in these animals. Clinical observations were tremors, hypersensitivity to touch, and urine-stained fur at doses of 75 ppm or more. Body weights and body-weight gains were decreased at doses of 100 ppm or more. There were no other compound-related effects. Based on the mortalities, the NTEL was 33.7 ppm (6.9 mg/kg/day).

4.4.2.2 Rats

4.4.2.2.1 Four-Week Oral (Diet) Study

Moxidectin was administered to groups of rats (5/sex/group) for 1 month in the diet at concentrations of 0, 100, 200, 400, or 600 ppm.³¹ The calculated dosages for 100, 200, 400, and 600 ppm were 12.2, 22.8, 26.3, and 31.2 mg/kg/day, respectively. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, organ weight, and macroscopic and microscopic examinations.

Two (2) females at doses of 200 ppm died on days 19 and 22 and all rats at doses of 400 ppm or more died or were sacrificed moribund within the first 8 days after dose administration. Macroscopically, urinary bladder filled with dark/bloody fluid was observed in 4 of 10 rats at doses of 600 ppm. Microscopic findings in animals that died consisted principally of diffuse atrophy of the liver, kidney, heart, spleen, adrenal glands, thyroid glands, testes, ovaries, and epididymides. These changes were typical of changes observed in anorexic animals; there was no evidence of a direct toxic effect.

Clinical observations included hypersensitivity to touch at doses of 100 ppm or more; and ataxia, tremors, salivation, piloerection, and diuresis at dose of 200 ppm or more. There were decreased body weight, body-weight gain, and food consumption at doses of 200 ppm or more compared with controls. At the end of the study, in the 200-ppm group (highest dosage group surviving until the end of study), body weights were decreased 12% in males and 15% in females and total body-weight gain was decreased 17% in males and 26% in

females. There were no compound-related macroscopic or microscopic findings in rats that did not die during the study. Based on the mortalities, the NTEL in this study was 100 ppm (12.2 mg/kg/day).

4.4.2.2.2 Thirteen-Week Oral (Diet) Study

Moxidectin was administered to rats (20/sex/group) for 13 weeks in the diet at concentrations of 0, 25, 50, 100, or 150 ppm.³² The calculated dosages for 25, 50, 100, and 150 ppm were 2.0, 3.9, 8.0, and 12.2 mg/kg/day, respectively. Evaluations of compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic and microscopic examinations.

Mortality (died or sacrificed in moribund condition) occurred in 3 females at doses of 150 ppm. Microscopic examination did not reveal the causes of death for these animals.

Clinical observations included hypersensitivity to touch at doses of 100 ppm; and lethargy, anorexia, aggressive behavior, loss of righting reflex, ataxia, tremors, and urine-stained coat at doses of 150 ppm. Body weight and body-weight gain were decreased in males at doses of 100 ppm or more and in females at doses of 150 ppm. Food consumption was decreased in males and females at doses of 150 ppm.

Adrenal gland and kidney weights (absolute and relative to body weight) were increased in females at doses of 100 ppm or more. There were no compound-related macroscopic or microscopic findings.

The NTEL in this study was 50 ppm (3.9 mg/kg/day).

4.4.2.3 Dogs

4.4.2.3.1 Four-Week Oral (Diet) Study

Moxidectin was administered to dogs (2/sex/group) for 1 month in the diet at concentrations of 0, 20, 80, or 160 ppm lowered to 50 ppm.³³ Dose administration at 160 ppm was stopped

after 5 days because these dogs experienced debilitating clinical observations; administration of test article was resumed at doses of 50 ppm after a 2-day recovery period. The calculated dosages for 20, 80, and 160/50 ppm were 0.8, 2.4, and 3.0/1.8 mg/kg, respectively.

Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, ophthalmic examinations, hematology, urinalysis, organ weights, macroscopic examinations, and microscopic examinations of selected tissues.

No dogs died during the study. Clinical observations included tremors, languid appearance, ataxia, emesis, and mydriasis at doses of 80 ppm or more. Body weight and food consumption were decreased at doses of 80 ppm or more during week 1, but increased or remained stable after week 1 with the exception of 1 female at a dose of 80 ppm that consistently showed anorexia, weight loss, tremors, ataxia, prostration, and thin appearance.

Testes weights (absolute, relative to body weight, and relative to brain weight) were decreased at doses of 80 ppm or more. Microscopic findings were decreased spermatogenic activity at doses of 80 ppm or more and decreased colloid in the thyroid gland in males at doses of 80 ppm. These findings may have been related to variations in age of maturation, as study dogs were 5 to 6 months old at study termination, and were not seen in the 1-year toxicity study with dogs (section 4.4.2.3.3). Based on the postmortem findings, the NTEL in this 4-week study was 20 ppm (0.8 mg/kg/day).

4.4.2.3.2 Thirteen-Week Oral (Diet) Study

Moxidectin was given to dogs (4/sex/group) for 13 weeks in the diet at concentrations of 0, 10, 30, or 60 ppm.³⁴ The calculated dosages for 10, 30, and 60 ppm were 0.3, 0.9, and 1.6 mg/kg/day, respectively. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, ophthalmic examinations, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic and microscopic examinations.

No dogs died during the study. Clinical observations included lacrimation at doses of 10 ppm or more, languid appearance and tremors at doses of 10 and 60 ppm, thin appearance at doses of 30 ppm more, and slight salivation and slight ataxia at doses of 60 ppm. Body

weight, body-weight gain, and food consumption were decreased in males at doses of 30 ppm or more and in females at doses of 60 ppm; these decreases were not statistically significant except for male body-weight gains and male and female food consumption at doses of 60 ppm. In the 60-ppm group, alanine aminotransferase (ALT) was increased in 1 male and 1 female, and serum alkaline phosphatase was increased in 3 males and 3 females compared with pretreatment and/or controls. There were no compound-related macroscopic or microscopic changes in any tissues or organs.

Based on the absence of toxicologically significant findings at any tested concentration, the NTEL in this study was 60 ppm (1.6 mg/kg/day).

4.4.2.3.3 One-Year Oral (Diet) Study

Moxidectin was administered to beagle dogs (6/sex/group) for 1 year in the diet at concentrations of 0, 10, 20, or 45 ppm.³⁵ The calculated dosages for 10, 20, and 45 ppm were 0.25, 0.5, and 1.1 mg/kg/day, respectively. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, ophthalmic examinations, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic and microscopic examinations.

No dogs died during the study. Total serum protein and serum albumin values were slightly decreased in females at doses of 10 ppm or more, but the values were within the normal range and the decreases were too minor in magnitude to be of biologic importance. Decreased ovarian weights (absolute and relative to body weight and brain weight) were observed at doses of 45 ppm; however, the absolute weights were within reference or historic control ranges and the decreases were not considered to be biologically important. There were no compound-related microscopic findings. Based on the absence of toxicologically significant findings at any tested concentration, the NTEL in this study was 45 ppm (1.1 mg/kg/day).

4.4.2.3.4 Veterinary Postmarketing Information, Subcutaneous ProHeart 6

Moxidectin Canine SR Injectable (ProHeart 6) is a novel SR injectable product developed for the prevention of heartworm in dogs to be administered twice a year. It has been marketed since June 2001. Allergic reactions have been reported in dogs receiving SC ProHeart 6 (approximately 1.4 reports per 10,000 doses administered). Similar reactions have not been reported in dogs receiving ProHeart Tablets, an oral formulation of moxidectin given as a monthly heartworm preventative. The relevance of the allergic reactions observed in dogs after SC administration of ProHeart 6 to the proposed clinical trials in which subjects will receive an oral formulation is unknown, but such effects are deemed unlikely given the lack of allergic reactions in dogs receiving the oral formulation.

4.4.3 Carcinogenicity Studies

4.4.3.1 Mice, Oral (Diet) Study

Moxidectin was administered to mice (65/sex/group) for 2 years in the diet at concentrations of 0, 15, 30, or 60 ppm lowered to 50 ppm.³⁶ The high dosage was reduced from 60 ppm to 50 ppm at week 9 due to high mortality in this group. The calculated dosages for 15, 30, and 60/50 ppm were 2.2, 4.5, and 10.7/6.3 mg/kg/day in males and 2.8, 5.7, and 13.0/8.5 mg/kg/day in females, respectively. Evaluations for compound-related effects were based on mortality, clinical observations, body weight, food consumption, hematology, organ weights, and macroscopic and microscopic examinations.

Mortality was increased in males and females in the 60-ppm group during the 8 weeks before dosage reduction. Mortality was increased in females at doses of 60/50 ppm during the last 13 weeks of the study. There were no compound-related clinical observations, except those related to mortality (eg, hunched posture, decreased activity, tremors, labored breathing, and cold to touch). During the first 8 weeks of the study, there were decreases in body weight (3% to 7%) and food consumption (2% to 12%) in males at doses of 60 ppm; after the dosage was decreased to 50 ppm, body-weight gain and food consumption were comparable to that of the controls. There were no compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence of moxidectin-related target-organ toxicity or tumorigenicity in this study.

4.4.3.2 Rats, Oral (Diet) Study

Moxidectin was administered to rats (65/sex/group) for 2 years in the diet at concentrations of 0, 15, 60, or 120 ppm lowered to 100 ppm.³⁷ The high dosage was reduced from 120 ppm to 100 ppm after 8 weeks due to high mortality in females in this group. The calculated dosages for 15, 60, and 120/100 ppm were 0.7, 2.8, and 8.5/4.0 mg/kg/day in males and 0.9, 3.7, and 11.0/5.6 mg/kg/day in females, respectively. Evaluations for compound-related effects were based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic and microscopic examinations.

Mortality was increased and body-weight gain was decreased in females at doses of 120 ppm during the 8 weeks prior to the dosage reduction. Clinical observations were related to mortality in this group (hunched posture, hypersensitivity to external stimuli, tremors, hypoactive behavior, rough haircoat, and urine-stained skin or fur). Body-weight gain was decreased (18% compared with controls) in females during the period they received 120-ppm doses. Body-weight gain for this group was similar to or greater than controls after the dosage was reduced to 100 ppm; however, body weights were generally lower than controls throughout the study. At various study time points and in various dosage groups, there were statistically significant changes in segmented neutrophils, mean cell volume, blood urea nitrogen, ALT, albumin, and sodium. However, these changes did not occur consistently or in a dose-related pattern and/or were not of a magnitude to be considered biologically important. There were no compound-related findings for organ weights or macroscopic or microscopic examinations; there was no evidence of moxidectin-related target-organ toxicity or tumorigenicity in this study.

4.4.4 Reproductive Toxicity Studies

4.4.4.1 Developmental Toxicity, Oral Gavage

4.4.4.1.1 Rats

Moxidectin was administered by oral gavage at once-daily dosages of 0, 2.5, 5, 10, or 12 mg/kg/day to presumed pregnant rats (25/group) from gestation day (GD) 6 through

GD 15.³⁸ Evaluations for compound-related maternal toxicity were based on mortality, clinical observations, body weight, food consumption, uterine weight, and macroscopic examinations. Evaluations for compound-related fetal effects were based on number of corpora lutea, number and placement of implantation sites, early and late resorptions, number of live and dead fetuses, fetal body weight, sex ratio, and macroscopic examination of external and soft tissue and skeletal development.

No rats died during the study. Clinical observations at doses of 12 mg/kg/day were urine-stained fur, red substance on fur, and chromodacryorrhea. At doses of 10 mg/kg/day or more, there were decreases in maternal body weight (4% to 6% at GD 16), in body-weight gain (18% to 36% for GD 6 to GD 16), and in food consumption (4% to 13% for GD 6 to GD 16) during the dose administration period compared with controls, which was indicative of maternal toxicity. After the dose administration period, body-weight gain and food consumption increased. At sacrifice (GD 20), body weights for both groups were 3% lower than that of controls, and the body weights adjusted for gravid uterine weights were 1% and 2% lower than that of controls.

Although not statistically significant, fetal body weights at doses of 5 mg/kg/day or greater tended to be lower ($\leq 6\%$) than controls. At doses of 10 mg/kg/day or more, there were statistically significant increases in the number of fetuses with malformations and/or variations (3.1%, 4.3%, 5.5%, 7.9%, and 8.4% at 0, 2.5, 5, 10, and 12 mg/kg/day, respectively). The number of litters with malformations and/or variations also tended to be increased (26.1%, 41.7%, 40.0%, 54.2%, and 54.2% at 0, 2.5, 5, 10, and 12 mg/kg/day, respectively). These increases largely reflected increases in cleft palate and/or reversible delays in ossification that were not considered related to reduced fetal weights. In conclusion, based on the available data, the yearly oral intake of 32 mg of moxidectin (or 16 mg every 6 months) by women is unlikely to pose a risk to the developing human fetus. It is well established in the scientific literature that maternal toxicity can result in fetal alterations including malformations and delays in ossification.³⁹

There were no compound-related effects on any other maternal or embryo-fetal parameters examined. The maternal and developmental NTEL was considered to be 5 mg/kg/day, with

increased incidences of cleft palate and delayed ossification in the presence of maternal toxicity at higher dosages. These results are comparable to those reported in rats with ivermectin and abamectin.⁴⁰

4.4.4.1.2 Rabbits

Moxidectin was administered by oral gavage at dosages of 0, 1, 5, or 10 mg/kg/day to groups of 18 artificially inseminated rabbits from GD 7 through GD 19.⁴¹ Evaluations for compound-related effects were based on mortality, clinical observations, body weights, food consumption, macroscopic examinations, number of corpora lutea, number and placement of implantations, early and late resorptions, fetal survival, fetal body weight, sex ratio, and macroscopic examinations of external and soft tissues and skeletal development.

One (1) control female and 1 female in the 10-mg/kg/day group were found dead (GD 14 and GD 7, respectively); the deaths were attributed to intubation accidents. Two (2) females in the 1-mg/kg/day and 1 female in the 10-mg/kg/day group aborted litters; the incidences were within historical ranges for rabbits given corn oil (the vehicle in this study) and were not considered compound related. Maternal toxicities (decreased body weight [$\leq 5\%$], decreased body-weight gain [$\leq 85\%$ for GD 7 to GD 20], and decreased food consumption [$\leq 20\%$ for GD 7 to GD 20]) were evident at doses of 5 and 10 mg/kg/day. Body-weight gain and food consumption were similar to that of controls after the dosing period (GD 20 to GD 29).

Evaluation of the results of cesarean sections excluded data from the deaths and full-litter abortions, and data from 2 females (1 at 5 mg/kg/day and 1 at 10 mg/kg/day) that had litters containing only 1 fetus. Reduced litter size (6.2 compared with 7.1 in controls) reflective of increased early resorptions (1.2 compared with 0.2 for controls) were observed at doses of 10 mg/kg/day. There were no other compound-related effects, including malformations or fetal alterations, in this study. The fetal effects occurred only at a dosage that elicited maternal toxicity, and the maternal and developmental NTEs were considered to be 1 and 5 mg/kg/day, respectively. These results are in contrast with those obtained in rabbits given ivermectin, in which a low but dose-related increase in the incidence of cleft palate and

clubbed forepaws occurred among fetuses, in the presence of maternal toxicities, at gavage dosages of 3 and 6 mg/kg/day.⁴⁰

4.4.4.2 Multigeneration, Oral (Diet)

4.4.4.2.1 Rats, Pilot 1-Generation

This study was initially designed to evaluate the effects of continuous treatment with moxidectin on fertility and reproductive performance in rats through 3 generations.⁴² However, at dietary concentrations of 25, 50, and 125 ppm there was considerable pup mortality. Therefore, the decision was made to terminate the first litters (F_{1a}) and reduce dietary concentrations to 5, 10, or 15 ppm to produce a second litter (F_{1b}). The calculated dosages are presented in Table 4.4.4.2.1A. Evaluations for compound-related effects were based on mortality, clinical observations, body-weight, food consumption, mating and fertility rates, gestation length, pup survival, pup body-weight, sex ratio, and parental and pup macroscopic examinations.

TABLE 4.4.4.2.1A. ESTIMATED MOXIDECTIN CONSUMPTION

**REDACTED COMMERCIALLY
SENSITIVE PROPRIETARY DATA**

There was no compound-related parental mortality; 1 female in the 50-ppm group was sacrificed moribund with an eye lesion that was not considered to be compound related. There were decreases in body-weight ($\leq 8\%$) and body-weight gain (12% weeks 1 to 9) in females in the 125-ppm group during the premating period. Food consumption for these

females during the same time was comparable to or greater than controls ($\leq 8\%$). There were no compound-related macroscopic findings.

For production of the F_{1a} generation, parental (P₁) animals (25/sex/group) were treated from 9 weeks before mating through gestation and lactation. At doses of 125 ppm, the total number of pups was lower than controls (11.0 compared with 13.5 in controls), the number of live pups was decreased (2.3 compared with 13.3 in controls), the number of dead pups was increased (8.7 compared with 0.2 in controls), and the pup viability index was decreased (21.0% compared with 98.5% for controls). No pups in this group survived to lactation day (LD) 4. By LD 4, pup survival was decreased at doses of 25 ppm or higher; the mean numbers of live pups were 12.9, 9.0, and 6.3 in the control, the 25-ppm, and the 50-ppm groups, respectively. Additionally, pup body weight was decreased at doses of 25 ppm or more by LD 4; between birth and day 7 the pups had gained 8.2 and 1.2 grams in the control and the 25-ppm groups, respectively, and lost 1.4 grams in the 50-ppm groups. There were no compound-related findings for the other parameters examined including pup macroscopic examinations.

For production of the F_{1b} generation, parental animals were treated during a 2-week rest period through mating, gestation, and lactation. Pup survival per litter was decreased by LD 4 at doses of 15 ppm (7.9 surviving compared with 13.2 surviving in the controls) and by LD 14 at doses of 10 ppm or higher (6.9 and 5.0 surviving in the 10 and 15 ppm groups, respectively, compared with 7.9 surviving in controls). Although pup weights were comparable to controls at birth, weights were decreased at doses of 15 ppm by LD 4 through LD 21 ($\leq 53\%$) and at doses of 10 ppm by LD 7 through LD 21 ($\leq 13\%$). There were no compound-related findings for the other parameters examined, including pup macroscopic examinations.

4.4.4.2.2 Rats, 3-Generation

This study was conducted to evaluate the effects of moxidectin on the fertility and reproductive performance of rats through 3 generations.⁴³ Moxidectin was administered in the diet at concentrations of 0, 1, 2, 5, or 10 ppm (calculated dosages of 0.07, 0.15, 0.4, or 0.8 mg/kg/day). Each parental generation (P₁, F₁, and F₂) consisted of 25 males and

25 females per group mated to produce 2 litters. Parental generations were dosed from 70 days before mating (to produce the first litter) through sacrifice. Evaluations for compound-related effects were based on mortality, clinical observations, body weights, food consumption, mating indices, male fertility, pregnancy rates, gestation length, parturition data, litter size, litter survival, pup weight, pup survival, sex distribution, and macroscopic examination of parental generations and pups, and microscopic examination of the parental generations.

There were no findings that were considered biologically relevant or compound related. Statistically significant decreases in male parental (F_1 or F_2) body weights at doses of 10 ppm at various periods did not correspond to statistically significant decreased body-weight gains. Decreased pup survival (approximately $\leq 8\%$ relative to controls) occurred across several litters of the 10-ppm group, and occurred with similar incidence between LD 0 to LD 4 and LD 4 to LD 21.

As a result of the pup mortalities at doses of 10 ppm, the NTEL in this study was 5 ppm (0.4 mg/kg/day).

4.4.4.3 Assessment of Potential Risk to the Developing Human Fetus

The highest dose of moxidectin to be studied in phase 2 and possibly phase 3 clinical trials is a single, oral dose of 16 mg for a human weighing 50 kg, which is a dosage of 0.32 mg/kg or 10.9 mg/m² (based on body surface area).^a Moxidectin was well tolerated in healthy male subjects after oral administration (liquid formulation) of single doses as high as 36 mg (24.5 mg/m²).⁴⁴ The developmental NTEL in both the rat and rabbit studies was 5 mg/kg/day administered in 10 and 13 consecutive daily doses in rats and rabbits, respectively. The NTEL of 5 mg/kg is approximately 16 times the highest single dose (16 mg) to be administered to humans based on body weight, and approximately 3 times (rat) or 8 times (rabbit) the highest dose based on body surface area. In the female rat,

^a The following formula was used to convert mg/kg to mg/m² dosages: $\text{mg/m}^2 = km \times \text{mg/kg}$, where km is a species' typical body weight-to-surface area ratio. The body weights used were 0.15, 3.5, and 50 kg, and the km values were 5.9, 17.5, and 34 for rats, rabbits, and humans, respectively.

moxidectin has a $t_{1/2}$ of 45 hours (data not available for the rabbit).⁴⁵ Therefore, daily administration of moxidectin to pregnant rats, as was done in the developmental toxicity study of moxidectin, would likely result in accumulation of the drug in the body, further increasing exposure of the fetus to the drug. Based on the dose per unit of body weight, or dose based on body surface area, the intake by a woman of a single 16-mg dose of moxidectin would be unlikely to pose a risk to the developing human fetus.

Developmental risk can also be assessed based on actual exposure of the body to moxidectin, assuming placental transfer is similar in rats and humans. In a phase 1 clinical trial using the liquid formulation of moxidectin, a single oral dose to healthy males of 18 mg of moxidectin resulted in an AUC value of 227 ng•day/mL, which is equivalent to 9.55 ng•hr/mL.⁴⁴ In female rats, a single oral gavage dosage of 0.2 mg/kg of moxidectin resulted in an AUC value of 470 ng•hr/mL,⁴⁵ which is approximately 50 times the human AUC after a single dose of 18 mg of moxidectin. Assuming linear pharmacokinetics in rats, the developmental NTEL of 5 mg/kg would correspond to an AUC value of approximately 11,750 ng•hr/mL, which is more than 1200 times the human AUC after a single dose of 18 mg of moxidectin. Assuming similar bioavailability of the liquid and tablet formulations of moxidectin in humans (as demonstrated in study 3110A1-101-EU), and based on the above exposure considerations, the oral administration of 16 mg of moxidectin is unlikely to pose a risk to the developing human fetus.

In conclusion, based on the available data, the yearly oral intake of even 32 mg of moxidectin (or 16 mg every 6 months) by women is unlikely to pose a risk to the developing human fetus. The adverse fetal effects observed in the rat and rabbit development toxicity studies occurred only in the presence of maternal toxicity, which in itself can result in fetal alterations and delays of ossification. No such toxicity is anticipated after administration of moxidectin to women (highest dose to be evaluated in patients is a single yearly 8-mg dose). This conclusion is consistent with that of the Food and Drug Administration (FDA) Center for Veterinary Medicine, which concluded that moxidectin is neither a selective developmental toxicant nor a teratogen in rats or rabbits.

4.4.5 Genotoxicity Studies

4.4.5.1 In Vitro

In a bacterial reverse mutation assay, moxidectin was negative in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP-2 uvrA-) at concentrations up to 2000 µg/plate, both with and without exogenous metabolic activation system prepared from Aroclor™-1254-induced rat liver cells (S9).⁴⁶

In the mammalian cell (Chinese hamster ovary [CHO] cell) test for mutagenicity at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus, positive results were observed in 1 replicate of the vehicle control in the absence of S9 and at a very low concentration of moxidectin (0.1 µg/mL) in the presence of S9 in the second trial.⁴⁷ Therefore, the assay was considered invalid and a mouse lymphoma assay was conducted.

In the mouse lymphoma (L5178Y thymidine kinase [TK^{+/+}]) assay, moxidectin was negative at the highest concentrations evaluated (25 µg/mL in the absence of S9 and 115 µg/mL in the presence of S9).⁴⁸

In the chromosome aberration assay in CHO cells, moxidectin did not induce statistically significant increases in the percentage of cells with aberrations at any of the concentrations evaluated (up to 10 µg/mL in the absence of S9 and up to 20 µg/mL in the presence of S9).⁴⁹

In the unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, moxidectin was negative at concentrations up to 5 µg/mL (higher concentrations of 10, 20, and 30 µg/mL were not analyzed for UDS due to excessive toxicity).⁵⁰

4.4.5.2 In Vivo

In the in vivo micronucleated polychromatic erythrocyte (PCE) assay in mouse bone marrow cells, moxidectin was administered as a single oral gavage dosage of 7.5, 15, or 30 mg/kg (5 mice/sex/group).⁵¹ Bone marrow was collected at 24, 48, and 72 hours after dose administration. There was no statistically significant increase in the number of micronucleated PCEs at any dosage at any harvest time.

In the in vivo chromosome aberration assay in rat bone marrow, moxidectin was administered as a single oral gavage dosage of 15, 30, or 60 mg/kg.⁵² Bone marrow cells were collected from 5 rats/sex/group/time point at 12, 24, and 48 hours after dose administration. Moxidectin did not induce chromosome aberrations in male or female rats at any dosage at any harvest time.

4.5 Conclusions

Following oral administration in rats, moxidectin was absorbed at a moderate rate, with a mean t_{max} of 4.8 hours. The bioavailability of moxidectin was moderate at 19% and the $t_{1/2}$ was long (22.9 to 44.6 hours). Following IV administration in rats, the clearance of moxidectin was low and the Vd_{ss} was high, indicating the compound is widely distributed to tissues.

In rats, the major site of distribution of moxidectin was fat. The $t_{1/2}$ in fat was 11.5 days. Moxidectin represented the major component of total radioactivity in tissues and feces, and was largely eliminated through feces (60% to 91% of the recovered dose over 7 days).

There were no differences between rat and human liver microsomes in the metabolites detected. Four (4) moxidectin-related peaks were detected in the presence of cofactors and were characterized by LC/MS/MS as apparent hydroxylations at the C-4-methyl, C6-C19, C-28-methyl, and C-14 methyl positions.

In human liver microsomes, there was no inhibition of CYP2A6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4 activity at the highest substrate concentration used (100 μ M) and weak inhibition of CYP1A2 and CYP2C9 activity (extrapolated IC_{50} values of 459 and 145 μ M, respectively). Based on plasma concentrations in humans and these IC_{50} values, clinical metabolic drug-drug interactions for all the CYPs tested are unlikely to occur.

In single-dose toxicity studies of mice and rats that received moxidectin by oral gavage, the LD_{50} values were 118 mg/kg in male mice, 42 to 78 mg/kg in female mice, and 122 and 97 mg/kg in male and female rats, respectively.

Repeat-dose toxicity was evaluated in oral (diet) studies of mice (4 weeks), rats (4 and 13 weeks), and dogs (4 and 13 weeks and 1 year) and in oral (diet) carcinogenicity studies of mice and rats (2 years). Results of the repeat-dose studies indicate that moxidectin was well tolerated with no toxicologic effects at calculated dosages of up to 6.9 mg/kg/day in mice for 4 weeks, 3.9 mg/kg/day in rats for 13 weeks, or 1.1 mg/kg/day in dogs for 1 year.

Moxidectin was not carcinogenic in mice or rats.

Reproductive toxicity was evaluated in developmental oral gavage studies of rats and rabbits and in pilot and definitive multigeneration diet studies. Maternal toxicity was evident at doses of 10 mg/kg/day or more in the rat developmental study, at doses of 125 ppm (calculated dosage averaging between 10.9 and 12.0 mg/kg/day) in the rat pilot multigeneration study, and at doses of 5 mg/kg/day or more in the rabbit developmental study; the toxicity consisted primarily of decreased body weight and/or food consumption. At maternally toxic dosages (≥ 10 mg/kg/day) in the rat developmental study only, there were statistically significant increases in the number of fetuses with malformations and/or variations, largely reflective of increases in cleft palate and reversible delays in ossification. Although there were no fetal alterations in the other 3 studies, there was decreased fetal and/or pup survival at doses of 10 mg/kg/day in the rabbit developmental study and at doses of 10 ppm or more (calculated maternal dosage of ≥ 0.8 mg/kg/day) in the rat pilot 1-generation and 3-generation studies. The reproductive NTEs in both the rat and rabbit developmental studies were 5 mg/kg/day and in the rat 3-generation study was 5 ppm (0.4 mg/kg/day).

Moxidectin was not genotoxic in a battery of in vitro and in vivo assays. In conclusion, the results of nonclinical studies support clinical trials for the oral administration of moxidectin in the treatment of onchocerciasis.

5. EFFECTS IN HUMANS

5.1 Introduction

Moxidectin is currently approved for use as a veterinary product and is registered worldwide for the prevention of canine heartworm (ProHeart) and for the treatment of internal and

external parasites in cattle, sheep, and horses (Cydectin). Moxidectin in a tablet formulation for oral administration is being developed for use in humans in the treatment of onchocerciasis. Preclinical studies have shown that orally administered moxidectin may be a useful treatment for onchocerciasis. As shown in Appendix 4 (Table A4-1), moxidectin has been given as an orally administered liquid to healthy male subjects in a phase 1 study (protocol 3110A1-100-EU) and as an orally administered liquid and tablet in a bioavailability study (protocol 3110A1-101-EU).

5.2 Pharmacokinetics and Product Metabolism in Humans

5.2.1 Clinical Pharmacokinetics

5.2.1.1 Single-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study

Based on pharmacokinetic data from the FIM study (protocol 3110A1-100-EU) for all dose groups, a mean $t_{1/2}$ of 20.2 to 35.1 days was seen in these subjects across all doses. Dose-proportional increases in the pharmacokinetic parameters such as AUC and C_{max} were observed in the studied dose range. The mean AUC was significantly higher for the fed group (fed a high-fat breakfast) compared with the fasting group within the same dose (9-mg dose, $p = 0.037$; 36-mg dose, $p = 0.029$); however, there was no significant food effect displayed for C_{max} . Pharmacokinetic parameters are shown in Table 5.2.1.1A.

TABLE 5.2.1.1A. PHARMACOKINETIC PARAMETERS (MEAN $\pm$ SEM) FOR THE MOXIDECTIN
FIRST-IN-MAN STUDY (STUDY 3110A1-100-EU)

**REDACTED COMMERCIALY
SENSITIVE PROPRIETARY DATA**

5.3 Potential Indications

Both its microfilaricidal and macrofilaricidal potency against *O. volvulus* and its possible longer duration of activity because of its lipophilicity make moxidectin a potentially useful agent in the control of onchocerciasis. Decisions on the dosage and treatment regimen of this drug will be made based on the safety, tolerability, and efficacy demonstrated in initial studies using moxidectin.

5.4 Efficacy

The activity of moxidectin has been evaluated against *Onchocerca* species and *B. pahangi* in both large and small animals. There have been no studies on the efficacy of moxidectin in human patients with onchocerciasis.

5.5 Safety

5.5.1 Single-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study

The FIM study (protocol 3110A1-100-EU) was conducted with healthy male subjects. Thirty-eight (38) subjects were randomly assigned to 1 of 6 sequential cohorts, with 37 subjects receiving study drug. The lowest dose of moxidectin administered in this study was 3 mg and the highest dose was 36 mg. All subjects in this study were men 18 to 45 years of age.

Unblinded safety and AE data suggested that the frequency and severity of dizziness and somnolence/lethargy (indicative of the pharmacologic action of moxidectin) may have increased in the higher dose groups (ie, the 18-mg and 36-mg groups). Changes in subject liver function test results were small and were not clinically apparent, but were considered to be drug related by the investigator. The changes were transient, resolved without sequelae, and did not appear to be dose related. Additionally, the preliminary pharmacokinetic profile of moxidectin indicated that absorption of the doses tested was in the anticipated therapeutic range of the drug. (The expected therapeutic dose range of moxidectin is 3 to 9 mg, based on comparison of the preliminary pharmacokinetic profile of moxidectin with C_{max} values of patients using the approved dose of ivermectin). These findings supported the conclusion to

discontinue dose administration in this study after the 36-mg cohort. Thus, subjects were never enrolled in the last cohort (54 mg, cohort 7).

5.5.1.1 Adverse Events

The clinical portion of the FIM study of moxidectin (study 3110A1-100-EU) was completed as of 20 Jan 2002. The total number and percentage of subjects reporting AEs after study drug administration are shown Table [5.5.1.1.A](#).

TABLE 5.5.1.1.A. NUMBER (%) OF SUBJECTS REPORTING ADVERSE EVENTS BY BODY SYSTEM IN STUDY 3110A1-100-EU

Body System Adverse Event ^a	Placebo (n = 6)	3-mg Fasting (n = 5)	9-mg Fasting (n = 5)	9-mg Fed (n = 6)	18-mg Fasting (n = 5)	36-mg Fasting (n = 5)	36-mg Fed (n = 5)	All Moxidectin (n = 31)	All Subjects (n = 37)
Any adverse event	5 (83)	4 (80)	5 (100)	4 (67)	4 (80)	4 (80)	5 (100)	26 (84)	31 (84)
Body as a Whole	4 (67)	4 (80)	3 (60)	4 (67)	2 (40)	3 (60)	2 (40)	18 (58)	22 (59)
Headache	2 (33)	3 (60)	2 (40)	2 (33)	2 (40)	1 (20)	1 (20)	11 (35)	13 (35)
Infection	1 (17)	2 (40)	1 (20)	2 (33)	0	3 (60)	1 (20)	9 (29)	10 (27)
Accidental									
Injury	1 (17)	0	1 (20)	0	0	1 (20)	0	2 (6)	3 (8)
Pain	0	0	1 (20)	1 (17)	1 (20)	0	0	3 (10)	3 (8)
Abdominal pain	0	0	1 (20)	0	0	0	1 (20)	2 (6)	2 (5)
Back pain	1 (17)	0	0	0	0	0	0	0	1 (3)
Chest pain	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Chills	1 (17)	0	0	0	0	0	0	0	1 (3)
Edema	1 (17)	0	0	0	0	0	0	0	1 (3)
Flu syndrome	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)
Cardiovascular System	1 (17)	0	0	0	0	0	2 (40)	2 (6)	3 (8)
Hematoma	1 (17)	0	0	0	0	0	0	0	1 (3)
Hypertension	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Vasodilatation	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Digestive System	0	3 (60)	0	0	1 (20)	2 (40)	3 (60)	9 (29)	9 (24)
Diarrhea	0	2 (40)	0	0	0	0	0	2 (6)	2 (5)
Gamma glutamyl transpeptidase increased	0	1 (20)	0	0	0	0	1 (20)	2 (6)	2 (5)
Nausea	0	0	0	0	0	1 (20)	1 (20)	2 (6)	2 (5)
Vomiting	0	0	0	0	0	1 (20)	1 (20)	2 (6)	2 (5)
Anorexia	0	0	0	0	0	1 (20)	0	1 (3)	1 (3)
Dyspepsia	0	0	0	0	1 (20)	0	0	1 (3)	1 (3)

TABLE 5.5.1.1.A. NUMBER (%) OF SUBJECTS REPORTING ADVERSE EVENTS BY BODY SYSTEM IN STUDY 3110A1-100-EU

Body System Adverse Event^a	Placebo (n = 6)	3-mg Fasting (n = 5)	9-mg Fasting (n = 5)	9-mg Fed (n = 6)	18-mg Fasting (n = 5)	36-mg Fasting (n = 5)	36-mg Fed (n = 5)	All Moxidectin (n = 31)	All Subjects (n = 37)
Enteritis	0	0	0	0	0	1 (20)	0	1 (3)	1 (3)
Mouth ulceration	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Tooth disorder	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)
Hemic and Lymphatic System	0	3 (60)	0	1 (17)	0	0	4 (80)	8 (26)	8 (22)
Leukopenia	0	1 (20)	0	0	0	0	3 (60)	4 (13)	4 (11)
Leukocytosis	0	1 (20)	0	0	0	0	1 (20)	2 (6)	2 (5)
Ecchymosis	0	0	0	1 (17)	0	0	0	1 (3)	1 (3)
Eosinophilia	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Monocytosis	0	0	0	0	0	0	1 (20)	1 (3)	1 (3)
Thrombocytopenia	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)
Metabolic and Nutritional	1 (17)	2 (40)	1 (20)	0	0	1 (20)	0	4 (13)	5 (14)
ALT increased	0	2 (40)	0	0	0	1 (20)	0	3 (10)	3 (8)
AST increased	1 (17)	1 (20)	1 (20)	0	0	1 (20)	0	3 (10)	4 (11)
Lactate dehydrogenase	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)
Musculoskeletal System	1 (17)	0	0	1 (17)	1 (20)	0	0	2 (6)	3 (8)
Arthralgia	0	0	0	1 (17)	0	0	0	1 (3)	1 (3)
Myalgia	0	0	0	0	1 (20)	0	0	1 (3)	1 (3)
Twitching	1 (17)	0	0	0	0	0	0	0	1 (3)
Nervous System	1 (17)	1 (20)	1 (20)	1 (17)	1 (20)	2 (40)	2 (40)	8 (26)	9 (24)
Dizziness	0	0	1 (20)	1 (17)	0	1 (20)	1 (20)	4 (13)	4 (11)
Somnolence	1 (17)	0	0	0	1 (20)	1 (20)	1 (20)	3 (10)	4 (11)
Hypesthesia	0	0	1 (20)	0	0	0	0	1 (3)	1 (3)
Nervousness	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)

TABLE 5.5.1.1.A. NUMBER (%) OF SUBJECTS REPORTING ADVERSE EVENTS BY BODY SYSTEM IN STUDY 3110A1-100-EU

Body System Adverse Event ^a	Placebo (n = 6)	3-mg Fasting (n = 5)	9-mg Fasting (n = 5)	9-mg Fed (n = 6)	18-mg Fasting (n = 5)	36-mg Fasting (n = 5)	36-mg Fed (n = 5)	All Moxidectin (n = 31)	All Subjects (n = 37)
Respiratory System	2 (33)	0	2 (40)	2 (33)	3 (60)	2 (40)	1 (20)	10 (32)	12 (32)
Pharyngitis	1 (17)	0	1 (20)	0	3 (60)	0	1 (20)	5 (16)	6 (16)
Rhinitis	2 (33)	0	1 (20)	1 (17)	1 (20)	0	0	3 (10)	5 (14)
Cough increased	0	0	0	1 (17)	0	2 (40)	0	3 (10)	3 (8)
Voice alteration	0	0	0	0	1 (20)	0	0	1 (3)	1 (3)
Skin and Appendages	1 (17)	0	1 (20)	0	0	0	0	1 (3)	2 (5)
Pruritus	1 (17)	0	1 (20)	0	0	0	0	1 (3)	2 (5)
Maculopapular rash	0	0	1 (20)	0	0	0	0	1 (3)	1 (3)
Rash	0	0	1 (20)	0	0	0	0	1 (3)	1 (3)
Special Senses	1 (17)	1 (20)	0	0	0	0	1 (20)	2 (6)	3 (8)
Amblyopia	0	1 (20)	0	0	0	0	1 (20)	2 (6)	2 (5)
Conjunctivitis	0	1 (20)	0	0	0	0	0	1 (3)	1 (3)
Ear pain	1 (17)	0	0	0	0	0	0	0	1 (3)
Urogenital System	0	0	1 (20)	0	1 (20)	1 (20)	0	3 (10)	3 (8)
Pyuria	0	0	1 (20)	0	0	1 (20)	0	2 (6)	2 (5)
Urinary frequency	0	0	0	0	1 (20)	0	0	1 (3)	1 (3)

a: This table excludes all adverse events that occurred before dose administration.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Only 1 AE higher than grade 2 (moderate toxicity) was reported (enteritis resulting from food poisoning [grade 3; severe toxicity] in the 36-mg fasting group) and was considered to be unrelated to study drug.

The most commonly reported AEs (by $\geq 10\%$ of subjects) in moxidectin-treated subjects, regardless of causality, were headache (35%) and infection (29%). The majority (7 of 9) of moxidectin-treated subjects reporting infection had colds or upper respiratory tract infections. Of the remaining 2 subjects, 1 had a right big toe infection and 1 had a tooth abscess. Only half of the headaches reported and none of the infections reported were regarded as study drug related. The subjects who reported infections, including dose group, infection type, and days after moxidectin administration are shown in Table 5.5.1.1B.

TABLE 5.5.1.1B. SUBJECTS REPORTING INFECTIONS
AFTER TREATMENT WITH MOXIDECTIN IN STUDY 3110A1-100-EU

Dose Group Subject Number	Age (y)	Study Day Relative to Dose	Adverse Event (Verbatim Term)	Drug Relationship
3 mg fasting				
1209-101	25	19	URTI	Not related
1209-101	25	63	URTI	Not related
1209-106	36	14	Viral URTI	Not related
9 mg fasting				
1209-203	40	52	Right toe infected	Not related
9 mg fed				
1209-303	23	78	URTI	Not related
1209-305	27	30	Mild URTI	Not related
36 mg fasting				
1209-504	31	47	Tooth abscess	Not related
1209-501	20	66	Head cold	Not related
1209-506	36	50	Head cold	Not related
36 mg fed				
1209-605	25	42	Cold	Not related
1209-605	25	59	Cold-like symptoms	Not related

Abbreviation: URTI = upper respiratory tract infection.

No serious AEs were reported in this study. Four (4) subjects withdrew from the study (1 before receiving study drug and 3 after receiving study drug; 1 each in the 3-mg fasting,

9-mg fed, and 36-mg fasting groups). The withdrawal of these subjects from the study was unrelated to AEs. These data suggest that moxidectin as administered in this study is safe and well tolerated.

5.5.1.2 Laboratory Test Results

Changes in subject liver function test results were small and not clinically apparent, but were considered to be drug related by the investigator. The changes were transient, resolved without sequelae, and did not appear to be dose related.

5.5.2 Relative Bioavailability of a Tablet and Liquid Formulation of Moxidectin in Healthy Subjects

A further study (protocol 3110A1-101-EU) compared the relative bioavailability of tablet and liquid formulations of moxidectin at the 10-mg dose strength. This was an open-label, randomized, single-dose, parallel-design study conducted in 58 young healthy male subjects. A parallel design was chosen because of the long $t_{1/2}$ of moxidectin (20 to 30 days in humans) and the consequent low probability of a sufficient number of subjects returning for all follow-up examinations in a crossover trial, which would have had a duration of approximately 300 days.

Each subject received 1 orally administered dose of moxidectin, either as five 2-mg tablets or as a 10-mg liquid. In both cases moxidectin was administered under fasting conditions. All subjects participated in the study for approximately 7 months. Participation included a screening evaluation within 3 weeks before test article administration, a 3-day inpatient period and a 180-day follow-up period. The mean age of the subjects (32 years, range 20 to 45 years) and weight (81 kg, range 57 kg to 107 kg) were similar for those receiving the tablet formulation (n = 29) and those receiving the liquid formulation (n = 29).

5.5.2.1 Adverse Events

A total of 36 of 58 (62.1%) subjects had TEAEs during the study, with the same number and percentage of subjects (18; 62.1% in each group) reporting TEAEs in both the moxidectin liquid and tablet groups. The most commonly reported TEAEs (by $\geq 5\%$ of subjects) were

flu syndrome (reported by 17.2% and 20.7% of subjects in the liquid and tablet groups, respectively), headache (reported by 17.2% and 13.8% of subjects in the liquid and tablet groups, respectively), infection (reported by 13.8% and 6.9% of subjects in the liquid and tablet groups, respectively), diarrhea (reported by 10.3% of subjects in the liquid group), myalgia (reported by 6.9% of subjects in the tablet group), and dizziness (reported by 6.9% of subjects in the tablet group).

A total of 19 of 58 subjects (32.8%) reported TEAEs within the first week after administration of study drug (on or before day 7). During this period, TEAEs were reported by 10 of 29 subjects (34.5%) in the group receiving moxidectin liquid and by 9 of 29 subjects (31.0%) in the group receiving moxidectin tablets. The most commonly reported TEAEs (by $\geq 5\%$ of subjects) during this period were asthenia (10.3% in the tablet group), headache (13.8% and 6.9% in the liquid and tablet groups, respectively), infection (6.9% in the liquid group), diarrhea (6.9% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group).

A total of 22 of 58 subjects (37.9%) reported TEAEs during the outpatient period of the study (after study day 7 and up to study day 180); 10 of 29 subjects (34.5%) were in the liquid group and 12 of 29 (41.4%) were in the tablet group. The most commonly reported events (by $\geq 5\%$ of subjects) were flu syndrome (17.2% and 20.7% in liquid and tablet groups, respectively), headache (6.9% in the tablet group), and infection (6.9% in the tablet group).

The total number and percentage of subjects for whom TEAEs were reported during the study are shown by treatment group in [Table 5.5.1.1A](#). The number and percentage of subjects with TEAEs within the first week after dose administration and during the outpatient period are summarized by treatment in [Table 5.5.2.1B](#) and [Table 5.5.2.1C](#), respectively.

TABLE 5.5.2.1A. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT
ADVERSE EVENTS IN STUDY 3110A1-101-EU

Body System ^a Adverse Event	-----Moxidectin 10 mg-----		Total (n = 58)
	Liquid (n = 29)	Tablet (n = 29)	
Any adverse event, n (%)	18 (62.1)	18 (62.1)	36 (62.1)
Body as a Whole	12 (41.4)	13 (44.8)	25 (43.1)
Abdominal pain	0	1 (3.4)	1 (1.7)
Asthenia	1 (3.4)	3 (10.3)	4 (6.9)
Chest pain	1 (3.4)	1 (3.4)	2 (3.4)
Fever	1 (3.4)	0	1 (1.7)
Flu syndrome	5 (17.2)	6 (20.7)	11 (19.0)
Headache	5 (17.2)	4 (13.8)	9 (15.5)
Infection	4 (13.8)	2 (6.9)	6 (10.3)
Injection site edema	0	1 (3.4)	1 (1.7)
Injection site pain	1 (3.4)	0	1 (1.7)
Malaise	0	1 (3.4)	1 (1.7)
Pain	1 (3.4)	1 (3.4)	2 (3.4)
Digestive System	4 (13.8)	3 (10.3)	7 (12.1)
Diarrhea	3 (10.3)	1 (3.4)	4 (6.9)
Flatulence	0	1 (3.4)	1 (1.7)
Gingivitis	0	1 (3.4)	1 (1.7)
Nausea	1 (3.4)	0	1 (1.7)
Vomiting	0	1 (3.4)	1 (1.7)
Musculoskeletal System	0	3 (10.3)	3 (5.2)
Arthralgia	0	1 (3.4)	1 (1.7)
Myalgia	0	2 (6.9)	2 (3.4)
Nervous System	0	3 (10.3)	3 (5.2)
Dizziness	0	2 (6.9)	2 (3.4)
Hypesthesia	0	1 (3.4)	1 (1.7)
Sleep disorder	0	1 (3.4)	1 (1.7)
Respiratory System	1 (3.4)	2 (6.9)	3 (5.2)
Epistaxis	0	1 (3.4)	1 (1.7)
Pharyngitis	0	1 (3.4)	1 (1.7)
Rhinitis	1 (3.4)	0	1 (1.7)
Skin and Appendages	0	2 (6.9)	2 (3.4)
Acne	0	1 (3.4)	1 (1.7)
Sweating	0	1 (3.4)	1 (1.7)

**TABLE 5.5.2.1A. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT
 ADVERSE EVENTS IN STUDY 3110A1-101-EU**

Body System^a	Moxidectin 10 mg		Total (n = 58)
	Liquid (n = 29)	Tablet (n = 29)	
Adverse Event			
Special Senses	2 (6.9)	1 (3.4)	3 (5.2)
Conjunctival injection	1 (3.4)	0	1 (1.7)
Eye pain	1 (3.4)	1 (3.4)	2 (3.4)
Tinnitus	1 (3.4)	0	1 (1.7)
Urogenital System	1 (3.4)	0	1 (1.7)
Urinary urgency	1 (3.4)	0	1 (1.7)
Adverse Event Assoc.W. Misc. Factors	1 (3.4)	0	1 (1.7)
Allergic reaction other than drug	1 (3.4)	0	1 (1.7)

a: Body system totals are not necessarily the sum of the individual adverse events because a subject may have had 2 or more different adverse events affecting the same body system.

TABLE 5.5.2.1B. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS THAT STARTED ON OR BEFORE DAY 7 IN STUDY 31101A-101-EU

Body System*	-----Moxidectin 10 mg-----		Total (n = 58)
	Liquid (n = 29)	Tablet (n = 29)	
Any adverse event, n (%)	10 (34.5)	9 (31.0)	19 (32.8)
Body as a Whole	6 (20.7)	6 (20.7)	12 (20.7)
Abdominal pain	0	1 (3.4)	1 (1.7)
Asthenia	0	3 (10.3)	3 (5.2)
Chest pain	1 (3.4)	1 (3.4)	2 (3.4)
Fever	1 (3.4)	0	1 (1.7)
Headache	4 (13.8)	2 (6.9)	6 (10.3)
Infection	2 (6.9)	0	2 (3.4)
Injection site edema	0	1 (3.4)	1 (1.7)
Injection site pain	1 (3.4)	0	1 (1.7)
Malaise	0	1 (3.4)	1 (1.7)
Pain	1 (3.4)	0	1 (1.7)
Digestive System	3 (10.3)	1 (3.4)	4 (6.9)
Diarrhea	2 (6.9)	0	2 (3.4)
Flatulence	0	1 (3.4)	1 (1.7)
Nausea	1 (3.4)	0	1 (1.7)
Musculoskeletal System	0	2 (6.9)	2 (3.4)
Myalgia	0	2 (6.9)	2 (3.4)
Nervous System	0	2 (6.9)	2 (3.4)
Dizziness	0	2 (6.9)	2 (3.4)
Hypesthesia	0	1 (3.4)	1 (1.7)
Respiratory System	1 (3.4)	0	1 (1.7)
Rhinitis	1 (3.4)	0	1 (1.7)
Skin and Appendages	0	1 (3.4)	1 (1.7)
Acne	0	1 (3.4)	1 (1.7)
Special Senses	1 (3.4)	1 (3.4)	2 (3.4)
Conjunctival injection	1 (3.4)	0	1 (1.7)
Eye pain	1 (3.4)	1 (3.4)	2 (3.4)
Urogenital System	1 (3.4)	0	1 (1.7)
Urinary urgency	1 (3.4)	0	1 (1.7)

a: Body system totals are not necessarily the sum of the individual adverse events because a subject may have had 2 or more different adverse events affecting the same body system.

TABLE 5.5.2.1C. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS THAT STARTED AFTER DAY 7 AND UP TO DAY 180 IN STUDY 3110A1-101-EU

Body System^a Adverse Event	-----Moxidectin 10 mg-----		Total (n = 58)
	Liquid (n = 29)	Tablet (n = 29)	
Any adverse event, n (%)	10 (34.5)	12 (41.4)	22 (37.9)
Body as a Whole	7 (24.1)	10 (34.5)	17 (29.3)
Abdominal pain	0	1 (3.4)	1 (1.7)
Asthenia	1 (3.4)	0	1 (1.7)
Flu syndrome	5 (17.2)	6 (20.7)	11 (19.0)
Headache	1 (3.4)	2 (6.9)	3 (5.2)
Infection	2 (6.9)	2 (6.9)	4 (6.9)
Pain	0	1 (3.4)	1 (1.7)
Digestive System	1 (3.4)	2 (6.9)	3 (5.2)
Diarrhea	1 (3.4)	1 (3.4)	2 (3.4)
Gingivitis	0	1 (3.4)	1 (1.7)
Vomiting	0	1 (3.4)	1 (1.7)
Musculoskeletal System	0	1 (3.4)	1 (1.7)
Arthralgia	0	1 (3.4)	1 (1.7)
Nervous System	0	1 (3.4)	1 (1.7)
Sleep disorder	0	1 (3.4)	1 (1.7)
Respiratory System	0	2 (6.9)	2 (3.4)
Epistaxis	0	1 (3.4)	1 (1.7)
Pharyngitis	0	1 (3.4)	1 (1.7)
Skin and Appendages	0	1 (3.4)	1 (1.7)
Sweating	0	1 (3.4)	1 (1.7)
Special Senses	1 (3.4)	0	1 (1.7)
Tinnitus	1 (3.4)	0	1 (1.7)
Adverse Event Assoc.W.Misc. Factors	1 (3.4)	0	1 (1.7)
Allergic reaction other than drug	1 (3.4)	0	1 (1.7)

a: Body system totals are not necessarily the sum of the individual adverse events because a subject may have had 2 or more different adverse events affecting the same body system.

All TEAEs that were reported during the study were considered to be mild to moderate in intensity; none were severe or life threatening and none were considered to be related to treatment. A total of 15 of 58 (25.9%) subjects had TEAEs that were considered moderate in severity. The most commonly reported TEAEs (by $\geq 5\%$ of subjects) considered to be moderate in severity were flu syndrome (reported by 4 of 29 subjects [13.8%] in the liquid group and by 3 of 29 subjects [10.3%] in the tablet group) headache (reported by 2 of 29 subjects [6.9%] in both the liquid group and tablet groups), and diarrhea (reported by 2 of 29 subjects [6.9%] in the liquid group). There were no serious AEs and no subject discontinued the study as the result of an AE. The number and percentage of subjects with TEAEs are summarized by severity in Table 5.5.2.1D.

TABLE 5.5.2.1D. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT ADVERSE EVENTS BY SEVERITY IN STUDY 3110A1-101-EU

Body System^a	Moxidectin 10 mg		
Adverse event	Liquid	Tablet	Total
Severity	(n = 29)	(n = 29)	(n = 58)
Any Adverse Event, n (%)	18 (62.1)	18 (62.1)	36 (62.1)
Mild	9 (31.0)	12 (41.4)	21 (36.2)
Moderate	9 (31.0)	6 (20.7)	15 (25.9)
Body as a Whole	12 (41.4)	13 (44.8)	25 (43.1)
Mild	6 (20.7)	7 (24.1)	13 (22.4)
Moderate	6 (20.7)	6 (20.7)	12 (20.7)
Abdominal pain	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Asthenia	1 (3.4)	3 (10.3)	4 (6.9)
Mild	1 (3.4)	3 (10.3)	4 (6.9)
Chest pain	1 (3.4)	1 (3.4)	2 (3.4)
Mild	1 (3.4)	1 (3.4)	2 (3.4)
Fever	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Flu syndrome	5 (17.2)	6 (20.7)	11 (19.0)
Mild	1 (3.4)	3 (10.3)	4 (6.9)
Moderate	4 (13.8)	3 (10.3)	7 (12.1)
Headache	5 (17.2)	4 (13.8)	9 (15.5)
Mild	3 (10.3)	2 (6.9)	5 (8.6)
Moderate	2 (6.9)	2 (6.9)	4 (6.9)
Infection	4 (13.8)	2 (6.9)	6 (10.3)
Mild	3 (10.3)	1 (3.4)	4 (6.9)
Moderate	1 (3.4)	1 (3.4)	2 (3.4)
Injection site edema	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)

**TABLE 5.5.2.1D. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT
ADVERSE EVENTS BY SEVERITY IN STUDY 3110A1-101-EU**

Body System^a	Moxidectin 10 mg		
Adverse event	Liquid	Tablet	Total
Severity	(n = 29)	(n = 29)	(n = 58)
Injection site pain	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Malaise	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Pain	1 (3.4)	1 (3.4)	2 (3.4)
Moderate	1 (3.4)	1 (3.4)	2 (3.4)
Digestive System	4 (13.8)	3 (10.3)	7 (12.1)
Mild	2 (6.9)	3 (10.3)	5 (8.6)
Moderate	2 (6.9)	0	2 (3.4)
Diarrhea	3 (10.3)	1 (3.4)	4 (6.9)
Mild	1 (3.4)	1 (3.4)	2 (3.4)
Moderate	2 (6.9)	0	2 (3.4)
Flatulence	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Gingivitis	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Nausea	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Vomiting	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Musculoskeletal System	0	3 (10.3)	3 (5.2)
Mild	0	2 (6.9)	2 (3.4)
Moderate	0	1 (3.4)	1 (1.7)
Arthralgia	0	1 (3.4)	1 (1.7)
Moderate	0	1 (3.4)	1 (1.7)
Myalgia	0	2 (6.9)	2 (3.4)
Mild	0	2 (6.9)	2 (3.4)
Nervous System	0	3 (10.3)	3 (5.2)
Mild	0	3 (10.3)	3 (5.2)
Dizziness	0	2 (6.9)	2 (3.4)
Mild	0	2 (6.9)	2 (3.4)
Hypesthesia	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Sleep disorder	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Respiratory System	1 (3.4)	2 (6.9)	3 (5.2)
Mild	1 (3.4)	2 (6.9)	3 (5.2)
Epistaxis	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)

**TABLE 5.5.2.1D. NUMBER (%) OF SUBJECTS WITH TREATMENT-EMERGENT
ADVERSE EVENTS BY SEVERITY IN STUDY 3110A1-101-EU**

Body System^a	Moxidectin 10 mg		
Adverse event	Liquid	Tablet	Total
Severity	(n = 29)	(n = 29)	(n = 58)
Pharyngitis	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Rhinitis	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Skin and Appendage	0	2 (6.9)	2 (3.4)
Mild	0	2 (6.9)	2 (3.4)
Acne	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Sweating	0	1 (3.4)	1 (1.7)
Mild	0	1 (3.4)	1 (1.7)
Special Senses	2 (6.9)	1 (3.4)	3 (5.2)
Mild	1 (3.4)	1 (3.4)	2 (3.4)
Moderate	1 (3.4)	0	1 (1.7)
Conjunctival injection	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Eye pain	1 (3.4)	1 (3.4)	2 (3.4)
Mild	1 (3.4)	1 (3.4)	2 (3.4)
Tinnitus	1 (3.4)	0	1 (1.7)
Moderate	1 (3.4)	0	1 (1.7)
Urogenital System	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Urinary urgency	1 (3.4)	0	1 (1.7)
Mild	1 (3.4)	0	1 (1.7)
Adverse Event Assoc W Misc Factors	1 (3.4)	0	1 (1.7)
Moderate	1 (3.4)	0	1 (1.7)
Allergic reaction other than drug	1 (3.4)	0	1 (1.7)
Moderate	1 (3.4)	0	1 (1.7)

a: Body system totals are not necessarily the sum of the individual adverse events because a subject may have had 2 or more different adverse events affecting the same body system.

5.5.2.2 Laboratory Test Results

No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory tests during this study.

5.5.3 Drug Interactions

The effects of administering moxidectin concomitantly with other drugs have not been studied. Therefore, caution should be used if moxidectin is given with any other medication.

5.6 Marketing Experience

Moxidectin is not currently marketed for human use in any country.

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

After oral administration in rats, moxidectin was absorbed at a moderate rate, with a mean t_{max} of 4.8 hours. The bioavailability of moxidectin was moderate at 19% and the $t_{1/2}$ was long (22.9 to 44.6 hours). After IV administration in rats, the clearance of moxidectin was low and Vd_{ss} was high, indicating that the compound is widely distributed to tissues.

In rats, the major site of distribution of moxidectin was fat. The $t_{1/2}$ in fat was 11.5 days. Moxidectin represented the major component of total radioactivity in tissues and feces, and was largely eliminated through feces (60% to 91% of the recovered dose over 7 days).

There were no differences between rat and human liver microsomes in the metabolites detected. Four (4) moxidectin-related peaks were detected in the presence of cofactors and were characterized by LC/MS/MS as apparent hydroxylations at the C-4-methyl, C6-C19, C-28-methyl, and C-14 methyl positions.

In human liver microsomes, there was no inhibition of CYP2A6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4 activity at the highest substrate concentration used (100 μ M) and weak inhibition of CYP1A2 and CYP2C9 activity (extrapolated IC_{50} values of 459 and 145 μ M, respectively). Based on plasma concentrations in humans and these IC_{50} values, clinical metabolic drug-drug interactions for all the CYPs tested are unlikely to occur.

In single-dose toxicity studies in mice and rats given moxidectin by oral gavage, the LD_{50} values were 118 mg/kg in male mice, 42 to 78 mg/kg in female mice, and 122 and 97 mg/kg in male and female rats, respectively.

Repeat-dose toxicity was evaluated in oral (diet) studies with mice (4 weeks), rats (4 and 13 weeks), and dogs (4 and 13 weeks and 1 year) and in oral (diet) carcinogenicity studies with mice and rats (2 years). Results of the repeat-dose studies indicate that moxidectin was well tolerated with no toxicologic effects at calculated dosages of up to 6.9 mg/kg/day in mice for 4 weeks, 3.9 mg/kg/day in rats for 13 weeks, or 1.1 mg/kg/day in dogs for 1 year. Moxidectin was not carcinogenic in mice or rats.

Reproductive toxicity was evaluated in developmental oral gavage studies with rats and rabbits and in pilot and definitive multigeneration diet studies. Maternal toxicity was evident at doses of 10 mg/kg/day or more in the rat developmental study, at doses of 125 ppm (calculated dosage averaging between 10.9 and 12.0 mg/kg/day) in the rat pilot multigeneration study, and at doses of 5 mg/kg/day or more in the rabbit developmental study; toxicity consisted primarily of decreased body weight and/or food consumption. At maternally toxic dosages (≥ 10 mg/kg/day) in the rat developmental study only, there were statistically significant increases in the number of fetuses with malformations and/or variations, largely reflective of increases in cleft palate and reversible delays in ossification. Although there were no fetal alterations in the other 3 studies, there was decreased fetal and/or pup survival at doses of 10 mg/kg/day in the rabbit developmental study and at doses of 10 ppm or more (calculated maternal dosage of ≥ 0.8 mg/kg/day) in the rat pilot 1-generation and 3-generation studies. The reproductive NTEs were 5 mg/kg/day in both the rat and rabbit developmental studies and 5 ppm (0.4 mg/kg/day) in the rat 3-generation study.

The NTEL of 5 mg/kg is approximately 16 times the highest single dose (16 mg) to be administered to humans based on body weight, approximately 3 times (rat) or 8 times (rabbit) the highest single dose based on body surface area, and approximately 1200 times the human exposure (based on AUC) after a single dose of 18 mg of moxidectin. In the female rat, moxidectin has a $t_{1/2}$ of 45 hours (data not available for the rabbit). Therefore, daily administration of moxidectin to pregnant rats, as was done in the developmental toxicity study of moxidectin, would likely result in accumulation of the drug in the body, further increasing exposure of the fetus to the drug. No such toxicity is anticipated after administration of moxidectin to women (highest dose to be evaluated in patients is a single

8-mg dose). Based on the available data, the yearly oral intake of even 32 mg of moxidectin (or 16 mg every 6 months) by women is unlikely to pose a risk to the developing human fetus. This conclusion is consistent with that of the FDA Center for Veterinary Medicine, which concluded that moxidectin is neither a selective developmental toxicant nor a teratogen in rats or rabbits. Moxidectin was not genotoxic in a battery of in vitro and in vivo assays.

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8. APPENDIXES

APPENDIX 1. LIST OF ABBREVIATIONS AND TERMS WITH DEFINITIONS

TABLE A1-1. LIST OF ABBREVIATIONS

TABLE A1-1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANOVA	
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-versus-time curve
AUC _{0-∞}	area under the plasma concentration-versus-time curve from 0 to infinity
AUC _{0-t}	area under the plasma concentration-versus-time curve from 0 to the last time point
CHO	Chinese hamster ovary
CL/F	
CYP	cytochrome P450
C _{max}	peak blood or serum concentration
ECG	electrocardiogram
eq	equivalents
F ₁	first filial (used to describe the generation produced by mating 2 individuals of the P ₁ generation)
F ₂	second filial (used to describe the generation produced by mating 2 members of the F ₁ generation)
FIM	first-in-man study
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GD	gestation day
h	hours
HPMC	hydroxypropyl methylcellulose or hypomellose
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	high-performance liquid chromatography
IC ₅₀	extrapolated concentration at which there is 50% inhibition
IP	intraperitoneal
IV	intravenous
IVM	ivermectin
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LD	lactation day
LD ₅₀	median lethal dosage
MOX	moxidectin
MTT	methylthiotetrazole
NADPH	nicotinamide-adenine dinucleotide phosphate
NTEL	no-toxicologic-effect level
P ₁	parental (used to describe the parental generation of an experimental mating)
PCE	polychromatic erythrocyte
PK	pharmacokinetics
PO	by mouth
ppm	parts per million
SC	subcutaneous
SD	standard deviation
S-D	Sprague-Dawley
SR	sustained release

TABLE A1-1. LIST OF ABBREVIATIONS

Abbreviation	Term
S9	exogenous metabolic activation system prepared from Aroclor™-1254-induced rat liver cells
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse events
TIC	tablet in capsule
TK ^{+/+}	thymidine kinase
t_{max}	time to peak concentration after compound administration
UDPGA	uridine diphosphate-glucuronic acid
UDS	unscheduled DNA synthesis
URTI	upper respiratory tract infection
$V_{d,ss}$	steady-state volume of distribution
$V_{d/F}$	apparent volume of distribution during the terminal phase
WHO	World Health Organization

APPENDIX 2. NONCLINICAL PHARMACOLOGY

TABLE A2-1. IN VITRO ACTIVITY OF MOXIDECTIN

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

TABLE A2-1. IN VITRO ACTIVITY OF MOXIDECTIN AGAINST *O. lienalis*, *O. gutturosa* AND *O. volvulus*

Description, Dose, Observations	Results, Conclusions	Reference
In vitro activity of moxidectin against <i>O. lienalis</i> and <i>O. volvulus</i> microfilaria		
Description: In vitro study of effect of moxidectin on <i>O. lienalis</i> and <i>O. volvulus</i> microfilaria motility.	Results: Reduction in microfilaria motility with ivermectin and moxidectin was simliar.	Townson S. TDR Project ID 960089 Progress Report. 23 Dec 1998.
Dose: 10 ⁻⁷ M ivermectin or moxidectin.	Conclusions: Moxidectin affects the microfilarial motility of <i>Onchocerca</i> species in vitro.	
Observations: Parasite motility over 7 days.		
In vitro activity of moxidectin against <i>O. gutturosa</i> macrofilaria		
Description: In vitro study of effect on <i>O. gutturosa</i> male adult worms.	Results: Significant reduction of macrofilaria motility within 2 hours followed by steady decline up to 120 hours. Mean percentage reduction in motility relative to control: 93% for moxidectin and 86% for ivermectin. Percent inhibition of viability relative to control: 51% for moxidectin and 58% for ivermectin.	
Dose: 10 ⁻⁵ M ivermectin or moxidectin.		
Observations: Parasite motility over 120 hours, parasite viability (via formazan formation from tetrazolium salt MTT).	Conclusions: Moxidectin affects the macrofilarial motility and viability of <i>Onchocerca</i> species in vitro.	
Abbreviations: MTT = methylthiotetrazole.		

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

Species	Description, Dose, Observations	Results and Conclusions	Reference																									
In vivo activity of moxidectin against <i>O. lienalis</i> and <i>O. volvulus</i>																												
Mouse	Description: In vivo study of <i>O. lienalis</i> and <i>O. volvulus</i> in CBA/Ca mice infected SC with <i>O. lienalis</i> or <i>O. volvulus</i>. Dose: Moxidectin or ivermectin, PO or SC with single dose 3 days after infection (1.5, 15, or 150 µg/kg, N=10/group) or 5 SC doses on days 3-7 infection (0.2, 0.4, 0.8, 1.6, or 3.2 µg/kg, n = 8/group) or single 150 µg/kg SC dose on day 4, 16, or 28 before infection (<i>O. lienalis</i> infection only). Observations: Ear tissue microfilaria counts on day 18 after infection.	Results: No difference between single-dose SC and PO; 1.5 µg/kg or 15 µg/kg moxidectin 3 days after infection resulted in 23% and 96%, respectively, reduction in <i>O. volvulus</i> microfilaria. 1.5 µg/kg or 15 µg/kg ivermectin 3 days after infection resulted in 2% increase and 48% decrease, in <i>O. volvulus</i> microfilaria. Reduction in <i>O. lienalis</i> microfilaria counts relative to control at 18 days after infection with single 150 µg/kg SC dose 4, 16, and 28 days before infection. 4 days before infection: 100% with both drugs. 16 days before infection: 100% with moxidectin, 67% with ivermectin. 28 days before infection: 99.9% with moxidectin, 57% with ivermectin. Conclusions: Moxidectin was more efficacious against microfilaria on a mg/kg basis than ivermectin. Moxidectin has a longer-lasting effect on microfilaria counts than ivermectin.	Tagboto SK, Townson S. <i>Ann Trop Med Parasitol.</i> 1996.																									
Effect of moxidectin on <i>Brugia pahangi</i> -infected jirds																												
Jird	Description: Jirds infected with <i>B. pahangi</i>, 8/group. Dose: One, three, six or twelve 4-weekly PO doses of 125, 500 or 2000 µg/kg moxidectin starting approximately 10 weeks after infection with 100 L3 stage larvae per jird. Observations: Necropsy at 8, 16, 24, 48 weeks after single-dose treatment to determine geometric mean number (range) of live worms recovered posttreatment.	Results: Geometric mean number (range) of live worms recovered after a single dose (µg/kg) of moxidectin: <table><tr><th>Dose</th><th>8 Weeks</th><th>16 Weeks</th><th>24 Weeks</th><th>48 Weeks</th></tr><tr><td>0</td><td>11.0 (4-24)</td><td>7.9 (4-23)</td><td>11.1 (2-23)</td><td>5.6 (0-18)</td></tr><tr><td>125</td><td>4.9 (1-11)</td><td>4.8 (1-13)</td><td>12.3 (2-31)</td><td>11.6 (4-24)</td></tr><tr><td>500</td><td>6.5 (2-14)</td><td>3.8 (0-12)</td><td>4.8 (1-11)</td><td>8.1 (0-14)</td></tr><tr><td>2000</td><td>3.1 (2-6)</td><td>3.9 (2-8)</td><td>4.9 (1-24)</td><td>3.2 (0-14)</td></tr></table> Conclusions: Moxidectin ≥ 6 monthly doses of 500 µg/kg or ≥ 3 monthly doses of 2000 µg/kg resulted in significant reductions of live adult worms in jirds.	Dose	8 Weeks	16 Weeks	24 Weeks	48 Weeks	0	11.0 (4-24)	7.9 (4-23)	11.1 (2-23)	5.6 (0-18)	125	4.9 (1-11)	4.8 (1-13)	12.3 (2-31)	11.6 (4-24)	500	6.5 (2-14)	3.8 (0-12)	4.8 (1-11)	8.1 (0-14)	2000	3.1 (2-6)	3.9 (2-8)	4.9 (1-24)	3.2 (0-14)	McCall JW. TDR Project ID 980386 Progress Report. 9 Sep 2000.
Dose	8 Weeks	16 Weeks	24 Weeks	48 Weeks																								
0	11.0 (4-24)	7.9 (4-23)	11.1 (2-23)	5.6 (0-18)																								
125	4.9 (1-11)	4.8 (1-13)	12.3 (2-31)	11.6 (4-24)																								
500	6.5 (2-14)	3.8 (0-12)	4.8 (1-11)	8.1 (0-14)																								
2000	3.1 (2-6)	3.9 (2-8)	4.9 (1-24)	3.2 (0-14)																								

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

Species	Description, Dose, Observations	Results and Conclusions	Reference												
Effect of moxidectin on <i>Brugia pahangi</i> -infected dogs															
Dog	Description: Beagles infected with <i>Brugia pahangi</i> with 200 L3 stage larvae per dog, 6 dogs/group Dose: One, three, six or twelve 4-weekly PO doses of 250 µg/kg, 1000 µg/kg moxidectin, or control starting 5 months after infection Observations: Necropsy 24 or 48 weeks posttreatment, examination of afferent and efferent lymphatics to hindlimbs, popliteal, inguinal, internal and external iliac, and lumbar nodes for dead and live worms. Macrofilaricidal activity: Difference between geometric mean number of worms in treated and control group in % of geometric mean number of worm counts in control group. Duncan's multiple range test.	Results: Geometric mean number (range) of live worms 48 weeks after a single dose (µg/kg) of moxidectin: <table><tr><th>Dose</th><th>Mean (range)</th><th>Live Worms Cleared/Total</th></tr><tr><td>0</td><td>22.2 (0-54)</td><td>2/6</td></tr><tr><td>250</td><td>0.2 (0-1)</td><td>5/6</td></tr><tr><td>1000</td><td>0.0</td><td>6/6</td></tr></table> No significant difference seen in number of dogs cleared of infection between different dose regimens (p > 0.05). Conclusions: Moxidectin at a single oral dose of ≥ 250 µg/kg can result in clearance of infection in dogs. Moxidectin can be microfilaricidal after a single dose in the dose range to be explored in the human studies.	Dose	Mean (range)	Live Worms Cleared/Total	0	22.2 (0-54)	2/6	250	0.2 (0-1)	5/6	1000	0.0	6/6	McCall JW, et al. <i>Am J Trop Med Hyg.</i> 1999. McCall JW. TDR Project ID 980389 Progress Report. Jan 2000.
Dose	Mean (range)	Live Worms Cleared/Total													
0	22.2 (0-54)	2/6													
250	0.2 (0-1)	5/6													
1000	0.0	6/6													

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

Species	Description, Dose, Observations	Results and Conclusions	Reference																																																								
Dog	Description: Beagles infected with 100 L3 stage <i>B. pahangi</i> larvae/dog, 8 dogs/group. Dose: Single 250 µg/kg oral dose of moxidectin (MOX), ivermectin (IVM), or untreated control (starting 4 months after infection). Observations: Necropsy for macrofilaria 334 days posttreatment, examination of afferent and efferent lymphatics to hind limbs, popliteal, inguinal, internal and external iliac and lumbar nodes for dead and live worms. Vessels and lymph nodes further examined for worms. Effect on microfilaria counts: blood films pretreatment and up to 333 days posttreatment. Macrofilaricidal activity: Geometric mean microfilaria counts/20 µL blood. ANOVA and Duncan's multiple range test for difference in natural logarithm of macro- and microfilaria counts (+1).	Results: Geometric Mean Microfilaria Counts/20 µL Blood <table><tr><th></th><th colspan="5">Days Posttreatment</th></tr><tr><th></th><th>0</th><th>26</th><th>84</th><th>196</th><th>333</th></tr><tr><td>Control</td><td>43</td><td>39.8</td><td>53.9</td><td>28.9</td><td>16.9</td></tr><tr><td>IVM</td><td>43.8</td><td>22.9</td><td>36.9</td><td>39.5</td><td>25.2</td></tr><tr><td>MOX</td><td>43.9</td><td>10.1*</td><td>5.4*</td><td>0.8*</td><td>0.09*</td></tr></table> *Difference is statistically significant <u>Dogs Without Microfilaremia 333 days Posttreatment</u> <table><tr><td>Control</td><td>1/8</td></tr><tr><td>IVM</td><td>1/8</td></tr><tr><td>MOX</td><td>6/8 (2/8 with ≤1 mf/20µl blood)</td></tr></table> <table><tr><th></th><th>Dogs With Live Worms</th><th colspan="2">Number Live Worms</th></tr><tr><th></th><th></th><th>Average</th><th>Geometric Mean</th></tr><tr><td>Control</td><td>5/8</td><td>2.25</td><td>1.21</td></tr><tr><td>IVM</td><td>4/8</td><td>7.25</td><td>2.35</td></tr><tr><td>MOX</td><td>1/8</td><td>1.25</td><td>0.35</td></tr></table> Conclusion: Moxidectin at a single oral dose of ≥250 µg/kg: • Reduces microfilaria and clearance of microfilaria long term • Impedes macrofilaria viability Limitations of the model (high percentage of self cures > 6 months after infection) preclude more definitive conclusions.		Days Posttreatment						0	26	84	196	333	Control	43	39.8	53.9	28.9	16.9	IVM	43.8	22.9	36.9	39.5	25.2	MOX	43.9	10.1*	5.4*	0.8*	0.09*	Control	1/8	IVM	1/8	MOX	6/8 (2/8 with ≤1 mf/20µl blood)		Dogs With Live Worms	Number Live Worms				Average	Geometric Mean	Control	5/8	2.25	1.21	IVM	4/8	7.25	2.35	MOX	1/8	1.25	0.35	McCall JW. TDR Project ID 980386. Progress Report. 9 Sep 2002?
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MOX	1/8	1.25	0.35																																																								

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

Species	Description, Dose, Observations	Results and Conclusions	Reference
Effect of moxidectin on <i>O. ochengi</i> infected-cattle			
Cattle	Description: 4- to 6-year-old cows naturally infected with <i>Onchocerca ochengi</i> with at least 20 skin nodules, 3 cows/group Dose: Moxidectin 500 µg/kg or control, 1 or 6 monthly SC doses. Observations: Skin biopsies for microfilaremia, adult worm viability via motility and MTT/formazan reduction, embryograms, nodule diameter over 24 months posttreatment	Results: Adult female worms treated 6 times had reduced motility at 18 months. No evidence of macrofilaricidal activity was seen at 24 months posttreatment. Embryogenesis profoundly abrogated with accumulation of dead microfilaria in utero. Microfilaria in skin were first detected at 12 months, present at 18 months in 1/3 cattle treated 6 times and in 2/2 cattle treated once, and at 24 months in all surviving cattle. Microfilaricidal effect more potent and persisting slightly longer than with ivermectin (historical control). Conclusions: Moxidectin is a potent microfilaricide and inhibitor of embryogenesis but not macrofilaricidal for <i>O. ochengi</i> (no PK information)	Trees A. TDR Project ID 980383 Progress Report. 28 Jan 2000. Trees A, et al. <i>Parasitology</i>. 2000.

TABLE A2-2. IN VIVO ACTIVITY OF MOXIDECTIN

Species	Description, Dose, Observations	Results and Conclusions	Reference																		
Prophylactic activity of moxidectin on <i>O. ochengi</i> - infected cattle																					
Cattle	Description: Gudali calves exposed from birth to <i>O. ochengi</i> natural challenge in Cameroon.	Results:	Trees A. TDR Project ID 980383 Progress Report. 28 Jan 2000.																		
	Dose: Ivermectin 150 µg/kg or moxidectin 200 µg/kg SC at monthly or 3-month intervals for 22 months.	<table><thead><tr><th>Treatment</th><th>Total Nodules at 22 Months</th><th>Prevalence Nodules*</th></tr></thead><tbody><tr><td>Control</td><td>110</td><td>11/14</td></tr><tr><td>IVM (monthly)</td><td>0</td><td>0/9</td></tr><tr><td>IVM (3-month)</td><td>2</td><td>2/11</td></tr><tr><td>MOX (monthly)</td><td>0</td><td>0/10</td></tr><tr><td>MOX (3-month)</td><td>0</td><td>0/10</td></tr></tbody></table>		Treatment	Total Nodules at 22 Months	Prevalence Nodules*	Control	110	11/14	IVM (monthly)	0	0/9	IVM (3-month)	2	2/11	MOX (monthly)	0	0/10	MOX (3-month)	0	0/10
	Treatment	Total Nodules at 22 Months		Prevalence Nodules*																	
	Control	110		11/14																	
IVM (monthly)	0	0/9																			
IVM (3-month)	2	2/11																			
MOX (monthly)	0	0/10																			
MOX (3-month)	0	0/10																			
Observations: Nodules were assessed at each treatment.	*Animals with nodules/total animals in group.																				
	Conclusions: Moxidectin completely prevented natural infection in cattle either when administered at monthly or 3-month intervals, whereas with ivermectin prevention failed if administered at 3-month intervals.																				
Moxidectin pharmacokinetic dog study																					
Dogs	Description: Moxidectin was determined in dog plasma using HPLC method.	Results: Very fast absorption phase, with pronounced distribution phase, indicating multicompartmental PK. The average time to achieving maximum plasma concentration was 3.6±1.1 hours. For single-dose treatment at 250 µg/kg and 1000 µg/kg and 6 and 12 monthly doses, the results were as follows: mean T _{1/2β} (terminal phase) were 601±247, 502±126, 453±181 and 472±190 hours respectively. The volume of distribution 17.3±7, 15.9±2.4, 12.4±5.1, 21.2 ±5.2 L/kg. The mean CL/F values were 0.4±0.3, 0.4±0.1, 0.3±0.1 and 0.6±0.1 mL/min/kg. C _{max} was 227.6 ng/mL and 840.9 ng/mL for the low and high dose, respectively. The mean AUC (0 to last) values were 10,116 and 43,642 ng/mL/h for the low- and high-dose groups, respectively. No gender differences were found.	Vanapalli SR, et al. <i>Biopharm Drug Dispos.</i> 2002. McCall JW. TDR Project ID 980386 Progress Report. 9 Sep 2002.																		
	Dose: Treatment groups selected for PK analysis were 250 µg/kg and 1000 µg/kg, given as a single dose, 6 monthly doses (every 28 days) and 12 monthly doses (every 28 days). Observations: Sampling times: predose and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 144, 192, 240, 312, 408, 504, 672, 1344, and 2016 hours post dose.	Conclusions: Bioavailability was roughly proportional to the dose and the C _{max} was significantly higher in the high-dose than in the low-dose group. Increased bioavailability was also demonstrated by the increased AUC(0 to last), which was higher in the high-dose group. No significant effects of sex were found. Some evidence of accumulation with multiple dosages was observed.																			

Abbreviations: SC = subcutaneous; PO = by mouth; MTT = methylthiotetrazole; HPLC = high performance liquid chromatography; PK = pharmacokinetic; MOX = moxidectin; IVM = ivermectin.

**APPENDIX 3. PHARMACOKINETICS, PRODUCT METABOLISM, AND
TOXICOLOGY IN ANIMALS - NOT APPLICABLE**

APPENDIX 4. CLINICAL INFORMATION

TABLE A4-1. PHASE I CLINICAL STUDIES FOR MOXIDECTIN

TABLE A4-1. PHASE I CLINICAL STUDIES FOR MOXIDECTIN

Protocol Number/ Design/Duration	Study Population/Dose	Study Status	Enrollment Planned/ Enrolled/ Completed/ Discontinued	Type and Purpose of Study
3110A1-100-EU A single-ascending-dose, placebo-controlled, double- masked study of the safety, tolerability, and PK of orally administered moxidectin in normal subjects.	Healthy male subjects, 18 to 45 years of age, with normal cardiac, hematologic, hepatic, renal, and respiratory function. Subjects were enrolled in cohorts of 6 (5:1, active: placebo) and received a single oral dose, followed by timed PK sampling over an 80-day period. At 2 of the dose levels, an additional cohort of subjects was enrolled and consumed a high-fat breakfast before dose administration to evaluate the effect of food on moxidectin PK. Cohort 1 – 3 mg fasting Cohort 2 – 9 mg fasting Cohort 3 – 9 mg fed Cohort 4 – 18 mg fasting Cohort 5 – 36 mg fasting Cohort 6 – 36 mg fed Cohort 7 – 54 mg fasting	Complete	42 planned (7 cohorts of 6 subjects each) 38 randomized 37 received drug 34 completed 4 discontinued (3 after receiving doses and 1 subject who never received drug)	Clinical pharmacology, PK, safety <u>Primary:</u> To assess the safety and tolerability of orally administered moxidectin in normal subjects, as measured by the incidence of clinical adverse events and clinically important laboratory test results. <u>Secondary:</u> To provide initial assessment of the PK of moxidectin.

TABLE A4-1. PHASE I CLINICAL STUDIES FOR MOXIDECTIN

Protocol Number/ Design/Duration	Study Population/Dose	Study Status	Enrollment Planned/ Enrolled/ Completed/ Discontinued	Type and Purpose of Study
3110A1-101-EU An open-label, randomized, single-dose, parallel-design study of the bioavailability and safety of moxidectin liquid and tablet formulations orally administered to healthy subjects.	Healthy male subjects, 18 to 45 years of age, inclusive, with normal cardiac, hematologic, hepatic, renal, and respiratory function. Each subject received 1 orally administered dose of moxidectin, either as five 2-mg tablets or as a 10-mg liquid. In both cases moxidectin was administered under fasting conditions.	Complete	58 planned 58 randomized 58 received drug 58 completed 0 discontinued	Clinical pharmacology, bioavailability, PK, safety <u>Primary:</u> To determine the relative bioavailability of moxidectin administered as a tablet and as a liquid. <u>Secondary:</u> To assess the safety of orally administered tablet and liquid formulations of moxidectin in normal subjects, as measured by the incidence of clinical adverse events and clinically important laboratory test results.

Abbreviation: PK = pharmacokinetics.

APPENDIX 5. MECTIZAN LABEL

SUMMARY OF PRODUCT CHARACTERISTICS

1. DENOMINATION

MECTIZAN® 3 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ivermectin, microcrystalline cellulose, pregelatinized corn starch, butylhydroxyanisol, anhydrous citric acid, magnesium stearate.

For a 60.00 mg tablet

3. PHARMACEUTICAL FORM

tablet

4. CLINICAL DATA

4.1. Indications

- for the treatment of onchocerciasis caused by *Onchocerca volvulus*.
- for the treatment of proven or suspected microfilaremia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*.

4.2. Dosage and administration

Treatment of onchocerciasis:

The recommended dosage of ivermectin in the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 µg/kg of body weight.

For the treatment of individual patients, retreatment may be considered after a 3-months interval.

In mass distribution campaigns for onchocerciasis, the most commonly used dose interval is 12 months. However, in some areas it may be preferable to repeat the administration every 6 months according to the prevalence or the cutaneous microfilarial density.

For your guidance, the dose as determined by the patient's weight is as follows:

Bodyweight (kg)	Dose Number of 3 mg tablets
15 to 25	one
26 to 44	two
45 to 64	three
65 to 84	four

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Alternatively, and if no scales are available, the dose of ivermectin for use in mass chemotherapy campaigns may be determined by the patient's height, as follows:

HEIGHT (cm)	Number of 3 mg tablets
90 to 119	one
120 to 140	two
141 to 158	three
> 158	four

Treatment of microfilaremia caused by *Wuchereria bancrofti*:

The recommended dosage for mass distribution for the treatment of microfilaremia caused by *Wuchereria bancrofti* is a single oral dose once every 6 months designed to provide approximately 150 to 200 µg/kg of body weight.

In endemic areas where treatment can only be administered once every 12 months, a dose of 300 to 400 µg/kg of body weight should be administered to maintain adequate suppression of microfilaremia.

For your guidance, the dose, as determined by the patient's weight, is as follows:

BODYWEIGHT (kg)	DOSE when given once every 6 months	DOSE when given once every 12 months
	Number of 3 mg tablets	Number of 3 mg tablets
15 to 25	one	two
26 to 44	two	four
45 to 64	three	six
65 to 84	four	eight

Alternatively, and if no scales are available, the dose of ivermectin for use in mass chemotherapy campaigns may be determined by the patient's height as follows:

HEIGHT (cm)	DOSE when given once every 6 months	DOSE when given once every 12 months
	Number of 3 mg tablets	Number of 3 mg tablets
90 to 119	one	two
120 to 140	two	four
141 to 158	three	six
> 158	four	eight

Method of administration:

Oral route.

In children less than 6 years of age, tablets should be crushed before swallowing.

Treatment is one single oral dose taken with water on an empty stomach.

The dosage may be taken at any time of the day, but no food should be taken within two hours before or after administration, as the influence of food on absorption is unknown.

4.3. Contraindication

Hypersensitivity to any component of this product.

4.4. Warnings and particular precautions for use

Warnings

Ivermectin has no macrofilaricidal effect against adult forms of *Onchocerca volvulus* parasites, nor against other adult filarial parasites.

Ivermectin is not a prophylactic therapy of infection with filarial parasites. There are no data available demonstrating the efficacy of ivermectin either for killing or preventing the maturation of infective larvae in humans.

Ivermectin has not been shown to have any beneficial effect on tropical pulmonary eosinophilia syndrome, lymphadenitis or lymphangitis observed in case of infection with filarial parasites.

The intensity and severity of adverse experiences, after administration of ivermectin, are probably related to the pretreatment microfilarial density, particularly in the blood. Patients with high microfilaremia of *Loa loa* are at an increased risk for the occurrence of serious adverse experiences after administration of ivermectin. CNS adverse experiences (encephalopathies) have been rarely reported in patients treated with ivermectin and infected by a high number of microfilariae of *Loa Loa*. Consequently, in *Loa loa* endemic areas, special measures should be taken before any treatment with ivermectin.

Concomitant treatment with DEC and ivermectin in mass chemotherapy campaigns for filariasis caused by *Wuchereria bancrofti* in Africa is not recommended. Co-infection with other microfilariae, such as *Loa loa*, may result in a high microfilaremia in infected patients. Systemic exposure of such patients to DEC may result in the occurrence of serious side effects related to the rapid and effective microfilaricidal effects of this drug.

Following administration of drugs with a rapid microfilaricidal action such as diethylcarbamazine citrate (DEC) in patients with onchocerciasis, cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions have been reported. These reactions are probably due to inflammatory responses to degradation products released following the death of microfilariae. Patients infected with *Onchocerca volvulus* who are treated with ivermectin for the first time may also experience these reactions. After treatment with a microfilaricidal drug, patients with hyperreactive onchodermatitis or "Sowda" (observed particularly in Yemen) may be more likely than others to experience severe cutaneous adverse reactions (edema and aggravation of onchodermatitis).

Precautions for use

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.

4.5. Pregnancy and nursing

Pregnancy

After administration of repeated doses of ivermectin close to or equal to maternotoxic doses, fetal abnormalities have been observed in several animal species in the laboratory. From these studies, it is difficult to assess the risk of a single low dose.

In clinical studies no malformations or fetotoxic effects have been attributed to ivermectin. The frequencies of congenital anomalies, spontaneous abortions, fetal deaths/stillbirths and infant mortalities in approximately 400 women inadvertently treated with ivermectin during the first trimester of pregnancy in mass treatment campaigns for onchocerciasis were similar to frequencies in women not treated with ivermectin during pregnancy. However, follow-up of pregnancies of women exposed to ivermectin is not sufficient to exclude any risk. Therefore, as a precaution, it is advisable not to use ivermectin during pregnancy.

Nursing

Less than 2% of the administered dose of ivermectin appeared in breast milk.

Safety in newborn infants has not been established; therefore, the drug should be given to nursing mothers only if the benefit to the mother outweighs the potential risk to the breast-fed infant, and treatment of mothers who intend to breast feed their infants should be delayed until 1 week after birth of the child.

4.6. Side effects

Side effects are related to the microfilarial density; most of them are mild and transient in nature but the incidence and severity may be higher in patients infected with more than one parasite, as in the case of infection with *Loa loa*.

- Following treatment of patients infected with *Onchocerca volvulus* with ivermectin, the following hypersensitivity reactions may occur due to the death of microfilariae; these are symptoms of Mazzotti type reaction: pruritus, frank urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, edema, lymphadenitis, lymphadenopathies, nausea, vomiting, diarrhea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache. These symptoms have been rarely severe. Some cases of worsening of bronchial asthma have been reported.
- Less frequently, ophthalmological side effects after treatment with ivermectin may occur. These include: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or chorioiditis. All of these can occur due to the disease itself but have occasionally been reported after therapy. These have rarely been severe and have generally resolved without corticosteroid treatment.

- In the treatment of filariasis caused by *Wuchereria bancrofti*, the intensity of the side effects does not seem to be dose-related but is related to the blood microfilarial density. The following have been reported: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, body pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, postural hypotension, chills, vertigo, diaphoresis, sore throat, testicular pain or discomfort.
- Very rarely, patients who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy following treatment with ivermectin.
- Transient hypereosinophilia, liver function abnormalities (SGPT) and hematuria have been reported.
- Cases of expulsion of adult ascaris worms have been described following administration of ivermectin.

4.7. Overdosage

There are reports of accidental overdosage of ivermectin, but no fatalities have been attributable to ivermectin overdosing.

In accidental intoxication with unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection or exposure to body surfaces, the following symptoms have been reported: rash, edema, headache, vertigo, asthenia, nausea, vomiting, diarrhea, abdominal pain. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, and urticaria.

Management in case of accidental poisoning:

- supportive therapy and supervision in specialized care unit with fluid replacement, and treatment for hypotension, if needed.

Although there are no data available in man, it seems advisable to avoid the use of GABA agonists in the treatment of accidental intoxications due to ivermectin.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

Anthelmintic

Ivermectin is derived from the avermectins, that are isolated from fermentation broths of *Streptomyces avermitilis*. It binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite.

Ivermectin may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

Mammals do not have glutamate-gated chloride channels. The avermectins have a low affinity for mammalian ligand-gated chloride channels. They do not readily cross the blood-brain barrier in humans.

In patients infected with *Onchocerca volvulus*, a single oral dose of 150 µg/kg ivermectin resulted in a decrease in the number of skin microfilariae to undetectable levels within a few days. This reduction was maintained at or under 10% of the pre-treatment microfilarial count for up to 12 months after treatment. This effect is due to the microfilaricidal effect and to the transient blockage of the release of microfilariae from the uterus of the adult worm. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3 and 6 months after the dose, a significant reduction in the number of microfilariae in the anterior chamber of the eye was observed in subjects treated.

Clinical studies conducted in Africa, Asia, South America, the Caribbean, and Polynesia in patients with microfilaremia caused by *Wuchereria bancrofti* demonstrated that a single oral dose of at least 100 µg/kg ivermectin resulted in reduction of microfilaremia to below 1% of the preresult value in the week following administration. These studies showed that the treatment effect was dose-dependent with regard to the duration of the reduction in microfilaremia and the prevalence in the population treated. The use of ivermectin in mass treatment of populations for the treatment of microfilaremia in man, the unique host for *Wuchereria bancrofti*, may be useful to decrease the transmission of *Wuchereria bancrofti* by vector insects, thus interrupting the infectious cycle of the disease.

5.2. Pharmacokinetics

With 12 mg single oral doses of MECTIZAN administered as tablets, the mean peak plasma concentration of the major component (H₂B_{1a}) was 46.6 (± 21.9) ng/ml at approximately 4 hours after dosing. Plasma concentration increases with increasing dose in a manner approximately proportional to the dose. Ivermectin is metabolized in humans, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 hours less than 1% of the administered dose being excreted in the urine. The plasma half-life of ivermectin in man is about 12 hours and that of the metabolites is about 3 days.

6. PHARMACEUTICAL DATA

6.1. Stability

3 years

6.2. Special precautions for storage

Do not store above 30°C.

6.3. Nature and content of the packaging

4 tablets in aluminium unit strip sealed
500 tablets in bottle (PE)

7. PRESENTATIONS AND ADMINISTRATIVE IDENTIFICATION NUMBERS

A.M.M. 354 573.5 (4 tablets in aluminium strips)

A.M.M. 343 368.5 (500 tablets in bottle [PE])

8. PRESCRIPTION AND DELIVERY CONDITIONS

List II

9. A.M.M. HOLDER

LABORATOIRES MERCK SHARP & DOHME - CHIBRET

3, Avenue Hoche - 75114 PARIS cedex 08

Tel. 01 47 54 87 00

10. APPROVAL/REVISION DATES

Approval date: 14.05.97

Revision date: 19.11.01

9. ATTACHMENTS

SAFETY ATTACHMENT

CHANGES FROM PREVIOUS EDITION OF THE INVESTIGATOR'S BROCHURE

SAFETY ATTACHMENT: APRIL 2004

LIST OF CONTENTS

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SAFETY ATTACHMENT: APRIL 2004

1. SELECTED DEFINITIONS

GLOSSARY

**Adverse Reaction /
Adverse Drug
Reaction**

In the preapproval clinical experience with a new medicinal product or its new usages in particular, as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product, related to any dose, should be considered adverse drug reactions. Regarding marketed medicinal products: a response that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function.

Adverse Event

An adverse event is defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a human being in a temporal relationship to the use of a Wyeth product regardless of causal relationship. This includes the following:

- any clinically important worsening of a preexisting condition;
- an adverse event occurring from overdose (ie, a dose higher than that prescribed by a health care professional for clinical reasons) of a Wyeth product, whether accidental or intentional;
- an adverse event occurring from abuse (ie, use for nonclinical reasons) of a Wyeth product;
- an adverse event associated with the discontinuation of the use of a Wyeth product.

Clinically important laboratory abnormalities (including, for example, abnormal x-ray films, electrocardiograms) that occur or worsen during the clinical study also are adverse events.

SAFETY ATTACHMENT: APRIL 2004

GLOSSARY

Product (Drug, Biological Product) Related	An adverse event will be considered “product related” (ie, drug related, vaccine related, etc) for studies if either the investigator, or the medical monitor assesses the adverse event(s) as possibly, probably, or definitely related. • An adverse event will be considered “not product related” for studies if the investigator and the medical monitor(s) assess the adverse event(s) as probably not related or definitely not related, or “relationship remote.” • Whenever the investigator’s assessment is unknown or unclear, the adverse event(s) will be treated as product related.
Definitely Related	The event can be fully explained by administration of the investigational product.
Probably Related	The event is more likely to be explained by administration of the investigational product rather than the patient/subject’s clinical state or other agents/therapies.
Possibly Related	The event may be explained by administration of the investigational product, or by the patient/subject's clinical state or other agents/therapies.
Probably Not Related	The event is more likely to be explained by the patient/subject's clinical state or other agents/therapies rather than the investigational product.
Definitely Not Related	The event can be fully explained by the patient/subject's clinical state or other agents/therapies.
Protocol Related	Adverse events from clinical trials that are not product related may nevertheless be considered by the investigator or medical monitor to be protocol related.

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Serious Adverse Event

A serious adverse event is defined as an adverse event occurring at any dose that

- results in death;
- is life threatening (see below);
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in a persistent or significant disability or incapacity (see below);
- results in cancer;
- results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, and the development of drug dependency or abuse.

A serious adverse event obtained from tests in laboratory animals is any experience suggesting a significant risk for human subjects, including any findings of mutagenicity, teratogenicity, or carcinogenicity.

Life Threatening

Life threatening refers to immediate risk of death as the event occurred. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death but as it actually occurred did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

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Disability	Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.
Unexpected Adverse Event	An unexpected adverse event is one that is not listed in the current product labeling. The current product labeling is either the package insert (for marketed products) or the current investigator's brochure (for investigational products). An unexpected adverse event includes any event that may be symptomatically and pathophysiologically related to an event listed in the labeling but that differs from the labeled event because of greater severity or specificity. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the product labeling referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. • An adverse event is considered unexpected for local reporting purposes if it does not appear in the labeling for the country to which the adverse event is being reported. • An adverse event is considered unexpected for core labeling purposes when it does not appear in the company's core data sheet, if it exists.

2. DEVELOPMENT CORE SAFETY INFORMATION

2.1 Contraindications, Special Warnings, and Special Precautions for Use

Contraindications, special warnings, and special precautions for use have not yet been determined for moxidectin. See section 5 (Other Considerations) for safety information relating to other macrocyclic lactone drugs.

2.2 Interactions With Other Therapeutic Substances and Other Forms of Interaction

Compounds that bind to gamma aminobutyric acid (GABA)-containing neurons and receptors may decrease the activity of moxidectin at the GABA binding sites of the

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peripheral nervous systems in nematodes and arthropods and decrease the efficacy of moxidectin. Package inserts for marketed ivermectin products in animals caution against the concomitant administration of ivermectin with Valium and other members of the benzodiazepine class. Because radiolabeled ligand studies suggest that moxidectin has activity at the GABA-A receptor in a manner similar to ivermectin, there is the potential for interaction of moxidectin with benzodiazepines.

The potential for moxidectin to inhibit the activity of cytochrome P450 (CYP) CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was evaluated in human liver microsomes at moxidectin concentrations ranging from 0.1 to 100 μ M. Moxidectin was a weak inhibitor of CYP1A2 and CYP2C9, with extrapolated IC₅₀ values of 459 μ M and 145 μ M, respectively. There was no inhibition of the other CYP enzymes examined. In humans, the mean C_{max} after an 18-mg oral dose was 141 ng/mL (0.2 μ M). Therefore, it is unlikely that clinical drug-drug interactions involving these CYP enzymes would occur.

2.3 Pregnancy and Lactation

There is no information on the effect of moxidectin on pregnancy and lactation in humans. Women of childbearing age should be given moxidectin only if they are practicing the birth control method specified in the study protocol. If a patient should become pregnant while receiving this drug, the patient should be apprised of the potential risks to the fetus based on what has been observed with other drugs in this class. Because of the unknown risk to nursing infants, treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the nursing infant. See section 5 (Other Considerations) for safety information relating to pregnancy and lactation in animal studies.

2.4 Adverse Drug Reactions (Undesirable Effects) Reported From Clinical Trials

To date, a total of 95 subjects have received oral moxidectin, 37 subjects in a phase 1 safety and tolerability study (protocol 3110A1-100-EU) and 58 subjects in a phase 1 bioavailability study of orally administered moxidectin liquid and tablets (protocol 3110A1-101-EU). Based on this limited exposure, no adverse events can be identified as expected adverse drug

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reactions. A summary of the adverse events for these studies may be found in section 5 of the Investigator's Brochure.

2.5 Overdose

There is no experience with moxidectin overdosage in humans. In general, the adverse events of an overdose with moxidectin are expected to be related to the pharmacologic effect of the drug, including central nervous system and neuromuscular effects. General supportive measures should be followed in all cases of overdoses of moxidectin. See section 5 (Other Considerations) for overdose information relating to other macrocyclic lactone drugs.

2.6 Drug Abuse and Dependence

Given the pharmacologic effects of this agent, the use of moxidectin is not anticipated to result in drug abuse or dependence.

3. SERIOUS DRUG-RELATED ADVERSE EVENTS FROM CLINICAL TRIALS

No drug-related serious adverse events were reported for the 37 healthy adult male subjects enrolled in the first-in-man (FIM) study (protocol 3110A1-100-EU) or for the 58 healthy adult male subjects enrolled in the moxidectin liquid and tablet bioavailability study (protocol 3110A1-101-EU).

4. SERIOUS NONDRUG-RELATED ADVERSE EVENTS FROM CLINICAL TRIALS

No nondrug-related serious adverse events were reported in the first-in-man (FIM) study (protocol 3110A1-100-EU) or in the moxidectin liquid and tablet bioavailability study (protocol 3110A1-101-EU).

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5. OTHER CONSIDERATIONS

5.1 Summary of Adverse Events Observed in Phase 1 Clinical Studies

5.1.1 Single-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study

In the first clinical moxidectin study (3110A1-100-EU), only 1 adverse event higher than grade 2 (moderate toxicity) was reported (enteritis resulting from food poisoning [grade 3; severe toxicity] in the 36-mg fasting group), which was considered unrelated to study drug. The most common adverse events (reported by $\geq 10\%$ of subjects) were headache (35%) and infection (29%). The majority (7 of 9) of moxidectin-treated subjects reporting infection had colds or upper respiratory tract infections. Of the remaining 2 subjects, 1 had a right big toe infection and 1 had a tooth abscess. Four (4) subjects withdrew from the study (1 before receiving study drug and 3 after dose administration: 1 each in the 3-mg fasting, 9-mg fed, and 36-mg fasting groups). The withdrawal of these subjects from the study was unrelated to adverse events. Adverse events affecting the central nervous system (nausea, vomiting, and somnolence) were found to occur more frequently in the later cohorts (the 18-mg and 36-mg groups) than in the earlier cohorts (the 3-mg and 9-mg groups). These adverse events were believed to be indicative of the mechanism of action of moxidectin, and similar events have been seen in humans treated with ivermectin.

No clinically significant adverse events were seen in the 3-mg and 9-mg treatment groups, so treatment at these levels is considered to be safe.

5.1.2 Relative Bioavailability of a Tablet and Liquid Formulation of Moxidectin in Healthy Subjects

A total of 36 of 58 (62.1%) subjects had treatment-emergent adverse events (TEAEs) during this study (protocol 3110A1-101-EU), with the same number and percentage of subjects (18; 62.1% in each group) reporting TEAEs in both the moxidectin liquid and tablet groups. The most commonly reported TEAEs (reported by $\geq 5\%$ of subjects) were flu syndrome (reported by 17.2% and 20.7% of subjects in the liquid and tablet groups, respectively), headache (reported by 17.2% and 13.8% of subjects in the liquid and tablet groups, respectively), infection (reported by 13.8% and 6.9% of subjects in the liquid and tablet

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groups, respectively), diarrhea (reported by 10.3% of subjects in the liquid group), myalgia (reported by 6.9% of subjects in the tablet group), and dizziness (reported by 6.9% of subjects in the tablet group).

A total of 19 of 58 subjects (32.8%) reported TEAEs within the first week after administration of study drug (on or before day 7). During this period, TEAEs were reported by 10 of 29 subjects (34.5%) in the group receiving moxidectin liquid and by 9 of 29 subjects (31.0%) in the group receiving moxidectin tablets. The most commonly reported TEAEs (reported by $\geq 5\%$ of subjects) during this period were asthenia (reported by 10.3% of subjects in the tablet group), headache (reported by 13.8% and 6.9% of subjects in the liquid and tablet groups, respectively), infection (reported by 6.9% of subjects in the liquid group), diarrhea (reported by 6.9% of subjects in the liquid group), myalgia (reported by 6.9% of subjects in the tablet group), and dizziness (reported by 6.9% of subjects in the tablet group).

A total of 22 of 58 subjects (37.9%) reported TEAEs during the outpatient period of the study (after study day 7 and up to study day 180); 10 of 29 subjects (34.5%) were in the liquid group and 12 of 29 (41.4%) were in the tablet group. The most commonly reported events (reported by $\geq 5\%$ of subjects) were flu syndrome (reported by 17.2% and 20.7% of subjects in the liquid and tablet groups, respectively), headache (reported by 6.9% of subjects in the tablet group), and infection (reported by 6.9% of subjects in the tablet group).

All TEAEs that were reported during the study were mild to moderate in intensity, and none were considered to be related to treatment. During the course of this study there were no serious adverse events and no subjects discontinued the study as the result of an adverse event.

No clinically relevant abnormalities were observed in vital sign measurements, electrocardiograms, or laboratory tests during the study.

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5.2 Mazzotti Reaction

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmologic reactions in patients with onchocerciasis. Observed signs and symptoms may include itching; rash; headache; arthralgia; myalgia; lymph node pain, swelling, and tenderness; fever; chills; tachycardia; postural hypertension; and polyarthrititis. These reactions are probably due to allergic and inflammatory responses of the host to the death of microfilariae. These tend to be seen within the first month after treatment because that is the time of the greatest microfilaricidal effect.

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

5.3 Relevant Safety Information From Animal Studies

5.3.1 Pregnancy and Lactation

In animal studies with repeated exposure to maternally toxic doses, there was decreased fetal and/or pup survival and there were significant increases in the number of fetuses born with malformations and/or variations. However, based on the available data, the yearly oral intake of even 32 mg of moxidectin (or 16 mg every 6 months) by women is unlikely to pose a risk to the developing human fetus (the highest dose to be evaluated in patients is a single yearly 8-mg dose).

Moxidectin is lipophilic and has been shown to be excreted into the milk of lactating cows. It is conceivable that moxidectin-treated nursing mothers may excrete moxidectin in their breast milk.

5.3.2 Clinical Experience With Oral Moxidectin in the Dog

ProHeart Tablets (moxidectin) are available in the United States and abroad for use as a monthly heartworm preventive in dogs (monthly oral dose of 3 µg/kg).

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Overall, adverse reactions were rare when the drug was administered orally at the labeled dose. Adverse reactions reported in clinical studies following the use of ProHeart Tablets included lethargy, vomiting, ataxia, anorexia, diarrhea, nervousness, weakness, increased thirst and itching. Postmarketing surveillance of field use from 1998 through 2002 in the United States reveals the following reporting pattern and frequency:

Total adverse drug reaction reports (6 reports) = .0005% of doses sold in the US market

- Lethargy/vomiting/diarrhea (4 reports) = .0003%
- Seizure after administration (1 report) = .0001%
- Toenail bruising (1 report) = .0001%

All of these potential side effects in dogs appear to be rare when the product is administered orally at the labeled dose.

5.3.3 Clinical Experience With Subcutaneous Moxidectin in the Dog

Allergic reactions (1.4 reports per 10,000 doses) have been reported in dogs receiving subcutaneous (SC) ProHeart 6, a sustained-release injectable moxidectin administered twice yearly for the prevention of heartworm. Similar reactions have not been reported in dogs receiving oral monthly ProHeart Tablets. The relevance of the allergic reactions observed in dogs after SC administration of ProHeart 6 to the proposed clinical trials in which subjects will receive an oral formulation is unknown.

5.4 Safety Information About Other Macrocyclic Lactone Drugs

5.4.1 Pregnancy and Lactation

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m²/day basis). Teratogenicity was characterized in the 3 species by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female.

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Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies with pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

5.4.2 Overdosage

In accidental intoxication with or significant exposure to unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other reported adverse effects include seizure, ataxia, dyspnea, abdominal pain, paresthesia, and urticaria. The manufacturer recommends that in cases of accidental ivermectin poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary), and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine antipoison measures, may be indicated if needed to prevent absorption of ingested material.

5.5 Safety Information Relative to the Excipients

Moxidectin tablets in capsules (TIC) for clinical studies will be supplied as 2-mg tablets encapsulated in hydroxypropyl methylcellulose (HPMC) capsules. The capsules will be filled with a mixture of inert ingredients including lactose, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. No unusual or novel excipients will be used in the tablets or capsules and as such no undesirable adverse effects relative to the excipients are expected.

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One (1) moxidectin TIC is required for a 2-mg dose; 2 TICs are required for a 4-mg dose; 4 TICs are required for an 8-mg dose. Matching placebo in HPMC capsules filled with the same inert ingredients as the moxidectin capsules will also be provided for clinical trials.

Summary of safety relevant animal and human volunteer data generated since April 2004

(i.e. since last Moxidectin Investigator Brochure update)

Summary April 2005

(Source documents provided as separate PDF files as available)

**Annette C. Kuesel, PhD
WHO/TDR**

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1 Potential of drug-drug interactions

Previous *in vitro* studies summarized in the 2004 IB (page 21-23) have shown that inhibitors of cytochrome P450s are unlikely to alter the pharmacokinetics and disposition of moxidectin and that moxidectin is unlikely to alter the pharmacokinetics and metabolism of drugs metabolised by cytochrome P450s.

Wyeth conducted a study evaluating the effect of moxidectin on p-glycoprotein in Caco-2 cell monolayers.

Moxidectin inhibited Caco-2 cell p-glycoprotein activity with digoxin as a probe substrate with an $IC_{50} > 100 \mu M$. Based on *in vitro* activity and serum concentrations of moxidectin in human volunteers, the serum concentrations of moxidectin required for efficacy in patients with onchocerciasis are anticipated not to exceed $0.1 \mu M$. Thus, it appears unlikely that moxidectin will alter the pharmacokinetics or disposition of concomitantly administered drugs that are substrates for p-glycoprotein.

Moxidectin appears to be a substrate for p-glycoprotein using Caco-2 cell monolayers, albeit weaker than digoxin. The effect of concomitant drugs that are p-glycoprotein inhibitors (e.g. HIV protease inhibitors) on the pharmacokinetics and disposition of moxidectin may be dependent on the inhibitory potency and clinical concentrations of the concomitant drug(s), and will need to be evaluated individually based on available literature data.

2 Binding of moxidectin to mammalian receptors

Moxidectin and moxidectin microspheres (as present in ProHeart 6) were recently tested *in vitro* for binding activity at 64 different mammalian receptors. Ivermectin was used as a comparator.

This assay is commonly used in drug discovery and development to identify any ancillary pharmacologic activities of a molecule, which may result in undesirable biological effects. A final concentration of 10 ng/mL ($0.16 \mu M$) moxidectin was tested,

The receptors tested included those for neurotransmitters and neurotransmitter-related receptors (including the γ -aminobutyric acid A receptor, i.e. the mammalian equivalent of a target of moxidectin in the parasite), ion channels (including glutamate-gated chloride channels, i.e. the mammalian equivalent of a target of moxidectin in the parasite), steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes.

Moxidectin (by itself or in the microspheres) did not significantly inhibit the binding of appropriate radio-ligands to any of these receptors, indicating a lack of binding activity for moxidectin.

These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels many fold those anticipated to be required for efficacy in onchocerciasis. (see 2004 IB, page 25 - 43).

3 Moxidectin concentrations in dogs and rats at doses used in the multiple dose toxicity studies

The results from a large number of toxicology studies ranging from single dose studies, over multiple dose (4 week, 13 week, 1 year) to 2 year carcinogenicity and three generation reproductive toxicity studies are available and summarized in the 2004 IB (page 25-43).

Fort Dodge and Wyeth Research recently conducted pharmacokinetic studies to obtain the data on the exposure of dogs and rats at the highest dose tested and/or the highest

dose that did not result in toxicologically significant findings in the 1 year dog study and the 4 week rat study.

These data are now available for comparison with exposure data in humans at the doses shown to be safe in the human volunteer studies.

1. PK data in dogs up to 28 days after a SINGLE dose of 45 ppm in the diet.

In the 1 year diet dog study, 45 ppm/day administered via the diet (appr. 1.1 mg/kg/day) was the highest dose tested and did not result in any toxicologically significant findings (see 2004 IB, page 33).

- The mean maximum serum concentration (C_{max}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) and the half life in dogs were 296 ng/ml, 861 ng day/ml and 8.3 days, respectively.
2. PK data up to 28 days in dogs administered 45 ppm of moxidectin once a day for 28 days in the diet, i.e. the dose that did not result in any toxicologically significant findings in the 1 year dog study.
 - On day 28, the mean trough moxidectin serum concentration (i.e. the concentration 24 hours after the last dose) was 340 ng/mL. Based on serum levels measured after 28 days of ingesting ~1 mg/kg/day moxidectin, daily exposure during the 1-year toxicology study was estimated as 540 ng•day/mL. Over a 6-month period, this exposure results in an AUC of 98550 ng.day/mL or approximately 500 – 700 times above the reported AUC in humans after a single 9 mg dose (liquid formulation).

For comparison: a single oral dose of 36 mg (liquid formulation) to human volunteers which was safe resulted in a mean C_{max} of 290-300 ng/mL, mean $AUC_{0-\infty}$ of 450-625 ng/ml days and had a mean half life of 20-26 days (range represents means obtained for administration in fasted and fed state). A single oral dose of 10 mg (tablet formulation), i.e. close to the dose range anticipated to be required for efficacy in patients with onchocerciasis resulted in a C_{max} of 67.1 ng/ml (range (39.6-162.6 ng/ml), , $AUC_{0-\infty}$ of 68-468 ng/ml days and an average half life of 43 days. (see section 4 in this document).

3. PK data up to 28 days in rats administered daily 100 pm of moxidectin in the diet
 - On day 28, the mean trough moxidectin serum concentration (i.e. the concentration 24 hours after the last dose) was 581 ng/mL.
 - Based on serum levels measured after 28 days of ingesting ~5 mg/kg/day moxidectin, daily exposure during the 2-year carcinogenicity study was estimated as 1022 ng•day/mL. Over a 6-month period, this exposure results in an AUC of 186515 ng•day/mL or approximately 1000 – 1400 times above the reported AUC in humans after a single 9 mg dose.

4 New pharmacokinetic data from human volunteer study with tablet formulation developed by Wyeth for use in patients with onchocerciasis

An open label, randomized, single-dose, parallel-design study was conducted in Germany in 58 healthy young males to assess the bioavailability of the newly developed tablet formulation with that of the liquid formulation used in the First in Man study. The liquid formulation was used in the first study in man (healthy volunteers, see IB pages 45-52). The tablet formulation was developed by Wyeth for use in all subsequent studies and post registration in patients with onchocerciasis.

Each subject received either 10 mg moxidectin in solution or 10 mg of moxidectin of tablet (5 2 mg tablets). Patients were followed up for safety for 180 days post dosing. Blood

samples for moxidectin concentration measurements were obtained 0 (predose), 2, 4, 6, 8, 12, 24, 48, 72, 96 hours and 6, 8, 21, 24, 30, 90 and 180 days post dosing.

The safety data from that study are provided in the IB (page 52-60). The pharmacokinetic data have become available since the April 2004 update of the IB. The results of the non-compartmental analysis are summarized below.

PK parameter	Solution Mean (range)	Tablet Mean (range)	Comparison of formulations
Time of maximum plasma concentration	2.3 hrs (2-4 hrs)	3.2 hrs (2-6)	Ratio Tablet to Solution* 132.3 % (CI _{90%} 114.0-153.6)
Maximum plasma concentration (C _{max})	86.3 ng/ml (53.6-156.9 ng/ml)	67.1 ng/ml (39.6-162.6 ng/ml)	Ratio Tablet to Solution* 76.1% (CI _{90%} 66.8-86.7)
Terminal half-life	47.5 days (1139 hrs) (113-2334 hrs)	43.0 days (1032 hrs) (263-1815 hrs)	Non statistically significantly different
Volume of distribution (V _z /F)	3031 L (599-5774 L)	3635 L (1334-8907 L)	Not statistically significantly different
Clearance (CL/F)	2280 mL/hr (54.7L/Day) (641-4712 mL/hr)	2830 mL/hr (67.9 L/day) (890-61217 mL/hr)	Not statistically significantly different
AUC _{0-∞}	5673 ng hr/mL (2122-15601 ng hr/mL)	4403 ng hr/mL (1632-11241 ng hr/mL)	Ratio Tablet to Solution* 79.0% (CI _{90%} 63.4-98.4)

* Output from 'Bioequivalence Wizard' of software WinNonLin using default model for parallel designs. Results indicate that formulations are not bioequivalent.

The CI_{90%} values outside the range of 80-120% indicate that the two formulations are not bioequivalent.

Relative to the first study in healthy volunteers the elimination half life and the AUC_{0-∞} (adjusted for dose) are higher in this study. This is likely due to the fact that this study sampled blood over 180 days post dosing, while the first study sampled only for 90 days. In addition, the current study had 29 subjects in each arm, while the previous had 5 subjects/arm (total number of arms determined by dose and fast/fed status 6).

Conclusion

The safety profile recorded in the two clinical pharmacology studies conducted so far up to a single dose up to 36 mg did not provide any evidence of clinically relevant human toxicity which would prevent further development (see Investigator Brochure section 5.5, p. 46 ff). Comparison of the PK data obtained with those obtained at the No Toxic Effect Level in the dog and rat toxicity studies suggest that the exposure in humans is below the highest exposure that was not associated with detectable toxic effects in rats and dogs.

5 Review of safety data from 2 healthy volunteer studies by Wyeth following Proheart6 recall

During each of the two healthy volunteer (clinical pharmacology) studies, the incoming data on adverse events were reviewed by the principal investigator as well as the Wyeth medical monitor for the study. The safety data of each study were reviewed in their entirety at the end of each study for any signals of potential toxicity. The results of this review did not give rise to any concerns and are included in the Investigator brochure (page 46 ff).

Following the recall of Proheart6, Wyeth initiated yet another review of the safety data from the two human volunteer studies with special emphasis on searching for signals for

toxicity consistent with the FDA view of the safety of Proheart6. The report of this review is included in this briefing package.

All reviews of the safety data from the human studies concluded that 'the safety profile recorded in the two healthy volunteer studies to a single oral dose of 36 mg did not provide any evidence of clinically relevant human toxicity which would prevent further development'.

6 Source documents provided as separate PDF files

- 6.1 Wyeth review of safety data from human volunteer studies, November 2004: Alain Patat, Moxidectin human safety evaluation of studies 100 and 101.**
- 6.2 Report on moxidectin pharmacokinetics after of a single dose of 10 mg of liquid or tablet formulation**

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Summary April 2005

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The receptors tested included those for neurotransmitters and neurotransmitter-related receptors (including the γ -aminobutyric acid A receptor, i.e. the mammalian equivalent of a target of moxidectin in the parasite), ion channels (including glutamate-gated chloride channels, i.e. the mammalian equivalent of a target of moxidectin in the parasite), steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes.

Moxidectin (by itself or in the microspheres) did not significantly inhibit the binding of appropriate radio-ligands to any of these receptors, indicating a lack of binding activity for moxidectin.

These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels many fold those anticipated to be required for efficacy in onchocerciasis. (see 2004 IB, page 25 - 43).

3 Moxidectin concentrations in dogs and rats at doses used in the multiple dose toxicity studies

The results from a large number of toxicology studies ranging from single dose studies, over multiple dose (4 week, 13 week, 1 year) to 2 year carcinogenicity and three generation reproductive toxicity studies are available and summarized in the 2004 IB (page 25-43).

Fort Dodge and Wyeth Research recently conducted pharmacokinetic studies to obtain the data on the exposure of dogs and rats at the highest dose tested and/or the highest

dose that did not result in toxicologically significant findings in the 1 year dog study and the 4 week rat study.

These data are now available for comparison with exposure data in humans at the doses shown to be safe in the human volunteer studies.

1. PK data in dogs up to 28 days after a SINGLE dose of 45 ppm in the diet.

In the 1 year diet dog study, 45 ppm/day administered via the diet (appr. 1.1 mg/kg/day) was the highest dose tested and did not result in any toxicologically significant findings (see 2004 IB, page 33).

- The mean maximum serum concentration (C_{max}), area under the curve from 0 extrapolated to infinity ($AUC_{0-\infty}$) and the half life in dogs were 296 ng/ml, 861 ng day/ml and 8.3 days, respectively.

2. PK data up to 28 days in dogs administered 45 ppm of moxidectin once a day for 28 days in the diet, i.e. the dose that did not result in any toxicologically significant findings in the 1 year dog study.

- On day 28, the mean trough moxidectin serum concentration (i.e. the concentration 24 hours after the last dose) was 340 ng/mL. Based on serum levels measured after 28 days of ingesting ~1 mg/kg/day moxidectin, daily exposure during the 1-year toxicology study was estimated as 540 ng•day/mL. Over a 6-month period, this exposure results in an AUC of 98550 ng.day/mL or approximately 500 – 700 times above the reported AUC in humans after a single 9 mg dose (liquid formulation).

For comparison: a single oral dose of 36 mg (liquid formulation) to human volunteers which was safe resulted in a mean C_{max} of 290-300 ng/mL, mean $AUC_{0-\infty}$ of 450-625 ng/ml days and had a mean half life of 20-26 days (range represents means obtained for administration in fasted and fed state). A single oral dose of 10 mg (tablet formulation), i.e. close to the dose range anticipated to be required for efficacy in patients with onchocerciasis resulted in a C_{max} of 67.1 ng/ml (range (39.6-162.6 ng/ml), , $AUC_{0-\infty}$ of 68-468 ng/ml days and an average half life of 43 days. (see section 4 in this document).

3. PK data up to 28 days in rats administered daily 100 pm of moxidectin in the diet

- On day 28, the mean trough moxidectin serum concentration (i.e. the concentration 24 hours after the last dose) was 581 ng/mL.
- Based on serum levels measured after 28 days of ingesting ~5 mg/kg/day moxidectin, daily exposure during the 2-year carcinogenicity study was estimated as 1022 ng•day/mL. Over a 6-month period, this exposure results in an AUC of 186515 ng•day/mL or approximately 1000 – 1400 times above the reported AUC in humans after a single 9 mg dose.

4 New pharmacokinetic data from human volunteer study with tablet formulation developed by Wyeth for use in patients with onchocerciasis

An open label, randomized, single-dose, parallel-design study was conducted in Germany in 58 healthy young males to assess the bioavailability of the newly developed tablet formulation with that of the liquid formulation used in the First in Man study. The liquid formulation was used in the first study in man (healthy volunteers, see IB pages 45-52). The tablet formulation was developed by Wyeth for use in all subsequent studies and post registration in patients with onchocerciasis.

Each subject received either 10 mg moxidectin in solution or 10 mg of moxidectin of tablet (5 2 mg tablets). Patients were followed up for safety for 180 days post dosing. Blood

samples for moxidectin concentration measurements were obtained 0 (predose), 2, 4, 6, 8, 12, 24, 48, 72, 96 hours and 6, 8, 21, 24, 30, 90 and 180 days post dosing.

The safety data from that study are provided in the IB (page 52-60). The pharmacokinetic data have become available since the April 2004 update of the IB. The results of the non-compartmental analysis are summarized below.

PK parameter	Solution Mean (range)	Tablet Mean (range)	Comparison of formulations
Time of maximum plasma concentration	2.3 hrs (2-4 hrs)	3.2 hrs (2-6)	Ratio Tablet to Solution* 132.3 % (CI _{90%} 114.0-153.6)
Maximum plasma concentration (C _{max})	86.3 ng/ml (53.6-156.9 ng/ml)	67.1 ng/ml (39.6-162.6 ng/ml)	Ratio Tablet to Solution* 76.1% (CI _{90%} 66.8-86.7)
Terminal half-life	47.5 days (1139 hrs) (113-2334 hrs)	43.0 days (1032 hrs) (263-1815 hrs)	Non statistically significantly different
Volume of distribution (V _z /F)	3031 L (599-5774 L)	3635 L (1334-8907 L)	Not statistically significantly different
Clearance (CL/F)	2280 mL/hr (54.7L/Day) (641-4712 mL/hr)	2830 mL/hr (67.9 L/day) (890-61217 mL/hr)	Not statistically significantly different
AUC _{0-∞}	5673 ng hr/mL (2122-15601 ng hr/mL)	4403 ng hr/mL (1632-11241 ng hr/mL)	Ratio Tablet to Solution* 79.0% (CI _{90%} 63.4-98.4)

* Output from 'Bioequivalence Wizard' of software WinNonLin using default model for parallel designs. Results indicate that formulations are not bioequivalent.

The CI_{90%} values outside the range of 80-120% indicate that the two formulations are not bioequivalent.

Relative to the first study in healthy volunteers the elimination half life and the AUC_{0-∞} (adjusted for dose) are higher in this study. This is likely due to the fact that this study sampled blood over 180 days post dosing, while the first study sampled only for 90 days. In addition, the current study had 29 subjects in each arm, while the previous had 5 subjects/arm (total number of arms determined by dose and fast/fed status 6).

Conclusion

The safety profile recorded in the two clinical pharmacology studies conducted so far up to a single dose up to 36 mg did not provide any evidence of clinically relevant human toxicity which would prevent further development (see Investigator Brochure section 5.5, p. 46 ff). Comparison of the PK data obtained with those obtained at the No Toxic Effect Level in the dog and rat toxicity studies suggest that the exposure in humans is below the highest exposure that was not associated with detectable toxic effects in rats and dogs.

5 Review of safety data from 2 healthy volunteer studies by Wyeth following Proheart6 recall

During each of the two healthy volunteer (clinical pharmacology) studies, the incoming data on adverse events were reviewed by the principal investigator as well as the Wyeth medical monitor for the study. The safety data of each study were reviewed in their entirety at the end of each study for any signals of potential toxicity. The results of this review did not give rise to any concerns and are included in the Investigator brochure (page 46 ff).

Following the recall of Proheart6, Wyeth initiated yet another review of the safety data from the two human volunteer studies with special emphasis on searching for signals for

toxicity consistent with the FDA view of the safety of Proheart6. The report of this review is included in this briefing package.

All reviews of the safety data from the human studies concluded that 'the safety profile recorded in the two healthy volunteer studies to a single oral dose of 36 mg did not provide any evidence of clinically relevant human toxicity which would prevent further development'.

6 Source documents provided as separate PDF files

- 6.1 Wyeth review of safety data from human volunteer studies, November 2004: Alain Patat, Moxidectin human safety evaluation of studies 100 and 101.**
- 6.2 Report on moxidectin pharmacokinetics after of a single dose of 10 mg of liquid or tablet formulation**

Clinical Pharmacokinetics Laboratory
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Project No.:101

TITLE PAGE

Title:

Protocol No. 3110A1-101-EU

Principal Investigators(s)

Author(s)

Internal Reports/Numbers Referenced

Compound(s) Referenced: Moxidectin

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**TITLE: Analysis of Moxidectin Plasma Samples and Pharmacokinetic Analysis for
Protocol No. 3110A1-101-EU: A Study of the Relative Bioavailability of a Tablet
and Liquid Formulation of Moxidectin in Healthy Subjects**

PREPARED BY:

Name: Sayer Al-Azzam, Pharm.D.

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Date

REVIEWED/APPROVED BY:

Name: Lawrence Fleckenstein, Pharm.D.

Title: Laboratory Director/PI

Signature

Date

TITLE: Analysis of Moxidectin Plasma Samples and Pharmacokinetic Analysis for Protocol No. 3110A1-101-EU: A Study of the Relative Bioavailability of a Tablet and Liquid Formulation of Moxidectin in Healthy Subjects

SYNOPSIS

This is an open-label, randomized, single-dose, parallel-design study conducted in 58 healthy male subjects. The primary objective of the study was to determine the relative bioavailability of moxidectin administered as a tablet. All subjects were between the ages of 18 and 45 years, with normal cardiac, hematologic, hepatic and renal function. All subjects received 10 mg of moxidectin orally, either in solution or tablet form (five 2-mg tablets) in the fasted state. Pharmacokinetic samples were collected just prior to dosing and at intervals until 180 days postdose. Moxidectin plasma concentrations were determined using high-performance liquid chromatography (HPLC) with fluorescence detection. The tablet was not bioequivalent to the reference solution formulation using the confidence interval approach. The ratio of AUC_{last}, AUC_{INF}, and C_{max} for moxidectin tablets and solution was 78.9% (CI_{90%} 63.0-99.0), 79.0% (CI_{90%} 63.4-98.4), and 76.1% (CI_{90%} 66.8-86.7), respectively. The mean C_{max} for the solution was 86.3 ng/ml and 67.1 ng/ml for the tablet. The mean T_{max} for the solution was 2.3 hr and 3.2 hr for the tablet. The elimination half-life was long, with a mean half-life of 43.0-47.5 days. The mean volume of distribution (V_z/F) was relatively large, 3031 – 3635 L. The mean moxidectin plasma clearance was 54.7-67.9 L/day. In summary, the tablet

formulation was not bioequivalent to the solution. However, the tablet formulation was rapidly absorbed and produced relatively consistent bioavailability.

COMPLIANCE STATEMENT

The moxidectin analysis was conducted in accordance with the applicable Standard Operating Procedures for the Analysis Protocol: “Quantitation of Moxidectin in Human Plasma.” Lawrence Fleckenstein served as the Principal Investigator. There were no deviations which were judged to have had any significant impact on the validity of the data or interpretation of the study.

Principal Investigator

Date

QUALITY ASSURANCE

“Analysis of Moxidectin Plasma Samples and Pharmacokinetic Analysis for Protocol No. 3110A1-101-EU: A Study of the Relative Bioavailability of a Tablet and Liquid Formulation of Moxidectin in Healthy Subjects” was audited and the findings reported to the Principal Investigator by the Quality Assurance Unit as shown below. The reported results accurately reflect the raw data of the study.

Quality Assurance

Date

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LIST OF INVESTIGATORS

The investigators from the Clinical Pharmacokinetics Laboratory participating in the HPLC analysis of moxidectin specimens and pharmacokinetic analysis are listed below.

Lawrence Fleckenstein, Pharm.D. – Laboratory Director/PI

Sayer Al-Azzam, Pharm.D. – Postdoctoral Fellow, Pharmacokinetic analysis

Paul Imming, B.S. – Research Assistant, Analyst

Saroj Vangani, B.S., M.S. – Research Assistant, Analyst

She-Yi Wei, B.S., M.S. – Research Assistant, Quality Control

From the Center for Advanced Drug Development, University of Iowa.

Robin Rossignol, B.S., M.A. Quality Assurance Manager

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Pharmacokinetic Parameters

λ_z	Lambdaz. First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration.
AUCall	Area under the curve from the time of dosing (Dosing_time) to the time of the last observation. If the last concentration is non-zero AUClast=AUCall. Otherwise, AUCall will be greater than AUClast as it includes the additional area from the last measurable concentration down to zero.
AUC_%Extrap	Percentage of AUCINF that is due to extrapolation from Tlast to infinity.

$$= \frac{AUCINF - AUClast}{AUCINF} * 100$$

AUCINF	AUC from the time of dosing (Dosing_time) extrapolated to infinity. $= AUClast + \frac{Clast}{\lambda_z}$
AUCINF_D	AUCINF divided by the administered dose.
AUClast	Area under the curve from the time of dosing (Dosing_time) to the last measurable concentration.
AUMC_%Extrap.	Percent of AUMCINF that is extrapolated. $= \frac{AUMCINF - AUMClast}{AUMCINF} * 100$
AUMCINF	Area under the first moment curve (AUMC) extrapolated to infinity. $= AUMClast + \frac{tlast * Clast}{\lambda_z} + \frac{Clast}{\lambda_z^2}$
AUMClast	Area under the moment curve from the time of dosing (Dosing_time) to the last measurable concentration.
BLQ	Below limit of quantitation.
Cl, Cl/F	Total body clearance for extravascular administration. $= \text{Dose}/AUCINF$
Clast	Concentration corresponding to Tlast.
Cmax	Concentration corresponding to Tmax.
Corr(x:y)	Correlation between time (X) and log concentration (Y) for the points used in the estimation of λ_z
Dosing_time	Time of the last administered dose. This is assumed to be zero unless otherwise specified.
HL_Lambda_z	Terminal half-life = $\ln(2) / \lambda_z$
HPLC	High performance liquid chromatography

Lambdaz_lower	Lower limit on Time for values to be included in z the calculation of λ_z .
Lambdaz_upper	Upper limit on Time for values to be included in the calculation of λ_z .
MRTlast	Mean residence time from the time of dosing (Dosing_time) to the time of the last measurable concentration. $= AUMC_{last} / AUC_{last}$
MRTINF	Mean residence time (MRT) extrapolated to infinity for non-infusion models. $= AUMC_{INF} / AUC_{INF}$
No._points_ Lambda_z	Number of points used in the computation of λ_z . If λ_z cannot be estimated, this is set to 0.
NDT	No Data
NXS	No sample
Obs.	Observed
Pred.	Predicted
Rsqr	Goodness of fit statistic for the terminal elimination phase.
Rsqr (adjusted)	Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z .
Tlag	Tlag is the time prior to the time corresponding to the first measurable (non-zero) concentration.
Tlast	Time of last measurable (non-zero) concentration.
Tmax	Time of maximum observed concentration. For non steady-state data, the entire curve is considered.
Vz, Vz/F	Volume of distribution based on the terminal phase. $= \frac{Dose}{\lambda_z * AUC_{INF}}$

Bioequivalence parameters

Dependent	Dependent variable name
Form Var	Formulation Variable
FormRef	Reference value of the formulation variable
RefLSM	Least square mean for the reference treatment
RefLSM_SE	Standard error of the least square mean for the reference treatment
RefGeoLSM	Geometric least square mean for the reference treatment
Test	Test formulation
TestLSM	Least square mean for the test treatment
TestLSM_SE	Standard error of the least square mean for the test treatment
TestGeoLSM	Geometric least square mean for the test treatment
Difference	Difference in the least square means: Reference - Test
DiffSED	Standard error of the difference in least square means
DiffDF	Degrees of freedom for the difference
Ratio	Ratio of least square means: Test/Reference
CL_80_Lower	Lower limit of an 80% classical confidence interval
CL_80_Upper	Upper limit of an 80% classical confidence interval
WL_80_Lower	Lower limit of an 80% Westlake confidence interval
WL_80_Upper	Upper limit of an 80% Westlake confidence interval
CL_90_Lower	Lower limit of an 90% classical confidence interval
CL_90_Upper	Upper limit of an 90% classical confidence interval
WL_90_Lower	Lower limit of an 90% Westlake confidence interval
WL_90_Upper	Upper limit of an 90% Westlake confidence interval
CL_95_Lower	Lower limit of an 95% classical confidence interval

CL_95_Upper	Upper limit of an 95% classical confidence interval
WL_95_Lower	Lower limit of an 95% Westlake confidence interval
WL_95_Upper	Upper limit of an 95% Westlake confidence interval
Prob<80.00	t-test: Prob < 80%
Prob>125.00	t-test: Prob > 125%
MaxProb	Maximum of Prob<80.00 and Prob >120.00
TotalProb	Prob < 80% or > 120%
AHpval	Anderson-Hauck p-value
Power	Power of the ANOVA

2. ETHICS

The clinical aspects of Study number 3110A1-101EU were conducted by MDS Pharma Services Germany GmbH, Hamburg, Germany. Dr. Petra Heinemann was the Principal Investigator of the Study. The study protocol and informed consent were reviewed and approved by the MDS Pharma Services Ethics Committee

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The investigators from the Clinical Pharmacokinetics Laboratory participating in the HPLC analysis of moxidectin specimens and pharmacokinetic analysis were under the direction of Lawrence Fleckenstein, Pharm.D. – Laboratory Director/PI.

Personnel from the Clinical Pharmacokinetics participating in this study were:

Sayer Al-Azzam, Pharm.D. – Postdoctoral Fellow, Pharmacokinetic analysis

Paul Imming, B.S. – Research Assistant, Analyst

Saroj Vangani, B.S., M.S. – Research Assistant, Analyst

She-Yi Wei, B.S., M.S. – Research Assistant, Quality Control

For quality assurance, Robin Rossignol, B.S., M.A., Quality Assurance Manager, is under the direction of Dr. Alta Botha of the Center for Advanced Drug Development, University of Iowa and is administratively independent from the Clinical Pharmacokinetics Laboratory.

4. INTRODUCTION

Moxidectin is a macrocyclic lactone drug that is derived from the actinomycete *Streptomyces cyanogriseus* (e.g., milbemycin). The compound is used as a veterinary product and is used for the prevention of canine heartworm and for the treatment of internal and external parasites in cattle, sheep and horses. Moxidectin is under development for the treatment of onchocerciasis, known as river blindness, caused by the parasitic worm, *Onchocerca volvulus*.

The pharmacokinetics of moxidectin has been studied in healthy male volunteers in a single oral dose Phase I study.¹ Doses of 3, 9, 18 and 36 mg in cohorts of 6 subjects each (5:1, moxidectin:placebo) were studied. The pharmacokinetics of moxidectin was dose proportional within the dose range studied. The elimination half-life was long (mean: 20.2-35.1 days). At the 9-mg and 36-mg doses, a high-fat breakfast was shown to delay and increase the overall absorption but did not increase maximal concentrations when compared to administration in the fasting state. *In vitro* and *in vivo* metabolism

studies of moxidectin in cattle, deer, rabbit and sheep have shown that there are two principal biotransformation products in these species, most likely the C₁₄ and C₂₉ monohydroxymethyl metabolites.^{2,3} Additional studies have shown that in many of these species, cytochrome P450 3A (CYP3A) plays a major role in the biotransformations.^{3,4} The route of human moxidectin metabolism has not been established. In mass balance studies of cattle,² horses,⁵ and sheep⁶ dosed with ¹⁴C-moxidectin, the principal route of excretion was found to be the feces accounting for a high percentage of the administered dose.

Ivermectin (Stromectol[®]), structurally related to moxidectin, is currently the treatment of choice for human onchocerciasis. Moxidectin is more lipophilic than ivermectin and is therefore expected to have larger volume of distribution, a much longer half-life and duration than ivermectin after oral administration. Moxidectin is more potent than ivermectin and may also disrupt additional stages in the parasitic life cycle.

The purpose of this study was to compare the relative bioavailability of a tablet formulation to a solution formulation in healthy volunteers based on results from a single dose clinical study.

5. OBJECTIVES(S)

The primary objective was to determine the relative bioavailability of moxidectin, administered as a liquid and as a tablet. The secondary objective is to assess the safety profile of the moxidectin tablet and liquid formulations.

6. INVESTIGATIONAL PLAN

6.1 Overall Study design and Plan Description

This was an open-label, randomized, single-dose, parallel-design study conducted in a group of 58 healthy male subjects. Each subject participated in the study for approximately 7 months. Participation included a screening evaluation within 3 weeks before test article administration, a 3-day inpatient period, and a 180-day follow-up period. The end of study evaluation was performed 180 days after the dose administration (on the last PK blood sample collection). A parallel design was chosen in view of the long half-life of moxidectin (20-30 days in humans) and the consequent lack of feasibility for conducting a crossover trial.

6.2 Study Population/Entry Criteria

All subjects gave informed consent prior to participation in study-specific screening procedures. The study population consisted of men aged 18 to 45 years, inclusive. Body mass index was in the range of 18 to 30 kg/m² and body weight was ≥ 50 kg. Subjects were determined healthy by the investigator on the basis of a medical history and physical examination, laboratory test results, vital signs, and 12-lead ECG. Laboratory test results for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and creatinine had to be within the normal range. Subjects

were nonsmokers or smoked fewer than 10 cigarettes per day as determined by history.

Subjects were required to abstain from smoking during the inpatient stay.

Subjects were excluded from the study by the following criteria

Medical History

1. Presence or history of any neuropsychiatric disorder that may prevent the successful completion of the study.
2. History of epilepsy or seizure disorder (except history of childhood febrile seizures).
3. Any surgical or medical condition that could interfere with the absorption, distribution, metabolism or excretion of the test article.
4. Acute disease state (e.g., nausea, vomiting, diarrhea) within 7 days of study day -1.
5. Alcohol abuse or consumption of more than 50 g of ethanol per day.

Physical and Laboratory Findings

6. Any clinically important deviation from normal limits in physical examination, vital signs, or clinical laboratory test results.
7. Positive serologic findings for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), and /or hepatitis C virus (HCV) antibodies.
8. Positive urine drug screen at screening examination.

Allergies and Adverse Drug Reactions

9. History of any clinically important allergy.

Prohibited Treatments

10. Use of any investigational or prescription drug within 30 days of dose administration.
11. Consumption of any caffeine-containing products, grapefruit, grapefruit-containing products, or alcoholic beverages within 48 hours before study day -1.
12. Use of any over-the-counter drugs (except the occasional use of acetaminophen and vitamins $\geq$ 100% recommended daily allowance).
13. Donation of blood within 90 days of study day -1.

6.3 Treatments

Subjects were admitted to the study unit on day -1. On study day 1, subjects are randomly assigned to receive either 10 mg moxidectin in solution or 10 mg moxidectin in tablet form at approximately 8 AM. A predose blood sample is taken prior to drug administration. Blood samples are taken for PK analysis on study day 1 at 2, 4, 6, 8, and 12 hours. Blood samples for PK analysis are also taken on study days 2 (24 hours post-dose), 3 (48 hr), 4 (72 hr), 5 (96 hr), 6, 8, 21, 24, 30, 90 and 180.

Intake of any food or beverage (excluding water) was prohibited during the first 2 hours after moxidectin administration. Beginning at 2 hours after moxidectin administration, standardized medium-fat meals and snacks were served until discharge from the unit on study day 3. Alcohol, nicotine, grapefruit juice and grapefruit-containing products were prohibited beginning 48 hours before study day -1 and throughout the inpatient period of the study.

The test articles were supplied as vials containing 200 mL of 1% (1 g/100 mL) IV solution and 2-mg tablets. For the solution, a syringe was prepared for each subject. One mL of the moxidectin solution was drawn into the syringe and 14 mL of sterile water was drawn into another syringe. The syringe containing moxidectin and the volume of sterile water were emptied into a small container and the subject drank the contents of the container. An additional thirty mL of sterile water drawn into a syringe was used to rinse the container and was then swallowed by the subject. Then each subject drank an additional volume of approximately 170 mL of sterile water. Moxidectin tablets were supplied for each subject as 5 x 2-mg dose strengths. Subjects swallowed the tablets with approximately 240 mL water.

6.4 Collection of Specimens for Analysis

Blood (10 mL) for moxidectin analysis was collected into single evacuated blood tubes containing sodium heparin. The blood collection tube was placed immediately on wet ice and then centrifuged at 1500 ×g for 10 minutes in a refrigerated centrifuge within 15 minutes after collection. The plasma was harvested and distributed evenly into two labeled polypropylene containers. The aliquots were stored frozen at approximately -70°C until shipped for analysis to the Clinical Pharmacokinetics Laboratory. The containers were shipped in watertight plastic bags in insulated shipping containers packed with drug ice. The plasma samples were shipped by World Courier air express service along with an inventory of the specimens. Upon receipt by the Clinical Pharmacokinetics Laboratory, the samples were inventoried and logged into the -80°C freezer and stored frozen until analysis by HPLC.

6.5 Bioanalytical Methodology

Moxidectin plasma concentrations were determined using high-performance liquid chromatography (HPLC) with fluorescence detection, as previously described.⁷ Briefly, the method used solid-phase extraction and fluorescent derivatization with trifluoroacetic anhydride and N-methylimidazole. Separation was achieved on a Symmetry C₁₈ column, 5 μ m particle size, 250 mm $\times$ 4.6 mm (Waters, Milford, MA), with a mobile phase of tetrahydrofuran-acetonitrile-water (40:38:22 v/v/v). The method used 200 μ L of plasma, and the lower limit of quantitation was 0.2 ng/mL. The validation of the method has been previously reported in the study report, entitled: “Validation of an LC Method for the Determination of Moxidectin in Human Plasma.”

6.6 Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters were calculated by noncompartmental analysis. The noncompartmental analysis was done using Model 200 in WinNonlin Professional (version 4.1, Pharsight Corporation, Mountain View, CA). Peak plasma concentration (C_{max}) and time to peak concentration (T_{max}) were determined after each treatment without interpolation. The log-linear portion of the last 4-5 points of each set of plasma concentrations was used to determine the terminal phase hybrid constant, λ_z (Lambdaz)

AUC_{INF} values were the sum of AUC_{last} and AUC extrapolated to infinity. The AUC_{last} was calculated by summation of each individual area between two consecutive time intervals from time 0 to the last measurable concentration (C_{last}) using the linear

trapezoidal rule. AUC extrapolated was calculated by dividing C_{last} by λ_z . Plasma half-life was calculated as $T_{1/2} = \ln(2) / \lambda_z$.

The first moment curve was constructed by the time course data obtained by multiplying the plasma concentration with the corresponding time point. The trapezoidal rule was then used to obtain the area under the first moment curve (AUMC). AUMCINF, the area under the first moment curve extrapolated to infinity, was calculated as:

$$= AUMC_{last} + \frac{t_{last} * C_{last}}{\lambda_z} + \frac{C_{last}}{\lambda_z^2}$$

Mean residence time extrapolated to infinity (MRTINF) was calculated as AUMCINF/AUCINF. Volume of distribution based on the terminal phase V_z/F , where F is the fraction of the dose absorbed, was calculated as:

$$= \frac{Dose}{\lambda_z * AUCINF}$$

Total body clearance for extravascular administration was calculated by dividing dose by AUCINF.

Pairwise comparisons of un-transformed age, weight, and pharmacokinetic parameters between treatment groups were conducted using *t*-tests. Significance level was set at $p < 0.05$ for all analyses.

Bioequivalence was calculated using the Bioequivalence Wizard in WinNonlin, using the default model for parallel designs. For parallel designs the fixed effects model

is formulation and there is no random model and no repeated specification, so the residual error term is included in the model.

6.7 Data Quality Assurance

Quality control and assurance checks are made on all analytical results. Information in the laboratory notebooks are reviewed and verified against source documents. Data are reviewed for legibility, completeness and logical consistency. Analytical results have been fully audited against the corresponding source documents.

7. STUDY POPULATION

Fifty-eight healthy male volunteers fulfilled entry criteria and were enrolled in the bioequivalence study. The ages and weights of the two study groups were similar (Tables 11.1.1 and 11.1.2). The mean age of volunteers that received oral solution was 33.5 years (range 21-44) and the mean age of volunteers receiving moxidectin tablets was 33.9 (range 22-46). The mean body weight for the solution treatment was 81.8 (range 57.9-107.2) and the mean weight for the moxidectin tablet group was 82.1 kg (range 59.7-103.5). No statistical difference was found in age or weight between the solution and tablet groups.

8. PHARMACOKINETIC RESULTS

Figure 11.2.1 illustrates the mean plasma concentration-time profiles of the two moxidectin test formulations. Figure 11.2.2 shows an expanded scale of the first 8 days

after drug administration. Figures 11.2.3-11.2.60 show the individual plasma concentration-time profiles of moxidectin for subjects 1-60.

The pharmacokinetic parameters from the noncompartmental analysis are displayed in Tables 11.1.18-11.1.33. The mean T_{max} for the solution was 2.3 hr (range 2.0-4.0 hr, Table 11.1.22) and for the tablet was 3.2 hr (range 2.0-6.0 hr, Table 11.1.23). The mean C_{max} was for the solution was 86.3 ng/mL (range 53.6-156.9 ng/mL, Table 11.1.22) and for the tablet was 67.1 ng/mL (range 39.6-162.6 ng/mL, Table 11.1.23).

The elimination of moxidectin is prolonged as indicated by the terminal half-life observed for the solution and the tablet. The mean terminal half-life (HL_{λ_z}) for the solution was 1139 hr or 47.5 days (range 113 -2334 hr) and for the tablet was 1032 or 43.0 days (range 263-1815 hr) as shown in Tables 11.1.20 and 11.1.21. No statistical difference was found in half-life between the solution and tablet groups.

The distribution of moxidectin in the body is extensive as indicated by the large mean V_z/F values observed for the solution and the tablet. The mean volume of distribution (V_z/F_{obs}) for the solution was 3031 L (range 599 -5774 L) and for the tablet was 3635 L (range 1334-8907 L) as shown in Tables 11.1.26 and 11.1.27. No statistical difference was found in V_z/F between the solution and tablet groups.

The clearance estimations for the moxidectin formulations are displayed in Tables 11.1.26 and 11.1.27. The mean moxidectin plasma clearance (CL/F) for the solution was

2280 mL/hr or 54.7 L/day (range 641-4712 mL/hr). The mean plasma clearance for the tablet was 2830 mL/hr or 67.9 L/day (range 890-6127 mL/hr). No statistical difference was found in CL/F between the solution and tablet groups.

Bioequivalence analysis. The AUC data are displayed in Tables 11.1.24 and 11.1.25. The mean moxidectin AUC calculated to the last measured concentration (AUClast) for the solution was 4756 ng-hr/mL (range 1679-13841 ng-hr/mL). The mean AUClast for the tablet was 3769 ng-hr/mL (range 1354-10787 ng-hr/mL). AUC calculated from time zero to infinity (AUCINF_obs) for the solution was 5673 ng-hr/mL (range 2122-15601 ng-hr/mL). The mean AUCINF_obs for the tablet was 4403 ng-hr/mL (range 1632-11241 ng-hr/mL).

The MRT data are displayed in Tables 11.1.32 and 11.1.33. The mean MRTINF_obs for the solution was 1239 hr (range 85.2-2806 hr) and for the tablet was 1069 hr (range 265-2204 hr). The AUMCINF data are displayed in Tables 11.1.30 and 11.1.31). The mean AUMCINF_obs for the solution was 8436200 ng-hr²/mL (range 231783-26702904 ng-hr²/mL) and for the tablet was 5344149 ng-hr²/mL (range 519981-21518687 ng-hr²/mL).

The CI_{90%} of C_{max}, as well as those of AUClast and AUCINF, did not fall within the range of 80% to 120% of the mean of the solution formulation after LN transformation (Table 11.1.34). The ratio of AUClast, AUCINF, and C_{max} for moxidectin tablets and solution was 78.9% (CI_{90%} 63.0-99.0), 79.0% (CI_{90%} 63.4-98.4),

and 76.1% (CI_{90%} 66.8-86.7), respectively. Thus, these two formulations cannot be considered bioequivalent.

9. DISCUSSION AND OVERALL CONCLUSIONS

In a previous Phase 1 study of oral moxidectin, the pharmacokinetics was studied at doses of 3, 9, 18, and 36 mg in healthy male volunteers.¹ There were 5 subjects per dose that received moxidectin as an oral solution. The pharmacokinetics of moxidectin was dose proportional within the dose range studied. Compared to the previous report, we found a longer elimination half-life in this study. The previous study reported a mean elimination half-life of 20.2 – 35.1 days and we found an elimination half-life of 47.5 days. The major difference in the 2 studies is that the current study sampled plasma for moxidectin analysis for 180 days postdose, whereas the previous study only sampled for a period of 80 days postdose. Some subjects in the current study had elimination half-lives as long as 76-97 days. Thus, sampling over 180 days allowed for a more accurate estimation of half-life, since characterization of the elimination half-life done over a period of approximately 2 half-lives for all subjects.

The extended plasma sampling over 180 days in this study in this study allowed us to capture a large percentage of the AUC over the sampling interval. Only 15.7% and 15.6% of the AUC was extrapolated for the solution and the tablet formulations, respectively. The AUC (adjusted for dose) was higher in the current study compared to the previous human Phase I study. We feel that the primary explanation for this difference relates to the prolonged sampling strategy used in this study compared to the

previous one. In addition, the current study had a substantially larger number of subjects per group (n = 29), compared to a limited sample size (n=5) in the previous study.

Compared to the previous human study, the values for volume of distribution were similar to the results of this study. The previous Phase 1 study reported a mean volume of distribution of 3549 and 2439 L for the 9 mg and 18 mg fasted dose groups, respectively. In the current study, we found a mean volume of distribution of 3031 L for the 10 mg fasted dose group that received oral solution. For clearance (CL/F), the previous human study found a mean clearance of 72.9 and 75.9 L/day (n=5) for the 9 and 18 mg fasted dose groups, respectively. For the current study a mean clearance of 54.7 L/day (n=29) was estimated for the 10 mg fasted dose group that received the oral solution. The lower clearance in the current study is a reflection of the higher AUC's determined as a result of the extended plasma sampling.

Moxidectin absorption is relatively rapid and the drug has a very pronounced distribution phase. The mean Tmax for the solution formulation in the current study was 0.096 days compared with 0.075 and 0.083 days for the 9 and 18 mg fasted dose groups in the earlier study, respectively. Thus, the mean Tmax values were similar in the two studies. Both studies had the initial sampling at 2 hours, which may have missed the Tmax for some individuals. The mean Cmax was for the solution formulation in the current study was 86.3 ng/ml compared with 57.9 and 141 ng/ml for the 9 and 18 mg fasted dose groups of the earlier study, respectively. The Cmax, on a dose adjusted basis, is slightly higher in the current study. However, considering the rapid rates of absorption

and distribution rates for moxidectin and the limited sampling around the peak concentration, the C_{max} determination for both studies is reasonably consistent.

Conclusion: Compared to the previous study, differences in pharmacokinetic parameters of half-life, AUC and clearance are attributed to the extended plasma sampling and more complete characterization of the elimination phase of moxidectin. The other pharmacokinetic parameters of V_z, T_{max} and C_{max} obtained in the current study are similar to those reported previously.

This study did not establish bioequivalence between the solution and tablet formulations of moxidectin studied. However, the tablet formulation is rapidly absorbed and produces relatively consistently bioavailability. Variability in the absorption of the tablet, as reflected in the AUC, is approximately the same order of magnitude as that observed for the solution formulation.

10. REFERENCE LIST

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11. SUPPORTIVE TABLES AND FIGURES

11.1 TABLES

11.1.1 Subject Age and Weight – Solution Formulation (Formulation A)

Subject	Age (yr.)	Weight (kg)
1	32	83.0
3	39	90.8
6	30	78.4
7	35	57.9
10	38	98.6
12	26	59.7
13	37	83.6
15	35	107.2
18	24	82.2
20	28	73.7
21	42	73.9
24	32	67.4
26	37	84.6
27	33	90.9
30	39	91.3
31	36	85.2
33	23	66.6
36	35	65.9
38	30	82.4
40	36	92.1
44	30	84.4
46	34	90.1
47	44	86.5
49	21	75.6
52	35	78.1
53	26	83.9
55	36	84.1
58	34	90.1
59	44	83.0
Mean	33.5	81.8
SD	5.9	11.1
Max	44	107.2
Min	21	57.9

11.1.2 Subject Age and Weight – Tablet Formulation (Formulation B)

Subject No.	Age (yr.)	Weight (kg)
2	44	81.3
4	33	91.6
5	32	73.4
8	41	83.6
9	29	73.6
11	38	73.0
14	46	93.1
16	32	95.3
17	34	87.0
19	37	93.8
22	40	81.2
23	24	82.2
25	40	82.2
28	38	80.1
29	24	75.7
32	29	78.7
34	22	80.1
35	23	59.7
37	27	89.9
39	45	65.5
43	32	81.7
45	44	77.9
48	40	68.6
50	29	88.0
51	30	91.7
54	29	103.5
56	41	87.4
57	22	67.8
60	38	92.5
Mean	33.9	82.1
SD	7.4	10.0
Max	46	103.5
Min	22	59.7

11.1.3 Moxidectin time and concentration data for subjects 1-4Subject 1
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	69.8
4	4	65.1
6	6	53.5
8	8	45.7
12	12	29.0
24	24	12.8
48	48	5.3
72	72.083	3.5
96	96	2.5
144	120	2.1
192	168.067	1.8
504	480.083	1.4
576	552	1.5
720	696	1.0
2160	2136	0.7
4320	4296	0.2

Subject 2
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	87.8
4	4	89.4
6	6	64.9
8	8	60.1
12	12	32.5
24	24	13.7
48	48	5.8
72	72	4.1
96	96	3.7
144	120	3.4
192	168.133	3.0
504	480	2.4
576	552	1.5
720	696	2.0
2160	2136	0.8
4320	4296	0.4

Subject 3
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	127.4
4	4	104.7
6	6	85.5
8	8	121.2
12	12	51.4
24	24	25.5
48	48	11.2
72	72	7.1
96	96	9.4
144	120	4.6
192	168.117	3.8
504	480	1.8
576	552	2.8
720	696	2.4
2160	2136	0.9
4320	4296	BLQ

Subject 4
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	21.8
4	4	48.6
6	6	48.8
8	8	40.1
12	12	27.9
24	24	12.7
48	48	5.7
72	71.95	3.3
96	96	2.1
144	120	2.4
192	168.117	1.7
504	479.983	1.2
576	552	1.2
720	696	0.9
2160	2136	0.4
4320	4296	BLQ

11.1.4 Moxidectin time and concentration data for subjects 5-8Subject 5
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	162.6
4	4	123.9
6	6	93.6
8	8	74.6
12	12	49.8
24	24	20.8
48	48	12.4
72	72	8.7
96	96	8.6
144	120.267	8.0
192	168.1	7.1
504	479.983	4.3
576	552	3.4
720	696	3.2
2160	2136	1.5
4320	4296	0.3

Subject 6
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	NDT
4	4	83.1
6	6	68.2
8	8.0167	56.8
12	12	41.7
24	24	19.9
48	48.017	10.1
72	72	7.1
96	96	3.4
144	120	4.5
192	168.083	3.2
504	479.967	2.6
576	552	2.0
720	719.383	2.5
2160	2136	0.9
4320	4296	0.3

Subject 7
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	76.3
4	4	63.0
6	6	59.1
8	8	46.0
12	12	31.7
24	24	14.1
48	48	6.7
72	72	4.5
96	96	3.5
144	120	3.1
192	168.133	2.6
504	479.983	1.6
576	552	1.4
720	696	1.2
2160	2160	BLQ
4320	4320	BLQ

Subject 8
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	65.8
4	4	46.6
6	6	35.7
8	8	28.3
12	12	18.6
24	24	8.6
48	48	4.9
72	72	3.5
96	96	2.9
144	120.033	2.8
192	168.117	2.4
504	479.983	1.8
576	552	1.5
720	696	1.3
2160	2136	0.5
4320	4320	BLQ

11.1.5 Moxidectin time and concentration data for subjects 9-12Subject 9
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	35.1
4	4	39.6
6	6	30.4
8	8	25.6
12	12	16.1
24	24	9.5
48	48	5.1
72	72	3.0
96	96	2.5
144	120.033	2.3
192	168.1	1.9
504	480	1.2
576	552	0.9
720	696	0.8
2160	2160	BLQ
4320	4320	BLQ

Subject 10
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	72.2
4	4	71.0
6	6	59.5
8	8	43.9
12	12	28.9
24	24	12.4
48	48	5.8
72	72	3.7
96	96	3.0
144	120.017	3.2
192	168.083	2.4
504	480	1.6
576	552	1.6
720	696	1.3
2160	2136.017	0.9
4320	4296.033	0.2

Subject 11
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	49.9
4	4	45.5
6	6	38.6
8	8	31.7
12	12	20.3
24	24	10.6
48	48	5.3
72	72	4.0
96	96	2.8
144	120.117	2.6
192	168.083	2.1
504	480	1.4
576	552	1.1
720	696	0.9
2160	2139.067	BLQ
4320	4296	BLQ

Subject 12
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	92.2
4	4	96.8
6	6	91.6
8	8	87.5
12	12	63.8
24	24	33.5
48	48	13.8
72	72	11.2
96	96	11.0
144	120	9.5
192	168.067	8.9
504	480	4.7
576	552	4.8
720	696	3.6
2160	2136	2.2
4320	4296	0.8

11.1.6 Moxidectin time and concentration data for subjects 13-16Subject 13
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	72.8
4	4	59.7
6	6	52.5
8	8	48.7
12	12	27.2
24	24	12.8
48	48	5.5
72	72.05	3.3
96	96	2.7
144	120.017	4.9
192	168.083	2.4
504	480	1.6
576	552	1.1
720	696	0.8
2160	2136	0.5
4320	4296.017	BLQ

Subject 14
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	89.5
4	4	75.7
6	6	54.7
8	8	45.6
12	12	29.5
24	24	11.5
48	48	5.3
72	72	3.5
96	96	5.1
144	120	3.7
192	168.083	3.9
504	480	3.3
576	552	2.4
720	696	2.0
2160	2136	1.6
4320	4296	0.6

Subject 15
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	75.3
4	4	72.5
6	6	59.5
8	8	45.9
12	12	26.9
24	24	16.7
48	48	5.1
72	72	3.2
96	96.017	2.0
144	120.067	2.9
192	168	2.2
504	480	1.9
576	552	1.4
720	696	1.3
2160	2136	0.7
4320	4296	0.4

Subject 16
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	53.7
4	4	37.6
6	6	33.5
8	8	24.4
12	12	18.5
24	24	16.6
48	48	4.1
72	72	2.7
96	96	1.8
144	120	1.6
192	168	1.3
504	480	0.9
576	552	0.9
720	696	0.4
2160	2136	0.4
4320	4296	BLQ

11.1.7 Moxidectin time and concentration data for subjects 17-20Subject 17
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	66.1
4	4	55.2
6	6	37.4
8	8	28.1
12	12	16.3
24	24	7.9
48	48	5.7
72	72	5.0
96	96	4.7
144	120	3.0
192	168	2.9
504	480	2.0
576	552	1.6
720	696	1.7
2160	2136	0.7
4320	4296	BLQ

Subject 18
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	140
4	4	71.6
6	6	70.6
8	8	68.9
12	12	37.9
24	24	27.8
48	48	11.5
72	72	7.9
96	96	5.4
144	120	5.0
192	168	4.9
504	480	2.3
576		NSX
720	695.233	1.5
2160	2138.4	1.0
4320	4296	0.4

Subject 19
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	41.1
4	4	39.2
6	6	36
8	8	30.3
12	12	19.4
24	24	14.0
48	48.017	7.2
72	72	4.3
96	96	2.4
144	120	2.9
192	168	2.0
504	480.017	1.5
576	552	1.1
720	696	0.9
2160	2159.583	0.6
4320	4296	0.2

Subject 20
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	103.8
4	4	77.8
6	6	63.6
8	8	51.7
12	12	35.8
24	24	22.7
48	48.067	6.6
72	72	5.2
96	96	3.8
144	120.017	3.6
192	168.05	3.6
504	482.967	3.0
576	552	2.6
720	696	1.3
2160	2136	0.9
4320	4296	BLQ

11.1.8 Moxidectin time and concentration data for subjects 21-24Subject 21
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	134.4
4	4	116.4
6	6	104.5
8	8	71.1
12	12	42.3
24	24	28.4
48	48.05	11.6
72	72	9.6
96	96	7.4
144	120	6.5
192	168.083	5.2
504	480	5.6
576	552	3.9
720	696.017	2.7
2160	2136	1.8
4320	4296	BLQ

Subject 22
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	58.1
4	4	53.7
6	6.017	46.8
8	8	45.0
12	11.95	40.2
24	24	25.1
48	48.017	10.1
72	72	8.0
96	96	2.7
144	120	3.3
192	168	2.4
504	479.983	1.7
576	552	1.7
720	696.1	1.2
2160	2136	0.9
4320	4296	BLQ

Subject 23
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	145.1
4	4	121.0
6	6	120.6
8	9	105.9
12	12	77.9
24	24	67.8
48	48	42.1
72	72	39.8
96	96	10.2
144	120.017	3.3
192	168.033	3.9
504	480	1.6
576	552	1.3
720	696	1.0
2160	2136	0.5
4320	4296	BLQ

Subject 24
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	156.9
4	4	72.2
6	6	60.6
8	8	40.3
12	12	21.4
24	24	21.4
48	48	18.1
72	72.083	7.8
96	96.017	4.3
144	120	4.2
192	168.05	2.4
504	480	0.6
576	552	0.2
720	696	BLQ
2160	2136	BLQ
4320	4294.6	BLQ

11.1.9 Moxidectin time and concentration data for subjects 25-28Subject 25
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	32.3
4	4	85.1
6	6	79.1
8	8	65.8
12	12	40.8
24	24	17.3
48	48	7.9
72	72	5.1
96	96	3.7
144	120.017	3.7
192	168.067	2.5
504	480.017	1.8
576	552	1.6
720	696	1.5
2160	2140.283	1.0
4320	4342.167	0.3

Subject 26
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	80.9
4	4	69
6	6	49.7
8	8	39.3
12	12	26.7
24	24	12.8
48	48	6.5
72	72	3.9
96	96	3.3
144	120	2.9
192	168.083	2.8
504	480.017	1.9
576	552	1.8
720	696	1.7
2160	2136	1.0
4320	4296.083	0.6

Subject 27
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	76.4
4	4	59.4
6	6	44.2
8	8	37.7
12	12	27.1
24	24	12.6
48	48	6.8
72	72	4.5
96	96	3.3
144	120	2.6
192	168.067	2.6
504	480.117	1.6
576	552	1.6
720	696	1.3
2160	2136	0.5
4320	4296	BLQ

Subject 28
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	72.2
4	4	66.9
6	6	50.6
8	8	47.9
12	12	28.7
24	24	16.6
48	48	6.4
72	72	4.6
96	96	3.6
144	120	3.2
192	168.35	2.4
504	480.017	1.6
576	551	1.5
720	696.05	1.6
2160	2136	0.6
4320	4295.25	0.2

11.1.10 Moxidectin time and concentration data for subjects 29-32Subject 29
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	70.3
4	4	79.1
6	6	72.9
8	8	55.0
12	12	34.6
24	24	17.1
48	48	7.7
72	72	6.5
96	96	5.6
144	120	4.2
192	168.033	3.9
504	505.167	1.8
576	552.45	1.7
720	696	1.5
2160	2136.017	0.2
4320	4297.45	BLQ

Subject 30
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	78.2
4	4	60.1
6	6	41.6
8	8	31.8
12	12	19.4
24	24	9.6
48	48	4.6
72	72	3.3
96	96	3.1
144	120	2.4
192	168.033	1.8
504	480	1.3
576	552.033	1.3
720	696.033	1.3
2160	2136	0.5
4320	4296	BLQ

Subject 31
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	60.8
4	4	61.1
6	6	39.8
8	8	33.7
12	12	21.8
24	24	8.1
48	48	4.5
72	72	2.2
96	96	2.2
144	120	1.9
192	168	1.6
504	480	1.0
576	552.033	0.9
720	696	0.9
2160	2136	0.3
4320	4296	BLQ

Subject 32
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	59.4
4	4	63.5
6	6	39.0
8	8	29.5
12	12	21.7
24	24	11.1
48	48	4.8
72	72	3.5
96	96	2.6
144	120	2.4
192	168	1.6
504	480	1.0
576	552	1.0
720	696	0.8
2160	2136	0.3
4320	4296	BLQ

11.1.11 Moxidectin time and concentration data for subjects 33-36Subject 33
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	61.5
4	4	54.9
6	6	43.0
8	8	38.9
12	12	24.6
24	24	13.8
48	48	7.1
72	72	5.3
96	96	4.2
144	120	3.3
192	168	2.8
504	480	1.1
576	552	0.8
720	696	0.7
2160	2136	BLQ
4320	4298.083	BLQ

Subject 34
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	48.8
4	4	42.0
6	6	30.4
8	8	26.1
12	12	16.6
24	24	9.2
48	48	4.8
72	72	3.7
96	96	3.4
144	120	3.5
192	168	2.7
504	480	1.7
576	552	1.4
720	696	1.3
2160	2136	0.3
4320	4296	BLQ

Subject 35
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	50.6
4	4	58.1
6	6	45.1
8	8	29.8
12	12	22.5
24	24	12.8
48	48	6.4
72	72	5.1
96	96	3.8
144	120	3.5
192	168	2.8
504	480	0.9
576	552.083	1.1
720	696	0.8
2160	2136	BLQ
4320	4296	BLQ

Subject 36
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	82.3
4	4	72.9
6	6	49.9
8	8	38.4
12	12	23.2
24	24	10.9
48	48	5.5
72	72	4.4
96	96	3.8
144	120	3.3
192	168	2.6
504	480	1.1
576	552	1.5
720	696	1.0
2160	2137.95	BLQ
4320	4296	BLQ

11.1.12 Moxidectin time and concentration data for subjects 37-40Subject 37
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	55.8
4	4	51.0
6	6	37.2
8	8	29.7
12	12	18.3
24	24	8.5
48	48	3.6
72	72	2.6
96	96	2.0
144	120	1.5
192	168	1.3
504	480	0.9
576	552.017	1.2
720	696	0.7
2160	2136.367	0.3
4320	4296	BLQ

Subject 38
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	66.8
4	4	69.1
6	6	64.9
8	8	51.6
12	12	36.6
24	24	18.0
48	48.05	7.8
72	72	6.2
96	96	4.6
144	120	3.8
192	168	2.9
504	480	2.0
576	552	2.0
720	696	1.8
2160	2136	1.0
4320	4296.067	0.5

Subject 39
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	60.6
4	4	61.5
6	6	40.6
8	8	30
12	12	19.1
24	24.017	9.1
48	48	4.5
72	72	3.0
96	96	2.2
144	120	2.1
192	168	2.2
504	480	1.0
576	552	0.9
720	696	0.7
2160	2136	BQL
4320	4296.017	0.2

Subject 40
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	91.5
4	4	82.4
6	6	56
8	8	49.5
12	12	27.9
24	24	11.4
48	48.033	5.7
72	72	3.7
96	96	3.5
144	120	2.8
192	168	2.5
504	480	1.5
576	552.017	1.5
720	696	1.5
2160	2136	0.9
4320	4297.217	0.5

11.1.13 Moxidectin time and concentration data for subjects 43-46Subject 43
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	62.9
4	4	51.0
6	6	34.0
8	8	29.3
12	12	34.8
24	24	9.0
48	48	4.5
72	72	3.3
96	96	2.7
144	120	2.4
192	168	1.9
504	480	0.9
576	552.017	0.9
720	696.017	0.8
2160	2136	BLQ
4320	4296	BLQ

Subject 44
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	78.6
4	4	64.9
6	6	46.0
8	8	35.3
12	12	23.6
24	24.017	13.3
48	48	6.5
72	72	5.1
96	96	3.4
144	120	3.4
192	168	2.8
504	480	2.5
576	552	1.5
720	696	1.1
2160	2136	0.3
4320	4296	BLQ

Subject 45
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	47.2
4	4	48.9
6	6	33.3
8	8	23.3
12	12	14.5
24	24	7.2
48	48	4.0
72	72	2.9
96	96	2.3
144	120	1.9
192	192	1.4
504	480	0.6
576	552	0.6
720	696	0.6
2160	2136	BLQ
4320	4296	BLQ

Subject 46
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	68.5
4	4	47.5
6	6	34.6
8	8	29.6
12	12	19.3
24	24.017	10.6
48	48.05	4.4
72	72.017	3.1
96	96	2.2
144	120	2.0
192	168	1.5
504	480	1.0
576	552	1.1
720	696	1.0
2160	2136	0.5
4320	4439.967	BLQ

11.1.14 Moxidectin time and concentration data for subjects 47-50Subject 47
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	101.6
4	4	90.3
6	6	71.3
8	8	61.8
12	12	46.9
24	24	23.6
48	48	10.4
72	72.033	7.3
96	96	7.0
144	120	6.3
192	168	4.8
504	480	2.9
576	552	3.3
720	696	2.8
2160	2136	1.2
4320	4296	0.7

Subject 48
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	60.1
4	4	68.1
6	6	53.2
8	8	43.9
12	12	24.7
24	24	14.4
48	48	7.3
72	72	6.2
96	96	4.6
144	120	3.6
192	168	2.7
504	480	1.6
576	552	1.4
720	696	1.0
2160	2137.7	0.3
4320	4298.733	BLQ

Subject 49
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	56.6
4	4	47.8
6	6	37.8
8	8	25
12	12	15
24	24	7.6
48	48	4.4
72	72.05	3.1
96	96	2.8
144	120	2.4
192	168.017	2.0
504	486.183	1.1
576	552	0.9
720	696.017	0.8
2160	2136	BLQ
4320	4296	BLQ

Subject 50
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	38.9
4	4	46.4
6	6	31.6
8	8	45.5
12	12	31.3
24	24	12.9
48	48	5.8
72	72	3.7
96	96	3.1
144	120	2.5
192	168	1.8
504	480	1.5
576	552	1.3
720	696.017	1.1
2160	2136	0.5
4320	4296	BLQ

11.1.15 Moxidectin time and concentration data for subjects 51-54Subject 51
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	41.6
4	4	48.3
6	6	59.2
8	8	34
12	12	27.7
24	24	10.2
48	48	4.4
72	72	3
96	96	1.9
144	120.167	1.7
192	168	1.5
504	480	1.0
576	552	0.9
720	696	0.9
2160	2136	0.3
4320	4296	BLQ

Subject 52
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	105.9
4	4	76.1
6	6	45.8
8	8	38.3
12	12	26.2
24	24	12.8
48	48	6.4
72	72	4.0
96	96	3.2
144	120	2.7
192	168	2.1
504	480	1.7
576	552	1.5
720	696	1.3
2160	2136	0.5
4320	4296	BLQ

Subject 53
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	85.5
4	4	61.2
6	6	27.4
8	8	43.4
12	12	31.5
24	24	14.1
48	48	6.7
72	72	4.8
96	96	3.1
144	120	2.7
192	168	2.3
504	480.183	1.7
576	552	1.9
720	696.017	1.5
2160	2136	0.5
4320	4296	BLQ

Subject 54
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	51.6
4	4	40.4
6	6	52.2
8	8	18.9
12	12	10.0
24	24	4.6
48	48	2.3
72	72	1.6
96	96	1.2
144	120.167	1.1
192	168	0.9
504	480.5	0.7
576	552	0.7
720	696.817	0.7
2160	2136	0.4
4320	4680.917	BLQ

11.1.16 Moxidectin time and concentration data for subjects 55-58Subject 55
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	53.6
4	4	47.7
6	6	46.1
8	8	32.3
12	12	23.7
24	24	11
48	48	5.1
72	72	4.0
96	98.633	2.8
144	120	2.3
192	168	2.0
504		NXS
576	552	1.1
720	696	1.2
2160	2136	0.7
4320	4296	0.3

Subject 56
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	28.9
4	4	61.4
6	6	38.8
8	8	44.7
12	12	27
24	24	12.3
48	48	5.3
72	72	4.3
96	96	2.5
144	120	2.1
192	168	1.9
504	480	1.3
576	552	1.3
720	696	1.2
2160	2136	0.6
4320	4296	0.3

Subject 57
Formulation B

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	61.2
4	4	44.0
6	6	55.8
8	8	31.9
12	12	19.5
24	24	11.2
48	48	5.2
72	72	3.9
96	96	3.2
144	120	2.8
192	168	2.1
504	480	1.1
576	552	1.0
720	696	0.8
2160	2136	BLQ
4320	4296.05	BLQ

Subject 58
Formulation A

Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL
2	2	65.9
4	4	44.5
6	6	28.8
8	8	27.4
12	12	20.8
24	24	8.5
48	48	3.2
72	72.083	2.5
96	96	1.7
144	120	1.4
192	168	1.3
504	503.9	0.8
576	552.117	0.7
720	696	0.7
2160	2136	0.3
4320	4296.017	BLQ

11.1.17 Moxidectin time and concentration data for subjects 59-60

Subject 59 Formulation A			Subject 60 Formulation B		
Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)	Protocol Time (h.)	Actual Time (h.)	Concentration (ng/mL)
Predose	Predose	BQL	Predose	Predose	BQL
2	2	77.3	2	1.95	51.2
4	4	56.5	4	4	47.3
6	6	46.3	6	6	39.5
8	8	37.4	8	8	31.8
12	12	25.2	12	12	20.9
24	24	13.1	24	24	9.6
48	48	7.1	48	48	4.4
72	72	5.3	72	72	2.9
96	96	3.5	96	96	2.2
144	120	2.9	144	120	1.8
192	168.117	2.8	192	168	1.5
504	480	1.2	504	480	1.0
576	552	1.3	576	552	0.9
720	696	0.8	720	695.983	0.8
2160	2136	BLQ	2160	2189.933	0.4
4320	4296	BLQ	4320	4295.983	BLQ

11.1.18 Summary of parameters from noncompartmental analysis

Formulation	Subject	Rsqr	Rsqr_adjusted	Corr_XY	No_points_lambda_z
A	1.00	0.9695	0.9593	-0.9846	5.0
	3.00	0.8451	0.7935	-0.9193	5.0
	6.00	0.9821	0.9761	-0.9910	5.0
	7.00	0.9873	0.9831	-0.9936	5.0
	10.00	0.9682	0.9576	-0.9840	5.0
	12.00	0.9877	0.9835	-0.9938	5.0
	13.00	0.7687	0.6915	-0.8767	5.0
	15.00	0.9823	0.9734	-0.9911	4.0
	18.00	0.9656	0.9484	-0.9826	4.0
	20.00	0.7626	0.6834	-0.8733	5.0
	21.00	0.7843	0.7124	-0.8856	5.0
	24.00	0.9648	0.9530	-0.9822	5.0
	26.00	0.9863	0.9817	-0.9931	5.0
	27.00	0.9663	0.9550	-0.9830	5.0
	30.00	0.9860	0.9813	-0.9930	5.0
	31.00	0.9711	0.9615	-0.9855	5.0
	33.00	0.9800	0.9734	-0.9900	5.0
	36.00	0.9104	0.8880	-0.9542	6.0
	38.00	0.9946	0.9928	-0.9973	5.0
	40.00	0.9957	0.9942	-0.9978	5.0
	44.00	0.9410	0.9213	-0.9700	5.0
	46.00	0.9516	0.9355	-0.9755	5.0
	47.00	0.9538	0.9384	-0.9766	5.0
	49.00	0.9781	0.9672	-0.9890	4.0
	52.00	0.9930	0.9907	-0.9965	5.0
	53.00	0.9895	0.9860	-0.9947	5.0
	55.00	0.9498	0.9331	-0.9746	5.0
	58.00	0.9315	0.9087	-0.9652	5.0
	59.00	0.9741	0.9655	-0.9870	5.0
N		29	29	29	29
NMiss		0	0	0	0
Mean		0.9455	0.9272	-0.9718	4.9
SD		0.0674	0.0895	0.0359	0.4
Min		0.7626	0.6834	-0.9978	4.0
Median		0.9695	0.9593	-0.9846	5.0
Max		0.9957	0.9942	-0.8733	6.0
CV%		7.1	9.7	-3.7	7.5

11.1.19 Summary of parameters from noncompartmental analysis

Formulation	Subject	Rsqr	Rsqr_adjusted	Corr_XY	No_points_lambda_z
B	2.00	0.9327	0.9102	-0.9657	5.0
	4.00	0.9669	0.9559	-0.9833	5.0
	5.00	0.9913	0.9884	-0.9956	5.0
	8.00	0.9775	0.9701	-0.9887	5.0
	9.00	0.9758	0.9677	-0.9878	5.0
	11.00	0.9802	0.9737	-0.9901	5.0
	14.00	0.9345	0.9127	-0.9667	5.0
	16.00	0.5587	0.4115	-0.7474	5.0
	17.00	0.9445	0.9260	-0.9718	5.0
	19.00	0.9610	0.9480	-0.9803	5.0
	22.00	0.7948	0.7264	-0.8915	5.0
	23.00	0.9257	0.8886	-0.9622	4.0
	25.00	0.9811	0.9748	-0.9905	5.0
	28.00	0.9942	0.9923	-0.9971	5.0
	29.00	0.9887	0.9849	-0.9943	5.0
	32.00	0.9709	0.9612	-0.9854	5.0
	34.00	0.9879	0.9839	-0.9939	5.0
	35.00	0.9288	0.9050	-0.9637	5.0
	37.00	0.9233	0.8977	-0.9609	5.0
	39.00	0.9763	0.9644	-0.9881	4.0
	43.00	0.9406	0.9208	-0.9698	5.0
	45.00	0.8922	0.8562	-0.9445	5.0
	48.00	0.9611	0.9482	-0.9804	5.0
	50.00	0.9800	0.9733	-0.9900	5.0
	51.00	0.9816	0.9755	-0.9908	5.0
	54.00	0.9707	0.9609	-0.9852	5.0
	56.00	0.9903	0.9871	-0.9951	5.0
	57.00	0.9923	0.9885	-0.9961	4.0
	60.00	0.9288	0.9050	-0.9637	5.0
	N	29	29	29	29
	NMiss	0	0	0	0
	Mean	0.9425	0.9227	-0.9697	4.9
	SD	0.0843	0.1125	0.0478	0.3
	Min	0.5587	0.4115	-0.9971	4.0
	Median	0.9707	0.9609	-0.9852	5.0
	Max	0.9942	0.9923	-0.7474	5.0
	CV%	8.9	12.2	-4.9	6.3

11.1.20 Summary of parameters from noncompartmental analysis

Formulation	Subject	Lambda_z (hr ⁻¹)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)
A	1	0.000494	480	4296	1404
	3	0.000654	168	2136	1060
	6	0.000557	480	4296	1243
	7	0.001627	120	696	426
	10	0.000526	480	4296	1319
	12	0.000455	480	4296	1525
	13	0.000693	168	2136	1001
	15	0.000335	552	4296	2069
	18	0.000417	480	4296	1661
	20	0.000673	168	2136	1029
	21	0.000547	168	2136	1268
	24	0.006138	96.0	552	113
	26	0.000301	480	4296	2299
	27	0.000777	168	2136	892
	30	0.000627	168	2136	1106
	31	0.000790	168	2136	878
	33	0.002850	120	696	243
	36	0.002138	96.0	696	324
	38	0.000368	480	4296	1884
	40	0.000297	480	4297	2334
	44	0.001132	168	2136	612
	46	0.000511	168	2136	1357
	47	0.000405	480	4296	1713
	49	0.001806	168	696	384
	52	0.000721	168	2136	962
	53	0.000778	168	2136	891
	55	0.000409	168	4296	1694
	58	0.000666	168	2136	1040
	59	0.002230	120	696	311
N		29	29	29	29
NMiss		0	0	0	0
Mean		0.001032	268	2653	1139
SD		0.001176	164	1420	606
Min		0.000297	96.0	552	113
Median		0.000654	168	2136	1060
Max		0.006138	552	4297	2334
CV%		114.0	61.0	53.5	53.1
Geometric Mean		0.000741	225	2190	935

11.1.21 Summary of parameters from noncompartmental analysis

Formulation	Subject	Lambda_z (hr ⁻¹)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)
B	2	0.000434	480	4296	1599
	4	0.000700	168	2136	990
	5	0.000662	480	4296	1048
	8	0.000765	168	2136	906
	9	0.001821	120	696	381
	11	0.001749	120	696	396
	14	0.000382	480	4296	1815
	16	0.000519	168	2136	1336
	17	0.000661	168	2136	1049
	19	0.000467	480	4296	1484
	22	0.000436	168	2136	1592
	23	0.000621	480	2136	1117
	25	0.000440	480	4342	1575
	28	0.000556	480	4295	1246
	29	0.001439	168	2136	482
	32	0.000795	168	2136	871
	34	0.001069	168	2136	648
	35	0.002632	120	696	263
	37	0.000738	168	2136	939
	39	0.000394	480	4296	1758
	43	0.001957	120	696	354
	45	0.002160	120	696	321
	48	0.001048	168	2138	662
	50	0.000639	168	2136	1085
	51	0.000772	168	2136	898
	54	0.000384	168	2136	1807
	56	0.000394	480	4296	1760
	57	0.001852	168	696	374
	60	0.000585	168	2190	1184
N		29	29	29	29
NMiss		0	0	0	0
Mean		0.000933	257	2437	1032
SD		0.000630	154	1300	502
Min		0.000382	120	696	263
Median		0.000662	168	2136	1048
Max		0.002632	480	4342	1815
CV%		67.5	59.8	53.3	48.6
Geometric Mean		0.000777	220	2056	892

11.1.22 Summary of parameters from noncompartmental analysis

Formulation	Subject	Tlag (hr)	Tmax (hr)	Cmax (ng/mL)	Tlast (hr)	Clast (ng/mL)
A	1	0.0	2.0	69.8	4296.0	0.2
	3	0.0	2.0	127.4	2136.0	0.9
	6	0.0	4.0	83.1	4296.0	0.3
	7	0.0	2.0	76.3	696.0	1.2
	10	0.0	2.0	72.2	4296.0	0.2
	12	0.0	4.0	96.8	4296.0	0.8
	13	0.0	2.0	72.8	2136.0	0.5
	15	0.0	2.0	75.3	4296.0	0.4
	18	0.0	2.0	140.0	4296.0	0.4
	20	0.0	2.0	103.8	2136.0	0.9
	21	0.0	2.0	134.4	2136.0	1.8
	24	0.0	2.0	156.9	552.0	0.2
	26	0.0	2.0	80.9	4296.1	0.6
	27	0.0	2.0	76.4	2136.0	0.5
	30	0.0	2.0	78.2	2136.0	0.5
	31	0.0	4.0	61.1	2136.0	0.3
	33	0.0	2.0	61.5	696.0	0.7
	36	0.0	2.0	82.3	696.0	1.0
	38	0.0	4.0	69.1	4296.1	0.5
	40	0.0	2.0	91.5	4297.2	0.5
	44	0.0	2.0	78.6	2136.0	0.3
	46	0.0	2.0	68.5	2136.0	0.5
	47	0.0	2.0	101.6	4296.0	0.7
	49	0.0	2.0	56.6	696.0	0.8
	52	0.0	2.0	105.9	2136.0	0.5
	53	0.0	2.0	85.5	2136.0	0.5
	55	0.0	2.0	53.6	4296.0	0.3
	58	0.0	2.0	65.9	2136.0	0.3
	59	0.0	2.0	77.3	696.0	0.8
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		0.0	2.3	86.3	2652.5	0.6
SD		0.0	0.7	25.6	1420.1	0.3
Min		0.0	2.0	53.6	552.0	0.2
Median		0.0	2.0	78.2	2136.0	0.5
Max		0.0	4.0	156.9	4297.2	1.8
CV%		-	30.8	29.7	53.5	58.8
Geometric Mean		-	2.2	83.2	2190.2	0.5

11.1.23 Summary of parameters from noncompartmental analysis

Formulation	Subject	Tlag (hr)	Tmax (hr)	Cmax (ng/ml)	Tlast (hr)	Clast (ng/ml)
B	2	0.0	4.0	89.4	4296.0	0.4
	4	0.0	6.0	48.8	2136.0	0.4
	5	0.0	2.0	162.6	4296.0	0.3
	8	0.0	2.0	65.8	2136.0	0.5
	9	0.0	4.0	39.6	696.0	0.8
	11	0.0	2.0	49.9	696.0	0.9
	14	0.0	2.0	89.5	4296.0	0.6
	16	0.0	2.0	53.7	2136.0	0.4
	17	0.0	2.0	66.1	2136.0	0.7
	19	0.0	2.0	41.1	4296.0	0.2
	22	0.0	2.0	58.1	2136.0	0.9
	23	0.0	2.0	145.1	2136.0	0.5
	25	0.0	4.0	85.1	4342.2	0.3
	28	0.0	2.0	72.2	4295.3	0.2
	29	0.0	4.0	79.1	2136.0	0.2
	32	0.0	4.0	63.5	2136.0	0.3
	34	0.0	2.0	48.8	2136.0	0.3
	35	0.0	4.0	58.1	696.0	0.8
	37	0.0	2.0	55.8	2136.4	0.3
	39	0.0	4.0	61.5	4296.0	0.2
	43	0.0	2.0	62.9	696.0	0.8
	45	0.0	4.0	48.9	696.0	0.6
	48	0.0	4.0	68.1	2137.7	0.3
	50	0.0	4.0	46.4	2136.0	0.5
	51	0.0	6.0	59.2	2136.0	0.3
	54	0.0	6.0	52.2	2136.0	0.4
	56	0.0	4.0	61.4	4296.0	0.3
	57	0.0	2.0	61.2	696.0	0.8
	60	0.0	2.0	51.2	2189.9	0.4
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		0.0	3.2	67.1	2437.4	0.5
SD		0.0	1.4	27.4	1300.2	0.2
Min		0.0	2.0	39.6	696.0	0.2
Median		0.0	2.0	61.2	2136.0	0.4
Max		0.0	6.0	162.6	4342.2	0.9
CV%		-	43.1	40.8	53.3	48.4
Geometric Mean		-	2.9	63.3	2056.4	0.4

11.1.24 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUClast (ng-hr/mL)	AUCall (ng-hr/mL)	AUCINF_obs (ng-hr/mL)	AUCINF_D_obs (ng-hr/mL/ng)	AUC_%Extrap_obs (%)
A	1	4346	4346	4751	0.00048	8.5
	3	6580	6580	7956	0.00080	17.3
	6	7133	7133	7671	0.00077	7.0
	7	2520	2520	3257	0.00033	22.6
	10	5184	5184	5565	0.00056	6.8
	12	13841	13841	15601	0.00156	11.3
	13	3268	3268	3990	0.00040	18.1
	15	5053	5053	6247	0.00062	19.1
	18	7314	7314	8272	0.00083	11.6
	20	5029	5029	6365	0.00064	21.0
	21	8561	8561	11855	0.00119	27.8
	24	2688	2688	2720	0.00027	1.2
	26	6252	6252	8242	0.00082	24.1
	27	3698	3698	4342	0.00043	14.8
	30	3237	3237	4035	0.00040	19.8
	31	2533	2533	2913	0.00029	13.0
	33	2250	2250	2496	0.00025	9.8
	36	2268	2268	2736	0.00027	17.1
	38	6644	6644	8004	0.00080	17.0
	40	5696	5696	7380	0.00074	22.8
	44	3629	3629	3894	0.00039	6.8
	46	2773	2773	3752	0.00038	26.1
	47	9242	9242	10972	0.00110	15.8
	49	1679	1679	2122	0.00021	20.9
	52	3690	3690	4384	0.00044	15.8
	53	3925	3925	4568	0.00046	14.1
	55	4407	4407	5140	0.00051	14.3
	58	2149	2149	2599	0.00026	17.3
	59	2328	2328	2687.0	0.00027	13.3
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		4756	4756	5673	0.00057	15.7
SD		2683	2683	3200	0.00032	6.3
Min		1679	1679	2122	0.00021	1.2
Median		3925	3925	4568	0.00046	15.8
Max		13841	13841	15601	0.00156	27.8
CV%		56.4	56.4	56.4	56.4	40.0
Geometric Mean		4167	4167	4956	0.00050	13.9

11.1.25 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUClast (ng-hr/mL)	AUCall (ng-hr/mL)	AUCINF_obs (ng-hr/mL)	AUCINF_D_obs (ng-hr/mL/ng)	AUC_%Extrap_obs (%)
B	2	6239	6239	7161	0.00072	12.9
	4	2830	2830	3401	0.00034	16.8
	5	10787	10787	11241	0.00112	4.0
	8	3386	3386	4040	0.00040	16.2
	9	1651	1651	2091	0.00021	21.0
	11	1931	1931	2445	0.00024	21.0
	14	8193	8193	9765	0.00098	16.1
	16	2142	2142	2914	0.00029	26.5
	17	4081	4081	5141	0.00051	20.6
	19	3953	3953	4381	0.00044	9.8
	22	4384	4384	6450	0.00065	32.0
	23	7587	7587	8392	0.00084	9.6
	25	6075	6075	6757	0.00068	10.1
	28	4982	4982	5341	0.00053	6.7
	29	4412	4412	4551	0.00046	3.1
	32	2571	2571	2949	0.00029	12.8
	34	3240	3240	3520	0.00035	8.0
	35	2154	2154	2458	0.00025	12.4
	37	2234	2234	2641	0.00026	15.4
	39	3396	3396	3904	0.00039	13.0
	43	1832	1832	2241	0.00022	18.2
	45	1354	1354	1632	0.00016	17.0
	48	3469	3469	3755	0.00038	7.6
	50	3229	3229	4012	0.00040	19.5
	51	2578	2578	2966	0.00030	13.1
	54	1885	1885	2928	0.00029	35.6
	56	4282	4282	5044	0.00050	15.1
	57	1926	1926	2358	0.00024	18.3
	60	2519	2519	3202	0.00032	21.3
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		3769	3769	4403	0.00044	15.6
SD		2202	2202	2360	0.00024	7.5
Min		1354	1354	1632	0.00016	3.1
Median		3240	3240	3755	0.00038	15.4
Max		10787	10787	11241	0.00112	35.6
CV%		58.4	58.4	53.6	53.6	47.9
Geometric Mean		3289	3289	3915	0.00039	13.8

11.1.26 Summary of parameters from noncompartmental analysis

Formulation	Subject	Vz_F_obs (mL)	Vz_F_pred (mL)	Cl_F_obs (mL/hr)	Cl_F_pred (mL/hr)
A	1	4263104	4244793	2105	2096
	3	1921615	1928140	1257	1261
	6	2338583	2343014	1304	1306
	7	1886853	1905257	3070	3100
	10	3418607	3392511	1797	1783
	12	1410152	1409398	641	641
	13	3618774	3696005	2506	2560
	15	4778253	4821604	1601	1615
	18	2896165	2896928	1209	1209
	20	2332715	2376227	1571	1600
	21	1543422	1565366	844	856
	24	598850	596454	3676	3661
	26	4024708	4065425	1213	1226
	27	2963053	2983526	2303	2319
	30	3954628	3957532	2478	2480
	31	4348385	4367845	3433	3449
	33	1405819	1422906	4007	4056
	36	1709407	1729789	3656	3699
	38	3396448	3413971	1249	1256
	40	4563487	4578599	1355	1360
	44	2268158	2276147	2568	2577
	46	5218409	5251411	2665	2682
	47	2252338	2286156	911	925
	49	2608645	2640796	4712	4770
	52	3164224	3172171	2281	2287
	53	2814427	2813401	2189	2188
	55	4755044	4774854	1946	1954
	58	5774009	5827492	3848	3883
	59	1668549	1661045	3722	3705
N		29	29	29	29
NMiss		0	0	0	0
Mean		3030925	3048233	2280	2293
SD		1314295	1321572	1098	1106
Min		598850	596454	641	641
Median		2896165	2896928	2189	2188
Max		5774009	5827492	4712	4770
CV%		43.4	43.4	48.1	48.2
Geometric Mean		2721709	2737145	2018	2029

11.1.27 Summary of parameters from noncompartmental analysis

Formulation	Subject	Vz_F_obs (mL)	Vz_F_pred (mL)	Cl_F_obs (mL/hr)	Cl_F_pred (mL/hr)
B	2	3220311	3249372	1396	1409
	4	4199474	4227169	2940	2959
	5	1344479	1341669	890	888
	8	3235960	3254784	2476	2490
	9	2626969	2651074	4783	4827
	11	2338073	2339014	4089	4091
	14	2681975	2665400	1024	1018
	16	6617325	6837166	3432	3546
	17	2944523	2969313	1945	1962
	19	4885631	4875056	2283	2278
	22	3559687	3639571	1550	1585
	23	1919519	1923777	1192	1194
	25	3362247	3338797	1480	1470
	28	3365117	3371275	1872	1876
	29	1526787	1528700	2198	2200
	32	4264007	4288151	3392	3411
	34	2656107	2663246	2841	2848
	35	1545843	1570823	4069	4135
	37	5131785	5148718	3787	3799
	39	6498718	6505676	2562	2565
	43	2279808	2332921	4463	4567
	45	2837078	2936585	6127	6342
	48	2541712	2555130	2663	2677
	50	3902994	3921472	2493	2504
	51	4366240	4380088	3371	3382
	54	8907036	8944568	3416	3430
	56	5035165	5069961	1983	1996
	57	2289987	2304278	4241	4267
	60	5335491	5397268	3123	3159
N		29	29	29	29
NMiss		0	0	0	0
Mean		3635174	3663139	2830	2858
SD		1720345	1737223	1246	1279
Min		1344479	1341669	890	888
Median		3235960	3254784	2663	2677
Max		8907036	8944568	6127	6342
CV%		47.3	47.4	44.0	44.7
Geometric Mean		3287610	3311526	2554	2573

11.1.28 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUCINF_pred (ng-hr/mL)	AUCINF_D_pred (ng-hr/mL)	AUC_%Extrap_pred (%)
A	1	4772	0.00048	8.9
	3	7930	0.00079	17.0
	6	7656	0.00077	6.8
	7	3226	0.00032	21.9
	10	5608	0.00056	7.5
	12	15610	0.00156	11.3
	13	3907	0.00039	16.3
	15	6191	0.00062	18.4
	18	8270	0.00083	11.6
	20	6249	0.00062	19.5
	21	11689	0.00117	26.8
	24	2731	0.00027	1.6
	26	8160	0.00082	23.4
	27	4312	0.00043	14.2
	30	4032	0.00040	19.7
	31	2900	0.00029	12.7
	33	2466	0.00025	8.7
	36	2703	0.00027	16.1
	38	7962	0.00080	16.6
	40	7356	0.00074	22.6
	44	3880	0.00039	6.5
	46	3729	0.00037	25.6
	47	10810	0.00108	14.5
	49	2096	0.00021	19.9
	52	4373	0.00044	15.6
	53	4570	0.00046	14.1
	55	5119	0.00051	13.9
	58	2575	0.00026	16.6
	59	2699	0.00027	13.7
N		29	29	29
NMiss		0	0	0
Mean		5641	0.00056	15.2
SD		3181	0.00032	6.0
Min		2096	0.00021	1.6
Median		4570	0.00046	15.6
Max		15610	0.00156	26.8
CV%		56.4	56.4	39.2
Geometric Mean		4928	0.00049	13.6

11.1.29 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUCINF_pred (ng-hr/mL)	AUCINF_D_pred (ng-hr/mL)	AUC_%Extrap_pred (%)
B	2	7097	0.00071	12.1
	4	3379	0.00034	16.2
	5	11264	0.00113	4.2
	8	4016	0.00040	15.7
	9	2072	0.00021	20.3
	11	2444	0.00024	21.0
	14	9825	0.00098	16.6
	16	2820	0.00028	24.0
	17	5098	0.00051	19.9
	19	4390	0.00044	10.0
	22	6309	0.00063	30.5
	23	8374	0.00084	9.4
	25	6804	0.00068	10.7
	28	5331	0.00053	6.6
	29	4545	0.00045	2.9
	32	2932	0.00029	12.3
	34	3511	0.00035	7.7
	35	2419	0.00024	11.0
	37	2632	0.00026	15.1
	39	3899	0.00039	12.9
	43	2190	0.00022	16.3
	45	1577	0.00016	14.1
	48	3735	0.00037	7.1
	50	3993	0.00040	19.1
	51	2957	0.00030	12.8
	54	2915	0.00029	35.4
	56	5009	0.00050	14.5
	57	2344	0.00023	17.8
	60	3165	0.00032	20.4
N		29	29	29
NMiss		0	0	0
Mean		4381	0.00044	15.1
SD		2371	0.00024	7.2
Min		1577	0.00016	2.9
Median		3735	0.00037	14.5
Max		11264	0.00113	35.4
CV%		54.1	54.1	47.8
Geometric Mean		3887	0.00039	13.3

11.1.30 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUMC _{last} (ng-hr ² /mL)	AUMC _{INF_obs} (ng-hr ² /mL)	AUMC_%Extrap_obs (%)	AUMC _{INF_pred} (ng-hr ² /mL)	AUMC_%Extrap_pred (%)
A	1	4481262	7042039	36.4	7171599	37.5
	3	3242804	8285792	60.9	8187121	60.4
	6	6789624	10067045	32.6	9978696	32.0
	7	418418	1384862	69.8	1343631	68.9
	10	5464944	7823347	30.1	8088680	32.4
	12	15269828	26702904	42.8	26757097	42.9
	13	1545725	4130494	62.6	3831991	59.7
	15	5629963	14324067	60.7	13915090	59.5
	18	7087912	13500705	47.5	13486118	47.4
	20	2698757	7537559	64.2	7115513	62.1
	21	5258303	18318864	71.3	17659847	70.2
	24	208490	231783	10.0	239598	13.0
	26	7977924	23131657	65.5	22503151	64.5
	27	1851759	4053147	54.3	3951183	53.1
	30	1773914	4751333	62.7	4740286	62.6
	31	1181557	2474390	52.2	2430234	51.4
	33	320548	577618	44.5	546248	41.3
	36	365855	910004	59.8	872496	58.1
	38	7609134	17142979	55.6	16854829	54.9
	40	6957019	19864458	65.0	19677752	64.6
	44	1521297	2321234	34.5	2279969	33.3
	46	1555646	5563733	72.0	5467195	71.5
	47	10100242	21807085	53.7	20708733	51.2
	49	290055	843472	65.6	811186	64.2
	52	1839029	4282431	57.1	4243738	56.7
	53	1981458	4181136	52.6	4186838	52.7
	55	5015938	9957909	49.6	9814175	48.9
	58	1028943	2666209	61.4	2579461	60.1
	59	361122	771557	53.2	785448	54.0
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		3787154	8436200	53.4	8283721	52.7
SD		3595221	7685630	14.2	7536673	13.5
Min		208490	231783	10.0	239598	13.0
Median		1981458	5563733	55.6	5467195	54.9
Max		15269828	26702904	72.0	26757097	71.5
CV%		94.9	91.1	26.6	91.0	25.6
Geometric Mean		2169629	4844887	50.6	4757986	50.4

11.1.31 Summary of parameters from noncompartmental analysis

Formulation	Subject	AUMC _{last} (ng-hr ² /mL)	AUMC _{INF_obs} (ng-hr ² /mL)	AUMC_%Extrap_obs (%)	AUMC _{INF_pred} (ng-hr ² /mL)	AUMC_%Extrap_pred (%)
B	2	6484832	12575000	48.4	12152153	46.6
	4	1382492	3419106	59.6	3339672	58.6
	5	9838840	12471737	21.1	12608436	22.0
	8	1851183	4101617	54.9	4021175	54.0
	9	295654	842746	64.9	819076	63.9
	11	342245	994586	65.6	993339	65.5
	14	10653508	21518687	50.5	21938553	51.4
	16	1042470	4176704	75.0	3795971	72.5
	17	2426842	6293972	61.4	6137333	60.5
	19	4061283	6816309	40.4	6877467	40.9
	22	2439183	11597934	79.0	10970469	77.8
	23	1860654	4878693	61.9	4809088	61.3
	25	6559185	11066875	40.7	11380750	42.4
	28	4475374	6665400	32.9	6605964	32.3
	29	1589779	1983131	19.8	1967016	19.2
	32	1139258	2419077	52.9	2362746	51.8
	34	1541727	2403216	35.8	2374236	35.1
	35	322962	649983	50.3	607931	46.9
	37	1068269	2487843	57.1	2457517	56.5
	39	2703176	6169804	56.2	6141280	56.0
	43	270629	763865	64.6	702295	61.5
	45	197964	519981	61.9	455880	56.6
	48	1383021	2268410	39.0	2207432	37.3
	50	1687093	4585251	63.2	4515274	62.6
	51	1179783	2513007	53.1	2480826	52.4
	54	1152251	6099871	81.1	6041601	80.9
	56	4653446	9861774	52.8	9625136	51.7
	57	305526	839482	63.6	821405	62.8
	60	1332389	3996268	66.7	3853402	65.4
N		29	29	29	29	29
NMiss		0	0	0	0	0
Mean		2560035	5344149	54.3	5278049	53.3
SD		2736258	4826110	15.1	4858951	14.8
Min		197964	519981	19.8	455880	19.2
Median		1541727	4101617	56.2	3853402	56.0
Max		10653508	21518687	81.1	21938553	80.9
CV%		106.9	90.3	27.8	92.1	27.7
Geometric Mean		1523851	3521280	51.7	3433666	50.9

11.1.32 Summary of parameters from noncompartmental analysis

Formulation	Subject	MRTlast (hr)	MRTINF_obs (hr)	MRTINF_pred (hr)
A	1	1031	1482	1503
	3	493	1041	1033
	6	952	1312	1303
	7	166	425	417
	10	1054	1406	1442
	12	1103	1712	1714
	13	473	1035	981
	15	1114	2293	2248
	18	969	1632	1631
	20	537	1184	1139
	21	614	1545	1511
	24	77.6	85.2	87.7
	26	1276	2806	2758
	27	501	934	916
	30	548	1178	1176
	31	467	850	838
	33	143	232	222
	36	161	333	323
	38	1145	2142	2117
	40	1221	2692	2675
	44	419	596	588
	46	561	1483	1466
	47	1093	1988	1916
	49	173	398	387
	52	498	977	971
	53	505	915	916
	55	1138	1937	1917
	58	479	1026	1002
	59	155	287	291
N		29	29	29
NMiss		0	0	0
Mean		658	1239	1224
SD		384	721	713
Min		77.6	85.2	87.7
Median		537	1178	1139
Max		1276	2806	2758
CV%		58.4	58.2	58.3
Geometric Mean		521	978	966

11.1.33 Summary of parameters from noncompartmental analysis

Formulation	Subject	MRTlast (hr)	MRTINF_obs (hr)	MRTINF_pred (hr)
B	2	1039	1756	1712
	4	489	1005	988
	5	912	1110	1119
	8	547	1015	1001
	9	179	403	395
	11	177	407	406
	14	1300	2204	2233
	16	487	1434	1346
	17	595	1224	1204
	19	1028	1556	1567
	22	556	1798	1739
	23	245	581	574
	25	1080	1638	1673
	28	898	1248	1239
	29	360	436	433
	32	443	821	806
	34	476	683	676
	35	150	265	251
	37	478	942	934
	39	796	1581	1575
	43	148	341	321
	45	146	319	289
	48	399	604	591
	50	523	1143	1131
	51	458	847	839
	54	611	2084	2072
	56	1087	1955	1921
	57	159	356	351
	60	529	1248	1217
N		29	29	29
NMiss		0	0	0
Mean		562	1069	1055
SD		328	580	579
Min		146	265	251
Median		489	1015	1001
Max		1300	2204	2233
CV%		58.5	54.3	54.9
Geometric Mean		463	900	884

11.1.34 Bioequivalence output from WinNonlin

Dependent	FormVar	FormRef	RefLSM	RefLSM_SE	RefGeoLSM
Ln(Tmax)	Form	A	0.7888	0.0631	2.2007
Ln(Cmax)	Form	A	4.4210	0.0550	83.1778
Ln(AUClast)	Form	A	8.3349	0.0956	4166.6413
Ln(AUCINF_obs)	Form	A	8.5083	0.0929	4955.7585

Dependent	Test	TestLSM	TestLSM_SE	TestGeoLSM	Difference
Ln(Tmax)	B	1.0688	0.0631	2.9120	0.2801
Ln(Cmax)	B	4.1483	0.0550	63.3262	-0.2727
Ln(AUClast)	B	8.0983	0.0956	3288.8669	-0.2366
Ln(AUCINF_obs)	B	8.2725	0.0929	3914.7585	-0.2358

Dependent	DiffSE	DiffDF	Ratio	CL_80_Lower	CL_80_Upper
Ln(Tmax)	0.0893	56	132.32	117.86	148.57
Ln(Cmax)	0.0778	56	76.13	68.83	84.22
Ln(AUClast)	0.1352	56	78.93	66.24	94.06
Ln(AUCINF_obs)	0.1314	56	78.99	66.62	93.67

Dependent	WL_80_Lower	WL_80_Upper	CL_90_Lower	CL_90_Upper	WL_90_Lower
Ln(Tmax)	57.27	142.73	113.97	153.64	51.44
Ln(Cmax)	71.27	128.73	66.84	86.72	68.83
Ln(AUClast)	70.37	129.63	62.96	98.96	66.23
Ln(AUCINF_obs)	70.66	129.34	63.41	98.41	66.61

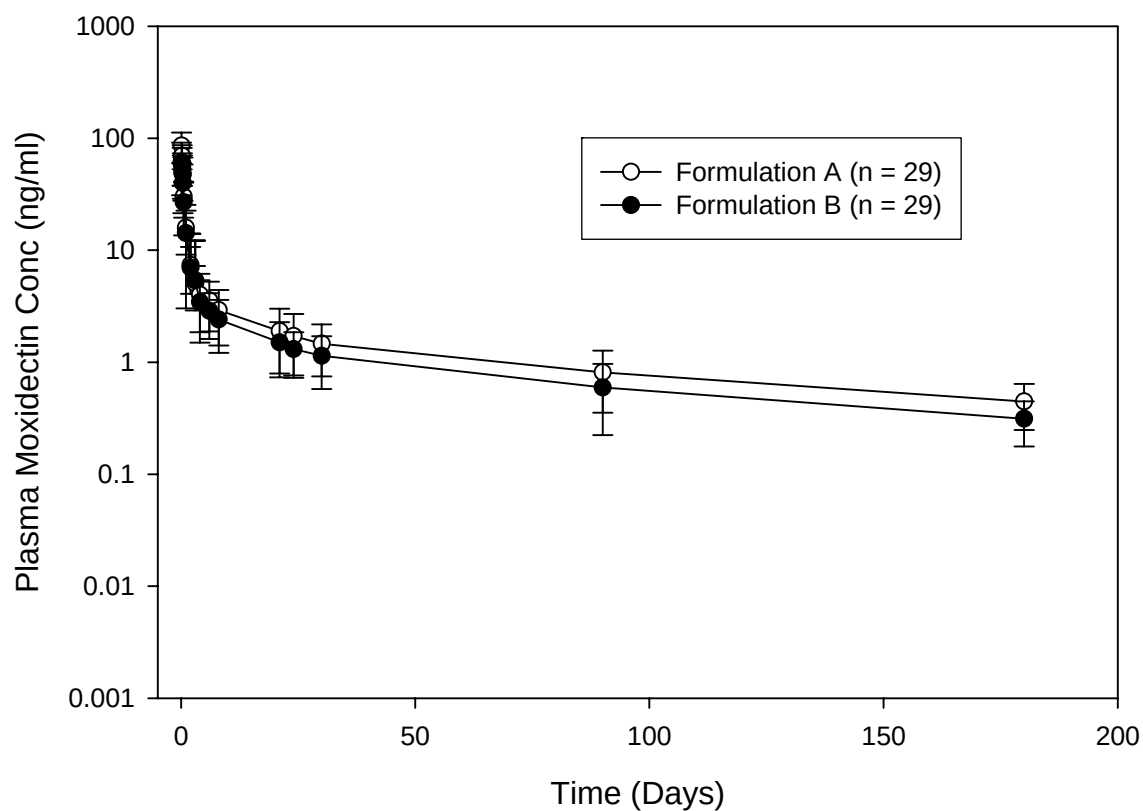
Dependent	WL_90_Upper	CL_95_Lower	CL_95_Upper	WL_95_Lower	WL_95_Upper
Ln(Tmax)	148.56	110.65	158.24	46.37	153.63
Ln(Cmax)	131.17	65.14	88.98	66.84	133.16
Ln(AUClast)	133.77	60.21	103.49	62.96	137.04
Ln(AUCINF_obs)	133.39	60.71	102.78	63.41	136.59

Dependent	Prob<80.00	Prob>125.00	MaxProb	TotalProb	AHpval
Ln(Tmax)	0.0000	0.7369	0.7369	0.7369	0.7369
Ln(Cmax)	0.7365	0.0000	0.7365	0.7365	0.7365
Ln(AUClast)	0.5394	0.0006	0.5394	0.5400	0.5388
Ln(AUCINF_obs)	0.5382	0.0005	0.5382	0.5387	0.5377

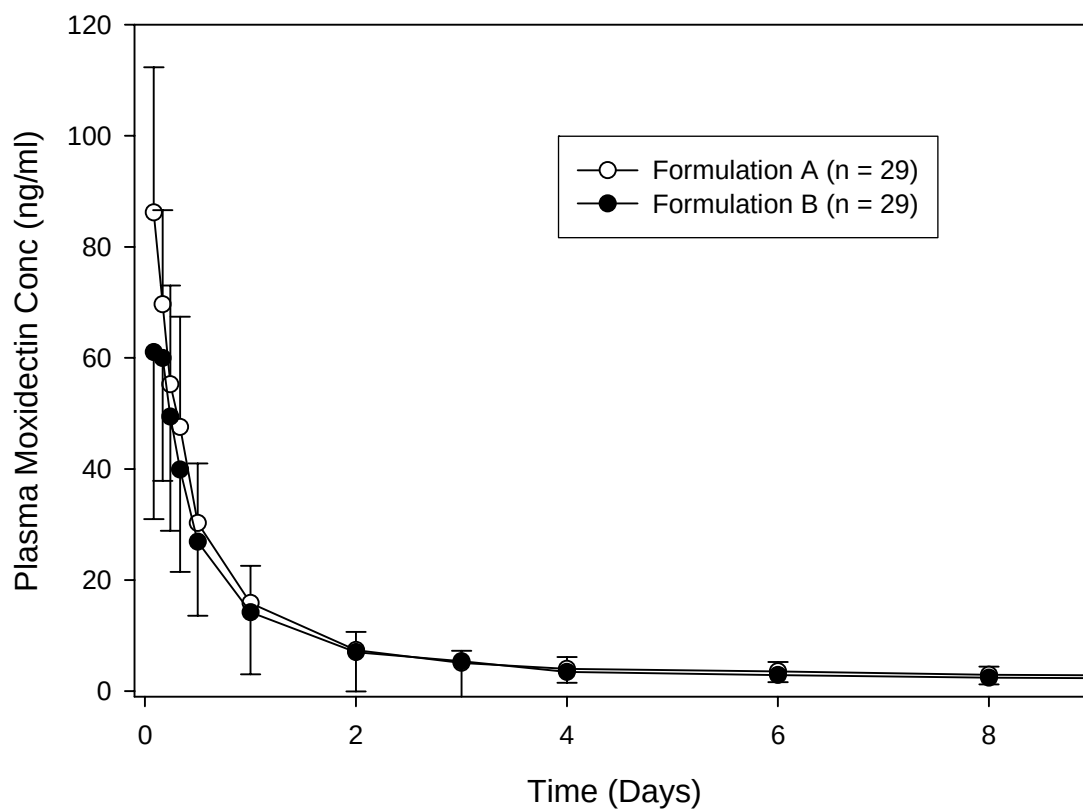
Dependent	Power
Ln(Tmax)	0.7942
Ln(Cmax)	0.8815
Ln(AUClast)	0.4920
Ln(AUCINF_obs)	0.5108

11.2 FIGURES

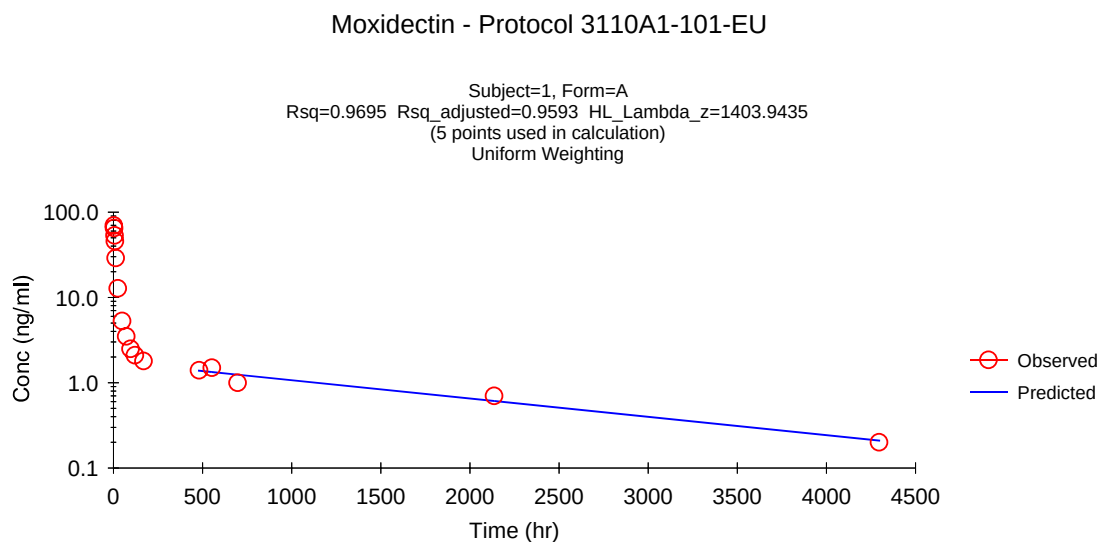
11.2.1 Mean plasma concentration-time profiles of moxidectin in healthy volunteers treated with oral solution (Formulation A) and tablets (Formulation B).



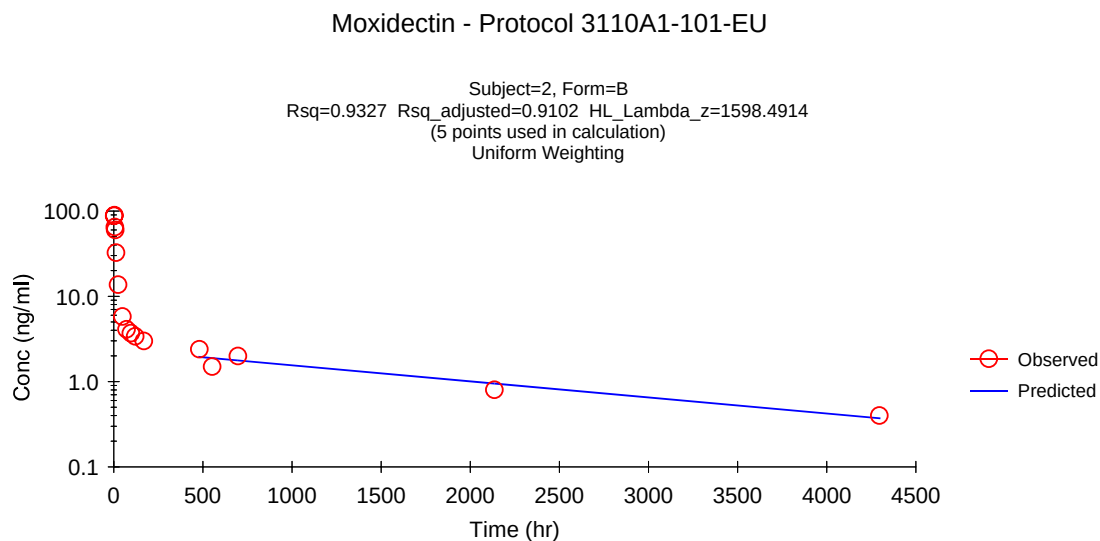
11.2.2 Mean Plasma concentration-time profiles of moxidectin in healthy volunteers treated with oral solution (Formulation A) and tablets (Formulation B) with expanded x-axis [Note linear scale].



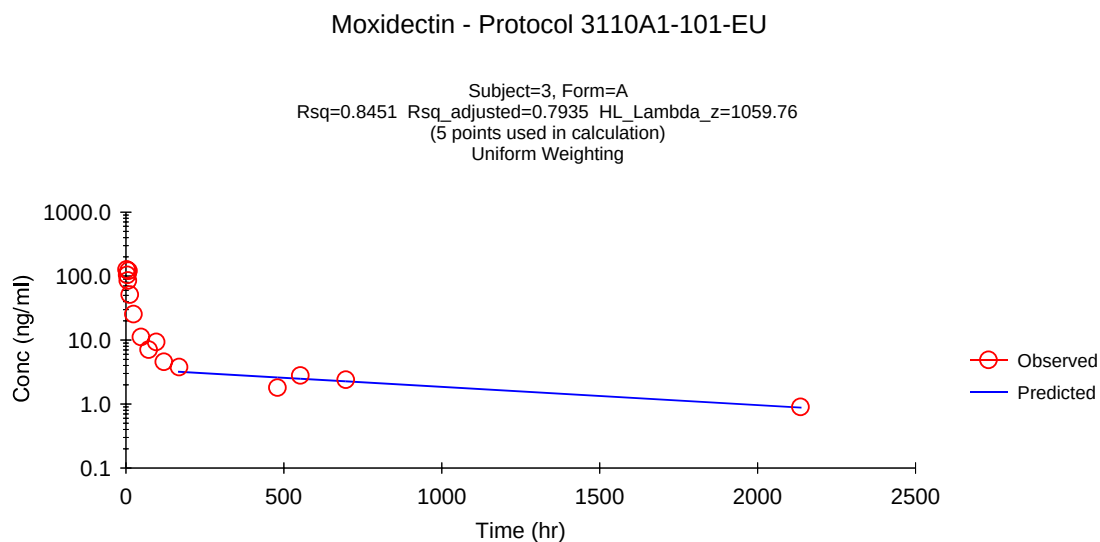
11.2.3 Plasma concentration-time profile of moxidectin for Subject 1.



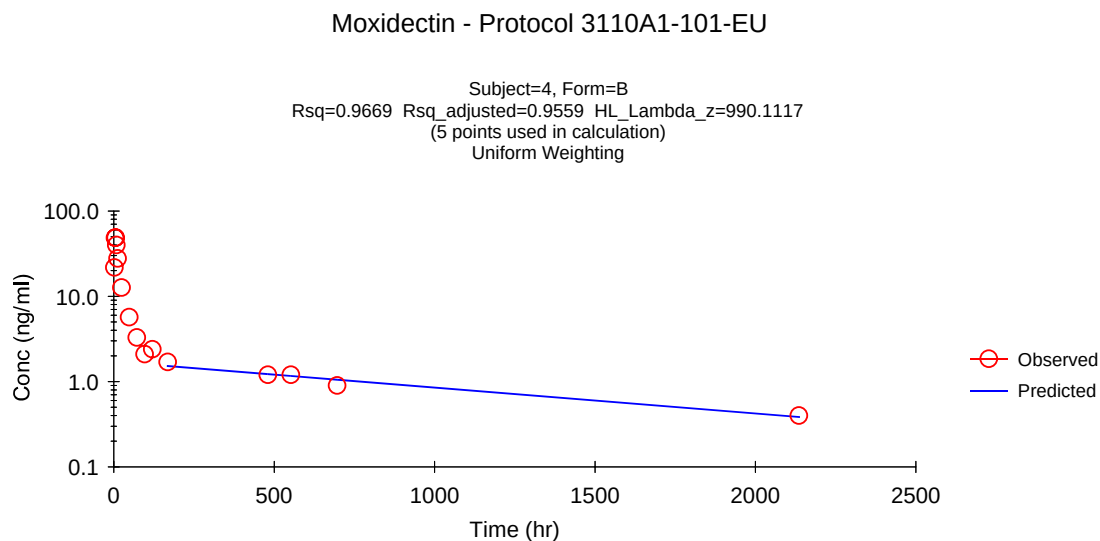
11.2.4 Plasma concentration-time profile of moxidectin for Subject 2.



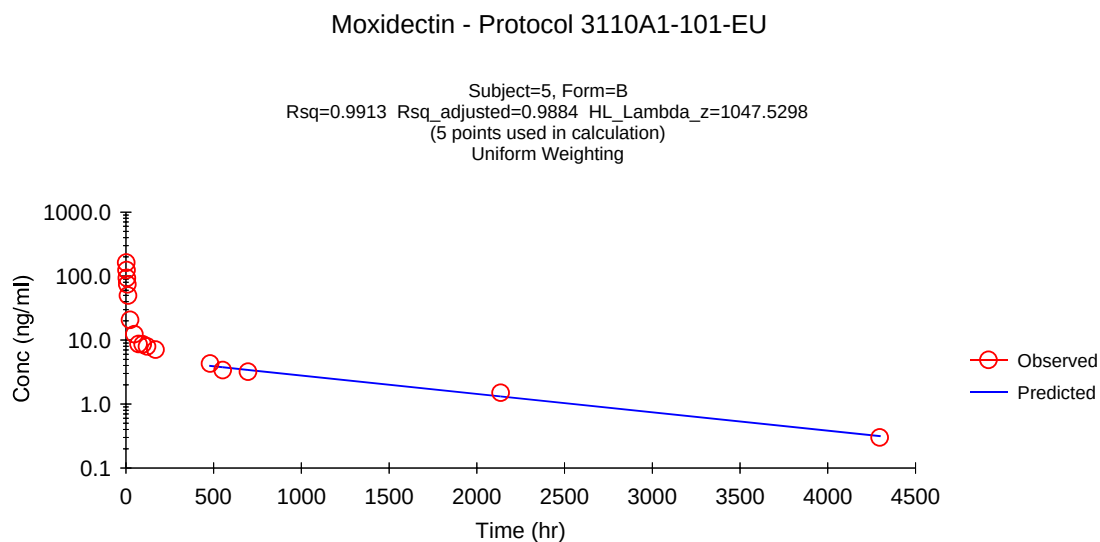
11.2.5 Plasma concentration-time profile of moxidectin for Subject 3.



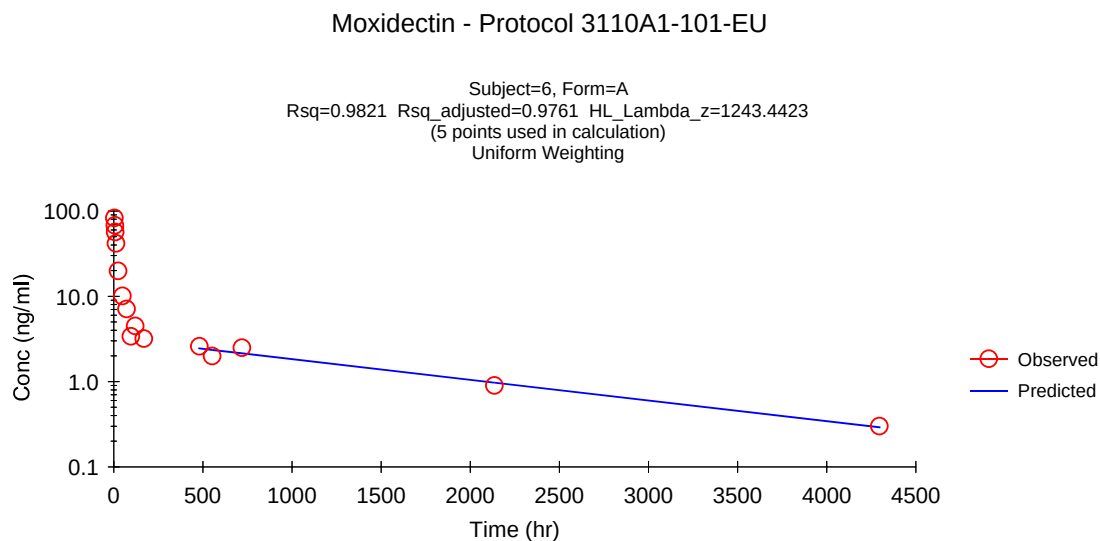
11.2.6 Plasma concentration-time profile of moxidectin for Subject 4.



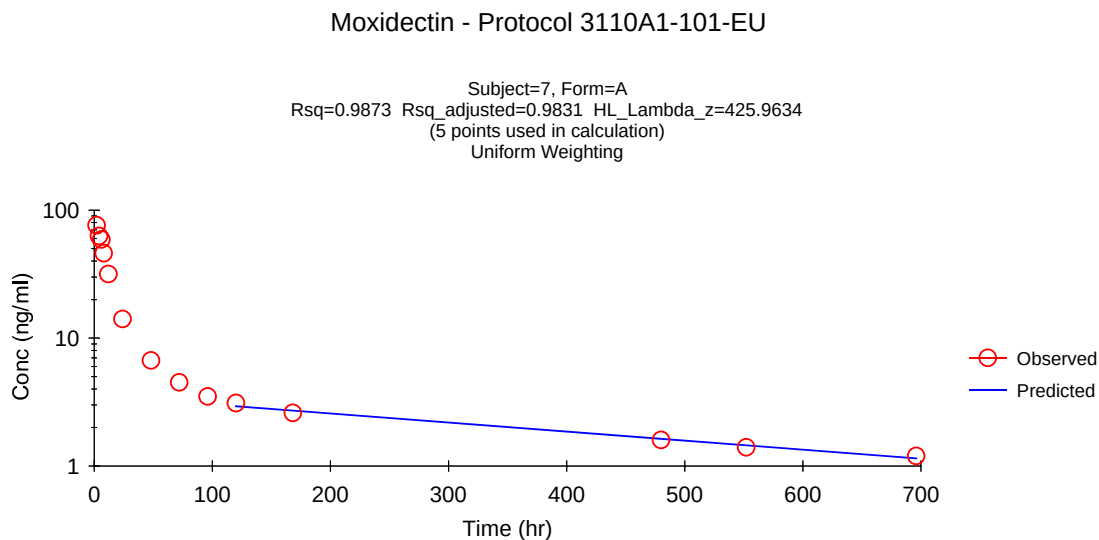
11.2.7 Plasma concentration-time profile of moxidectin for Subject 5.



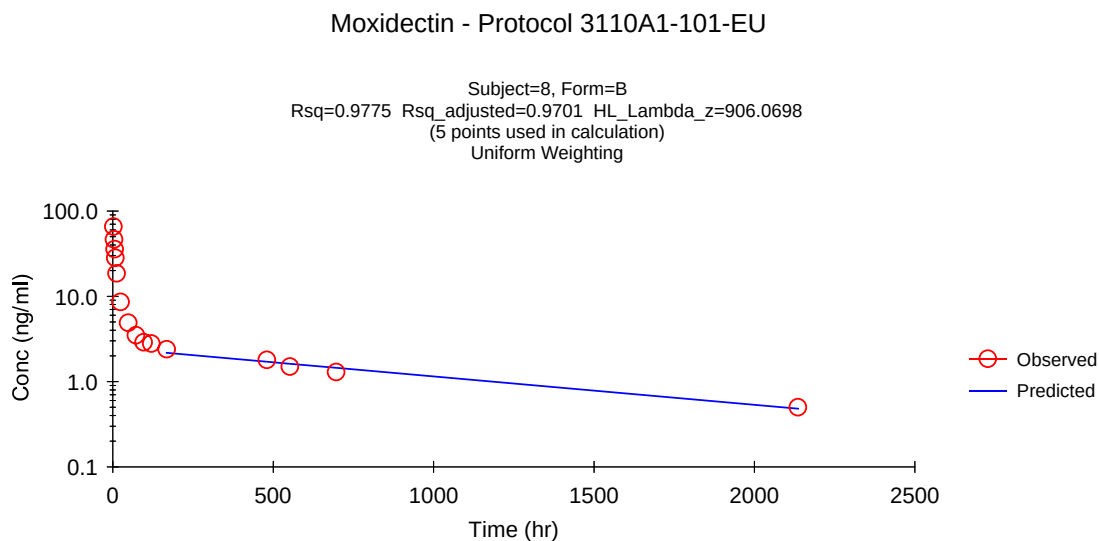
11.2.8 Plasma concentration-time profile of moxidectin for Subject 6.



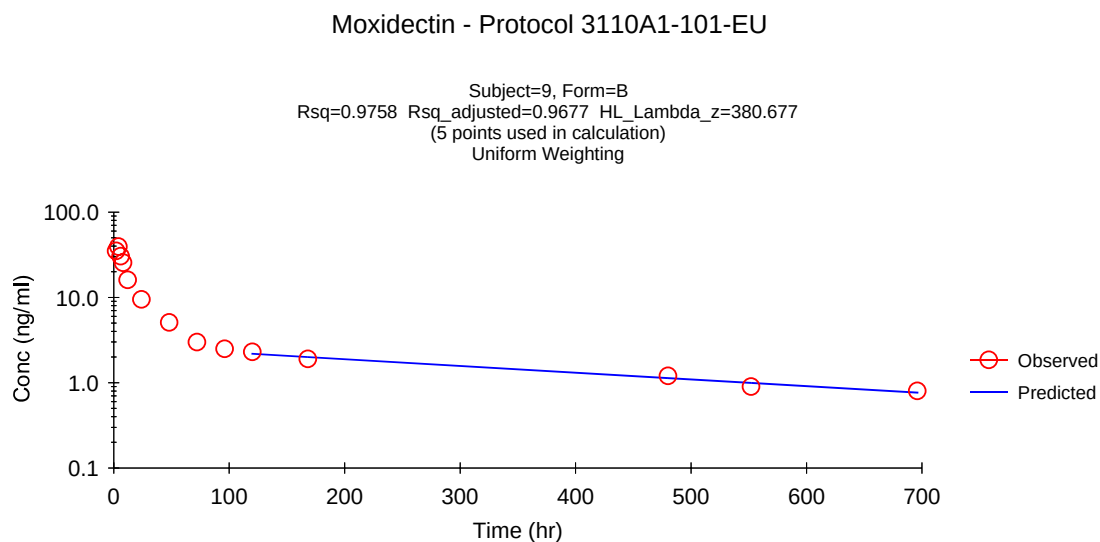
11.2.9 Plasma concentration-time profile of moxidectin for Subject 7.



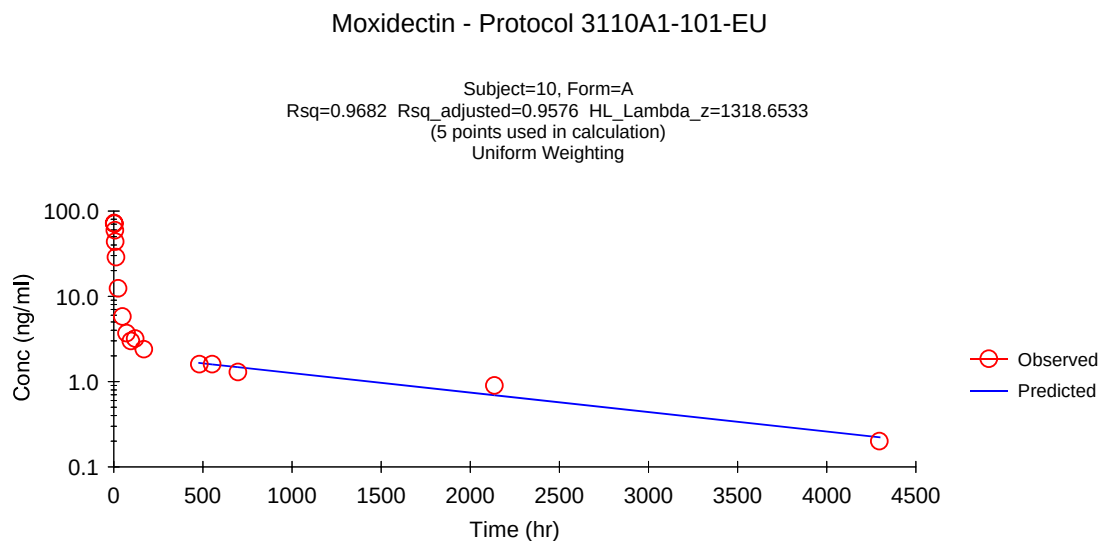
11.2.10 Plasma concentration-time profile of moxidectin for Subject 8.



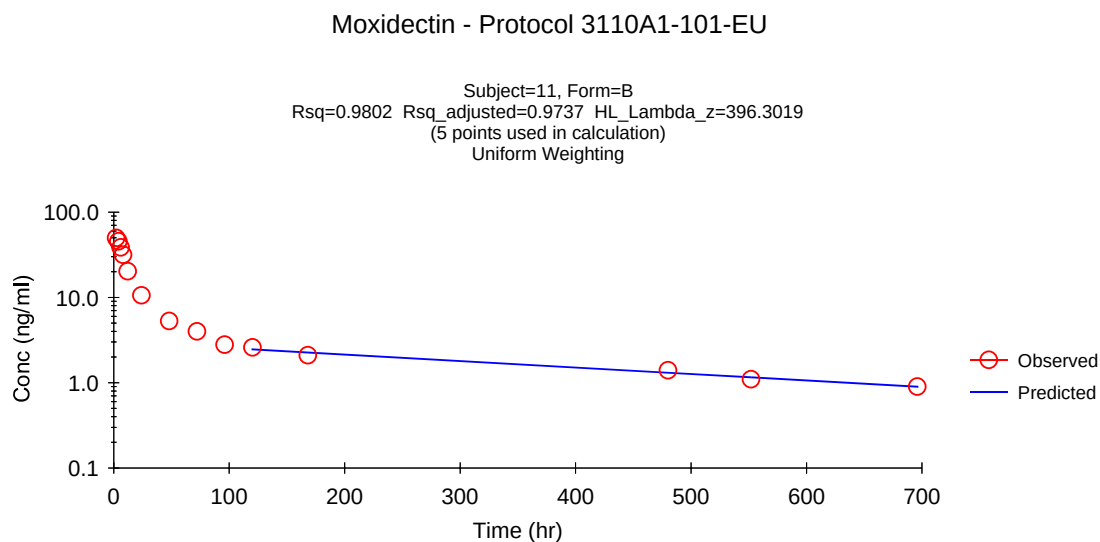
11.2.11 Plasma concentration-time profile of moxidectin for Subject 9.



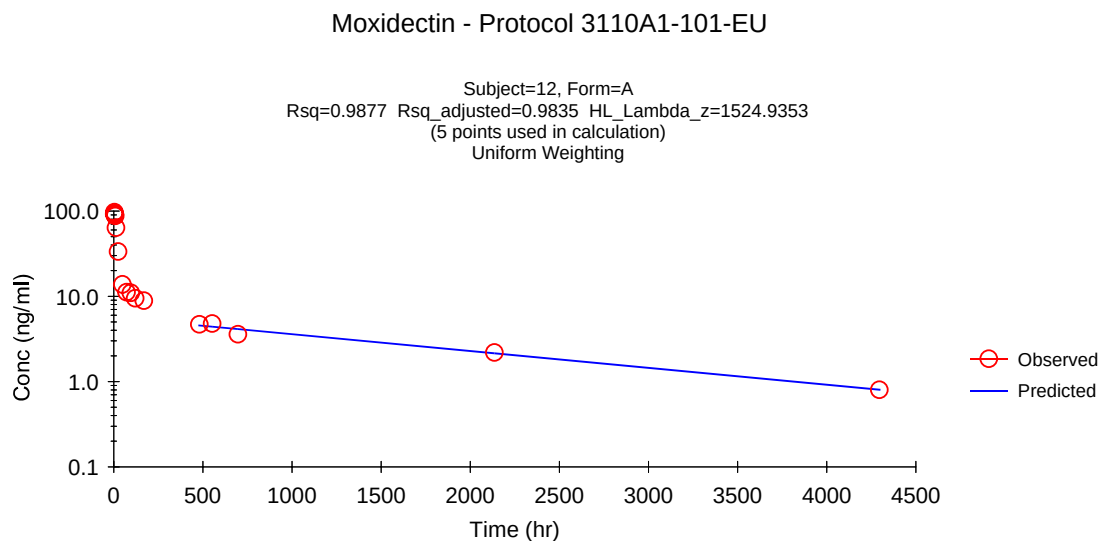
11.2.12 Plasma concentration-time profile of moxidectin for Subject 10.



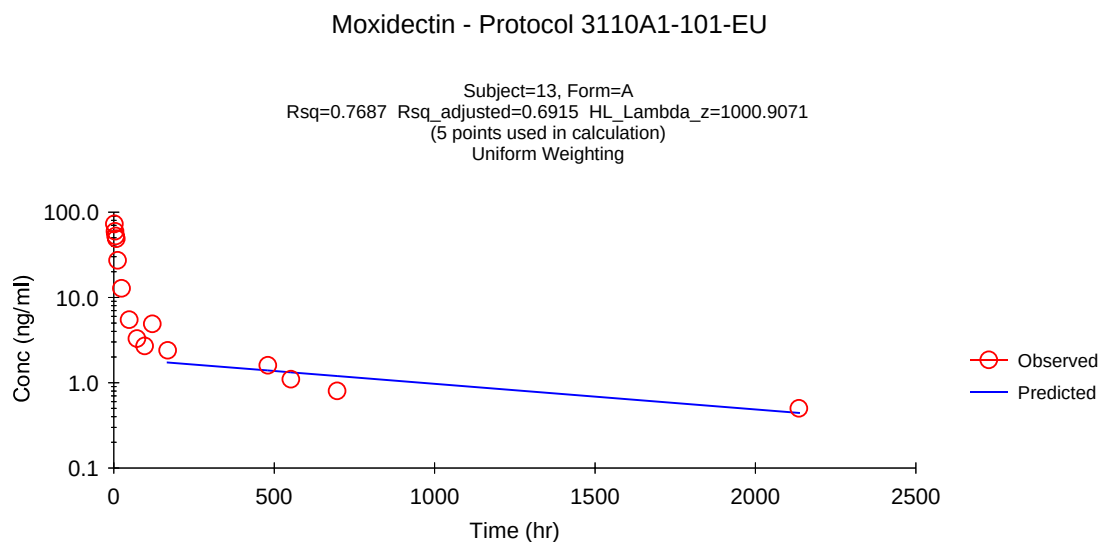
11.2.13 Plasma concentration-time profile of moxidectin for Subject 11.



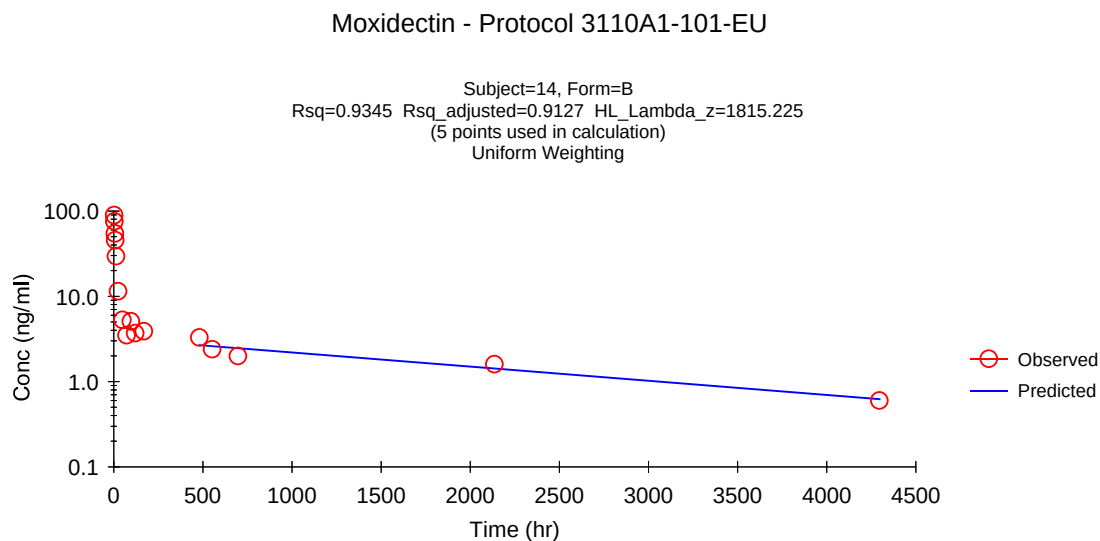
11.2.14 Plasma concentration-time profile of moxidectin for Subject 12.



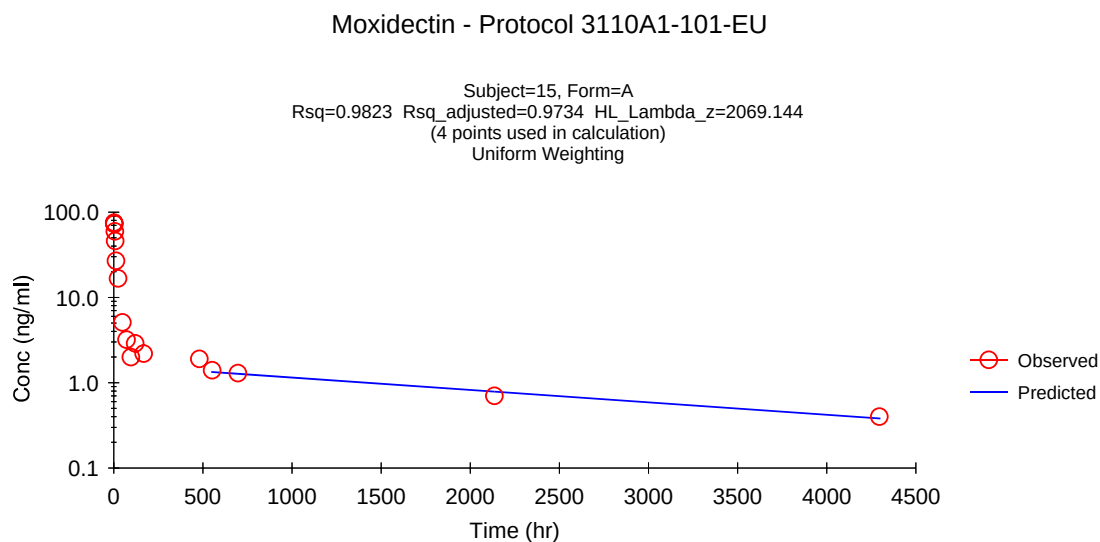
11.2.15 Plasma concentration-time profile of moxidectin for Subject 13.



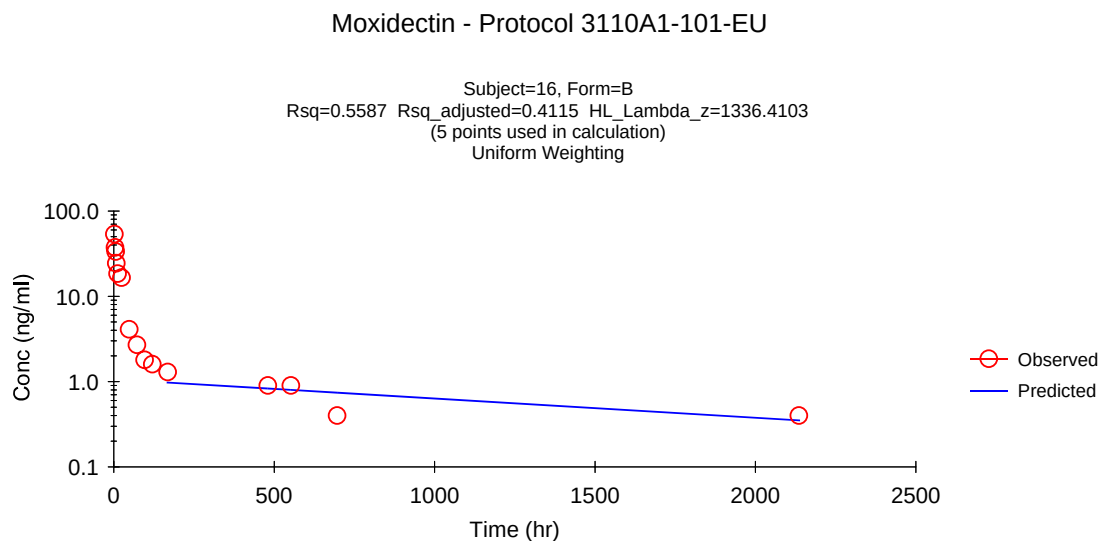
11.2.16 Plasma concentration-time profile of moxidectin for Subject 14.



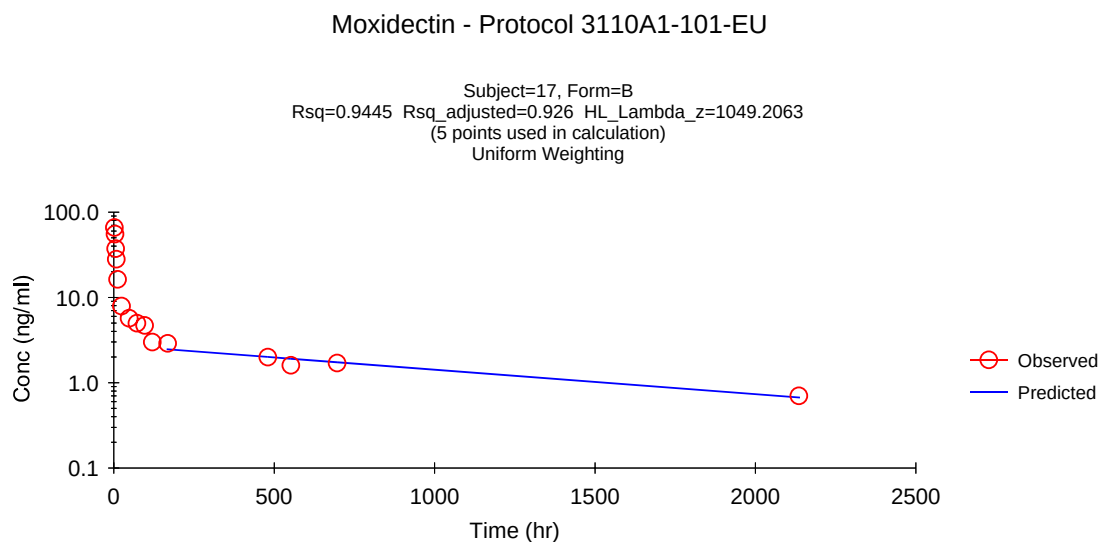
11.2.17 Plasma concentration-time profile of moxidectin for Subject 15.



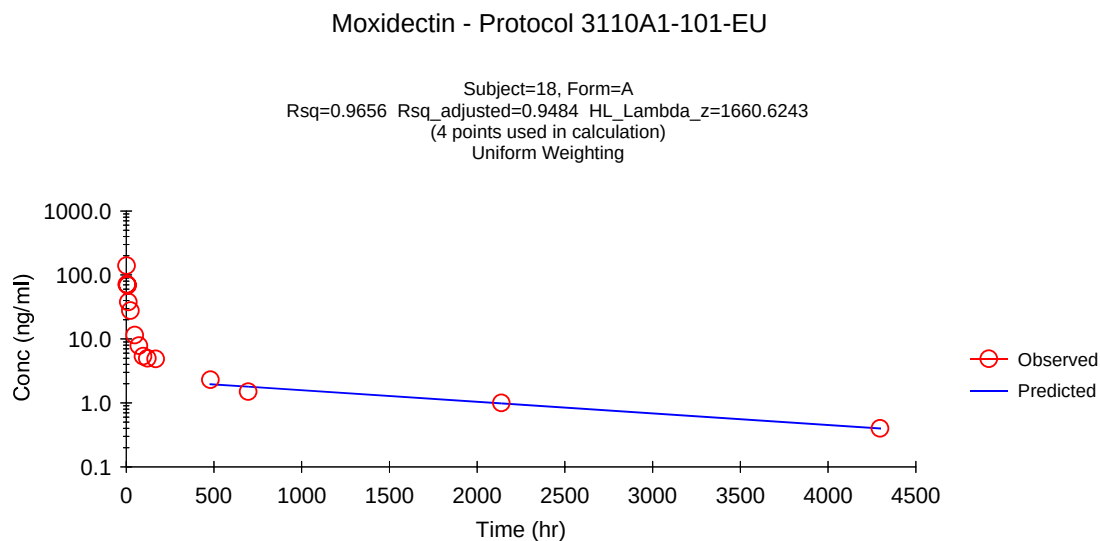
11.2.18 Plasma concentration-time profile of moxidectin for Subject 16.



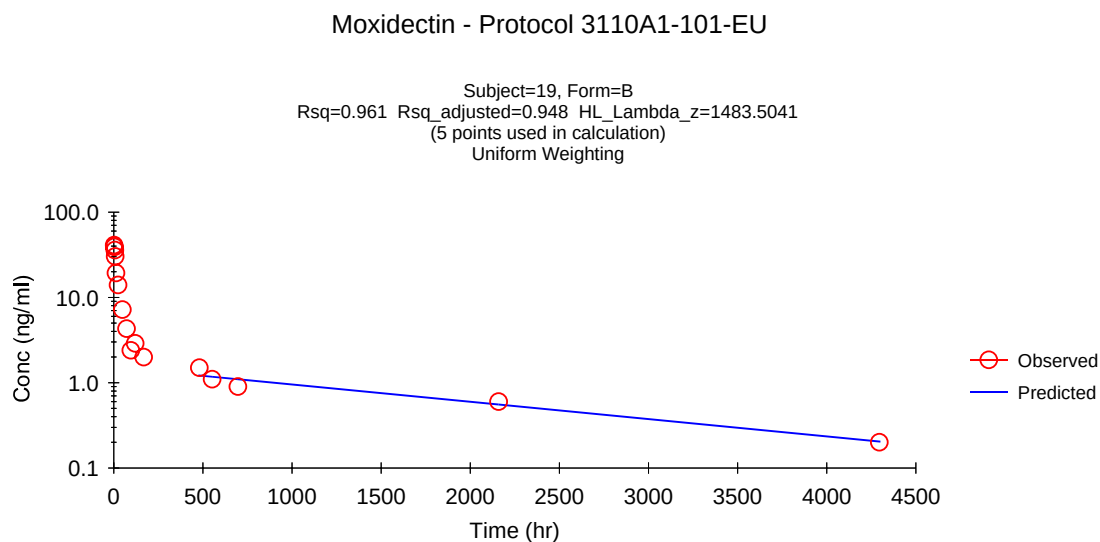
11.2.19 Plasma concentration-time profile of moxidectin for Subject 17.



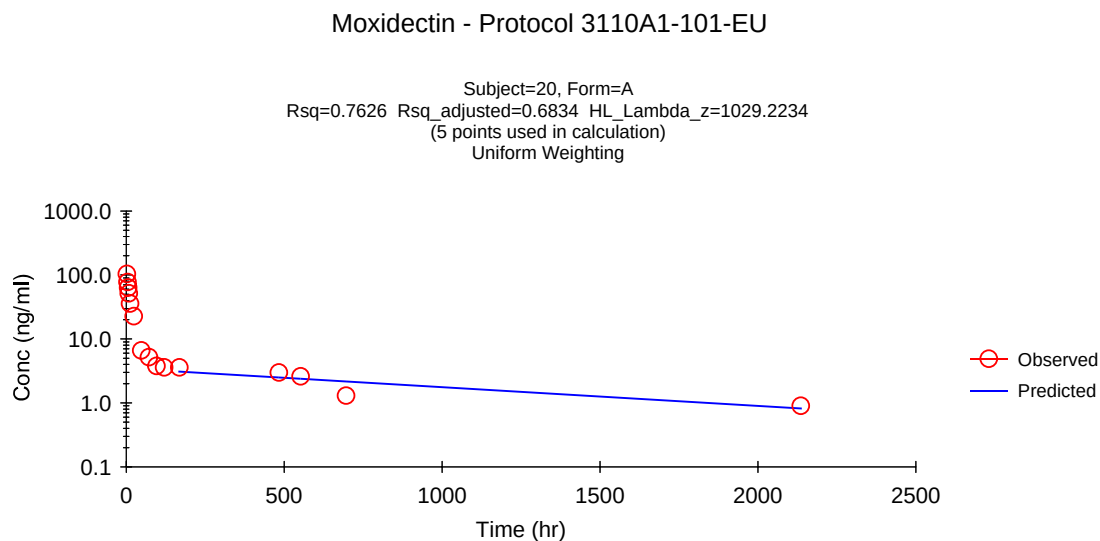
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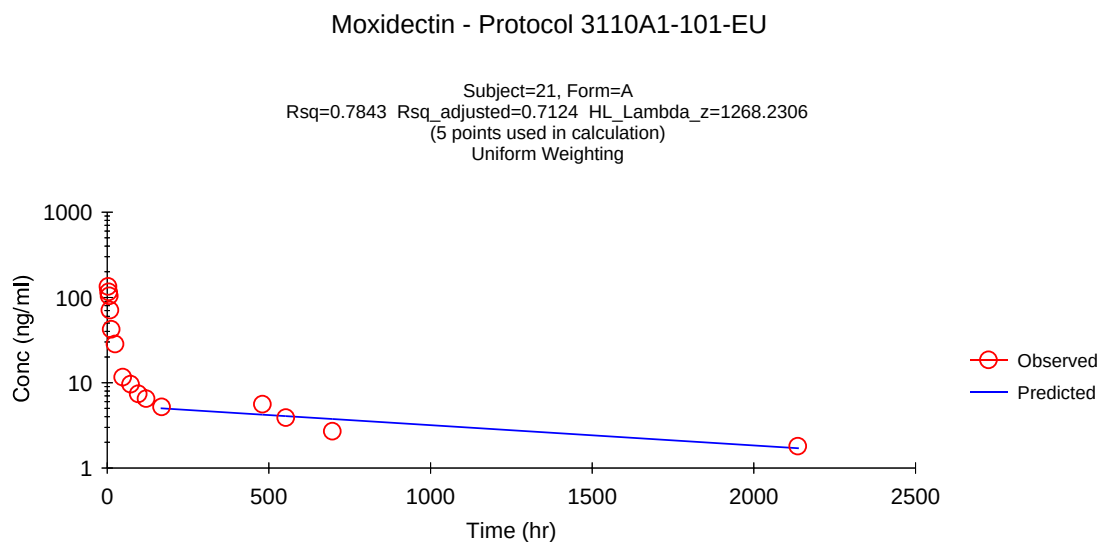
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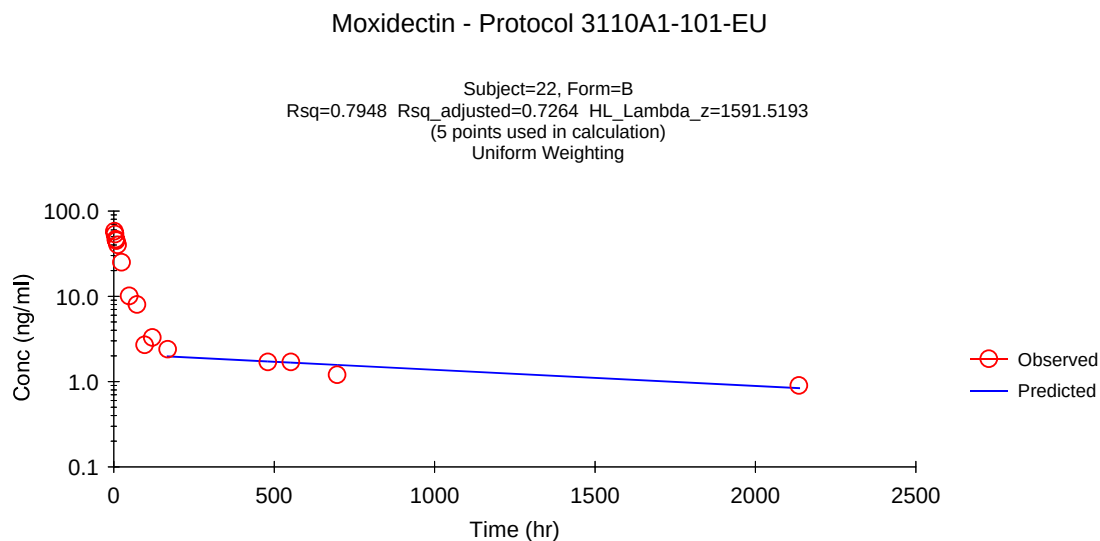
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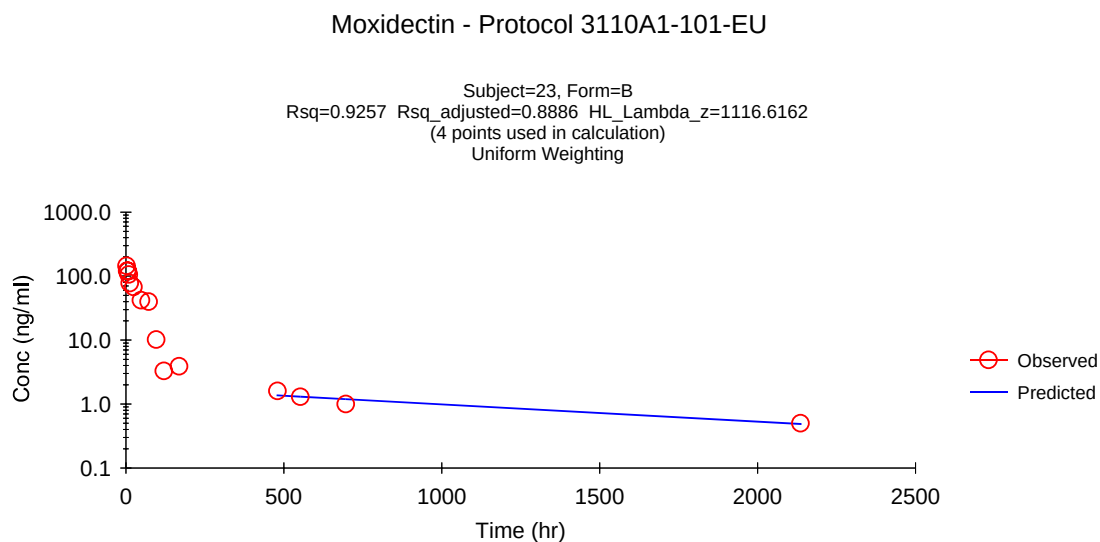
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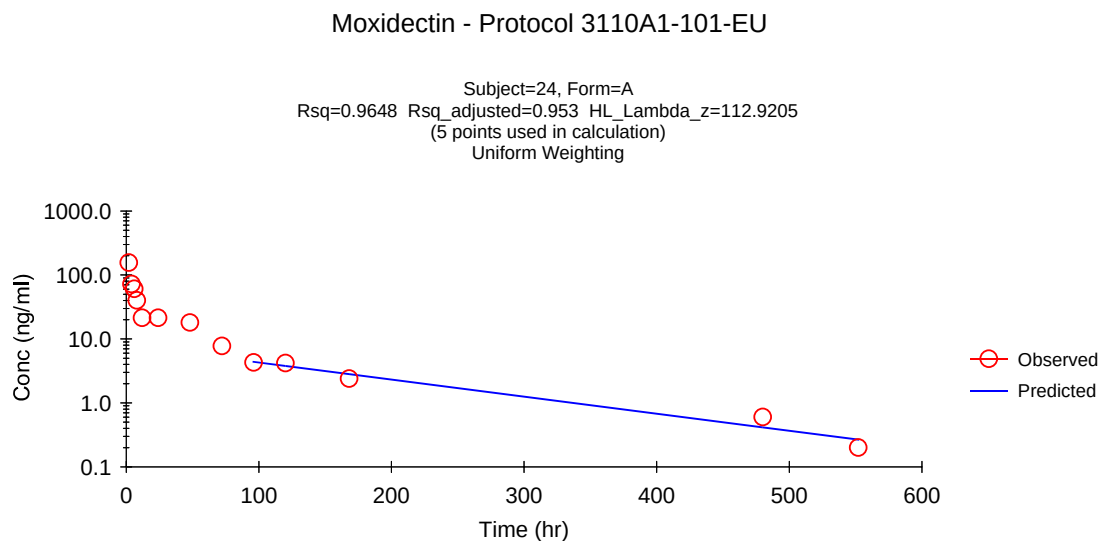
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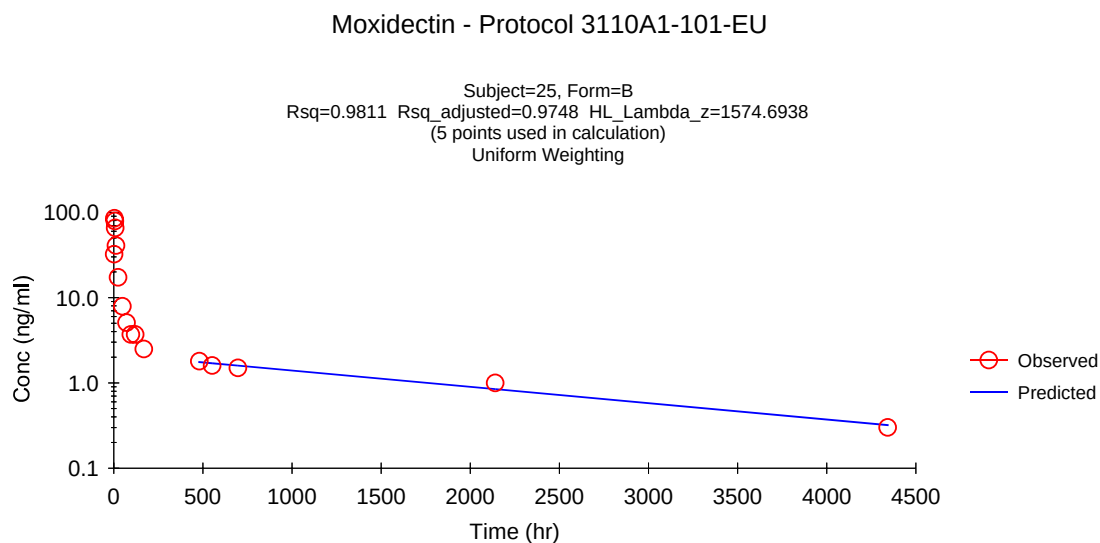
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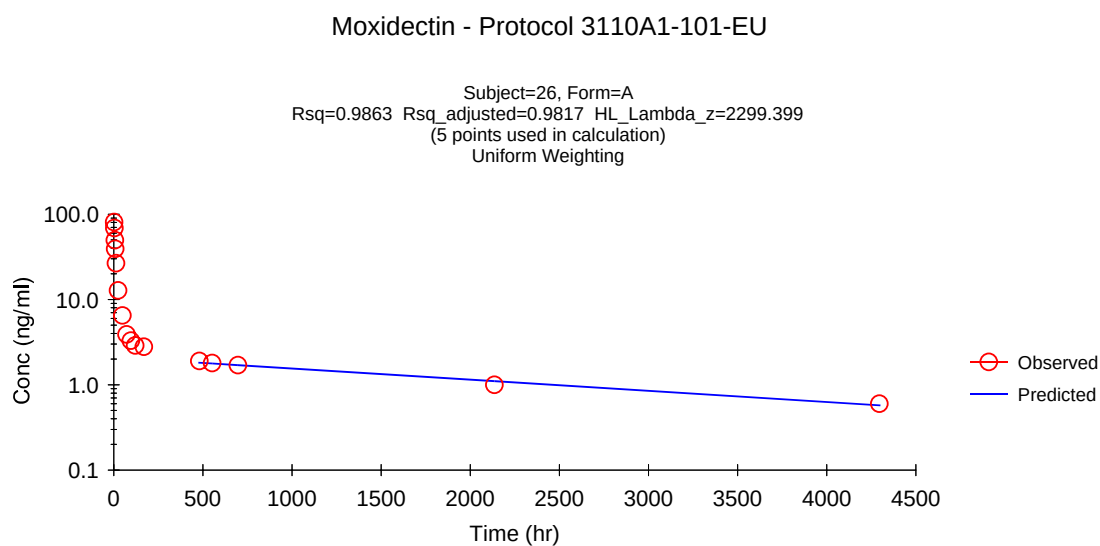
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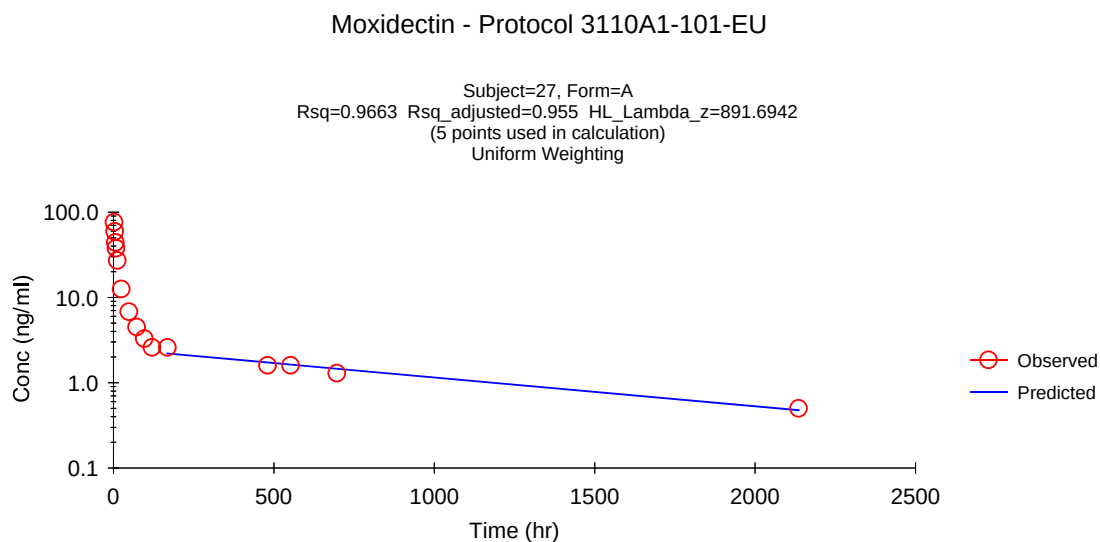
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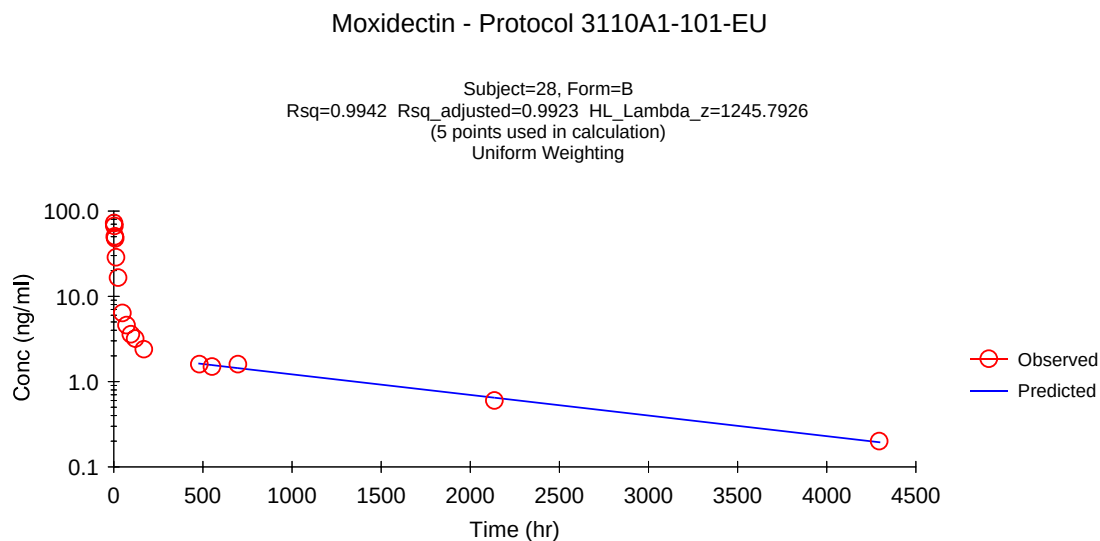
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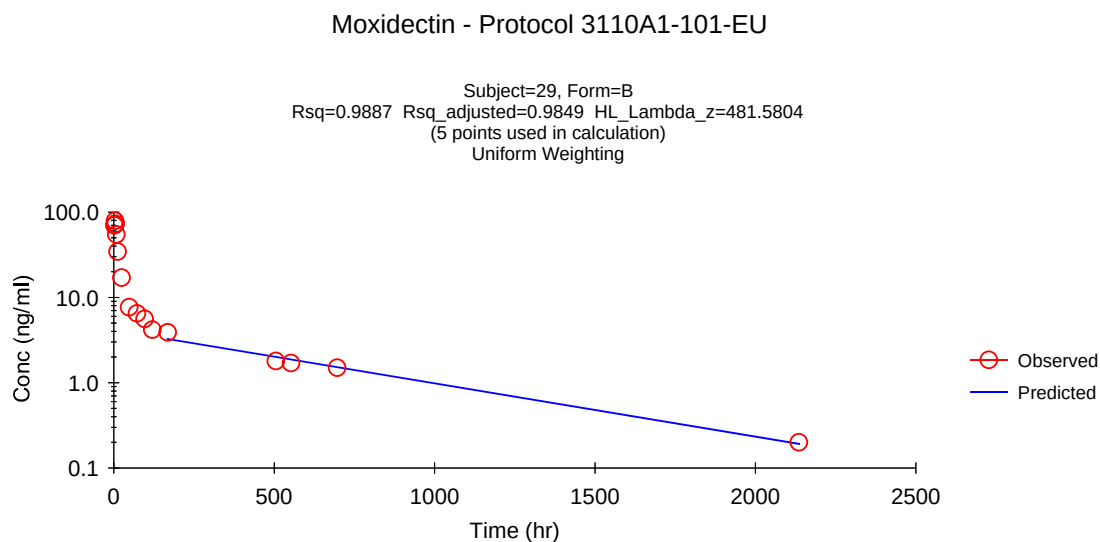
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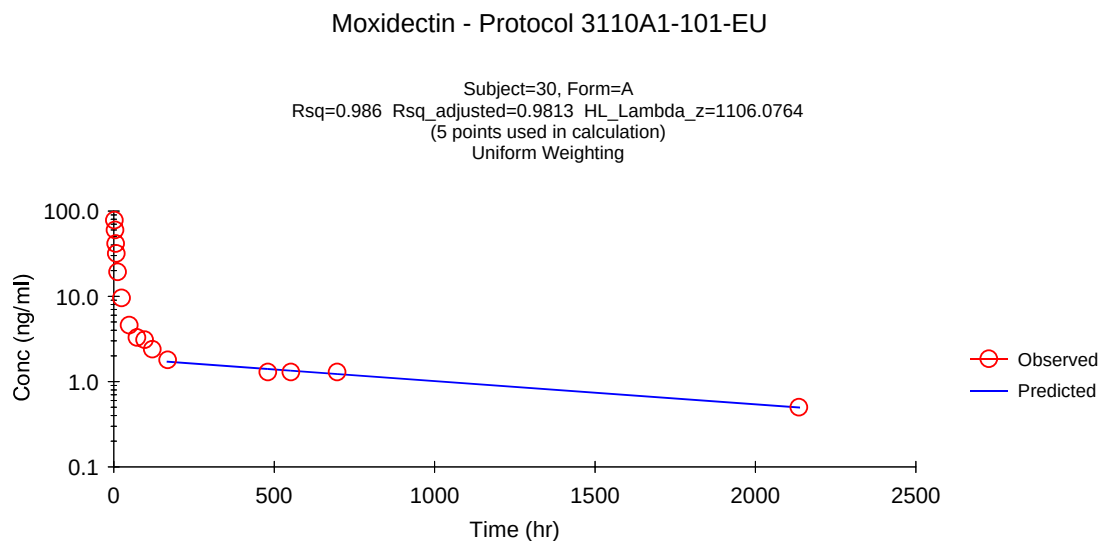
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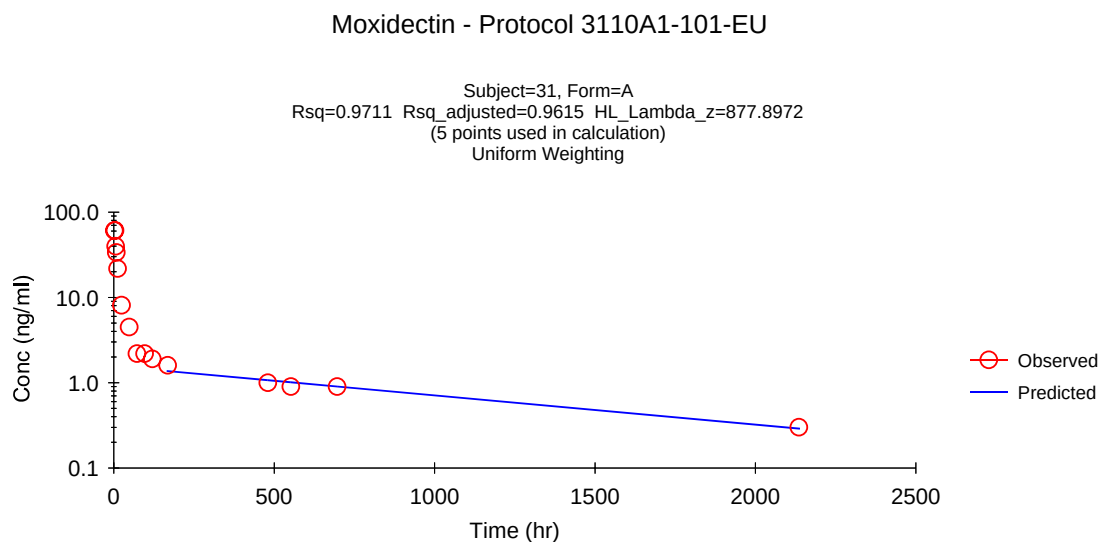
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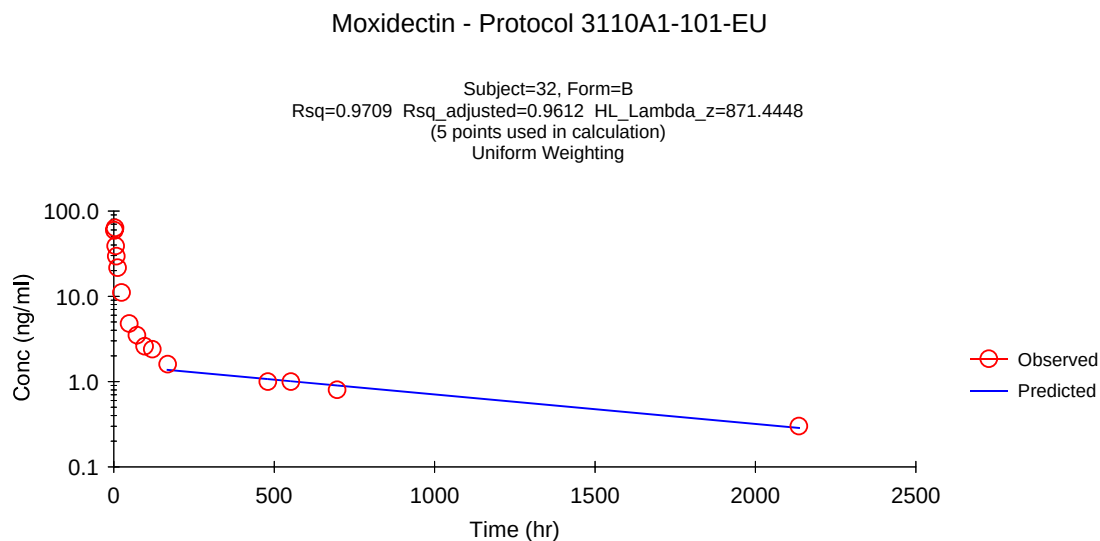
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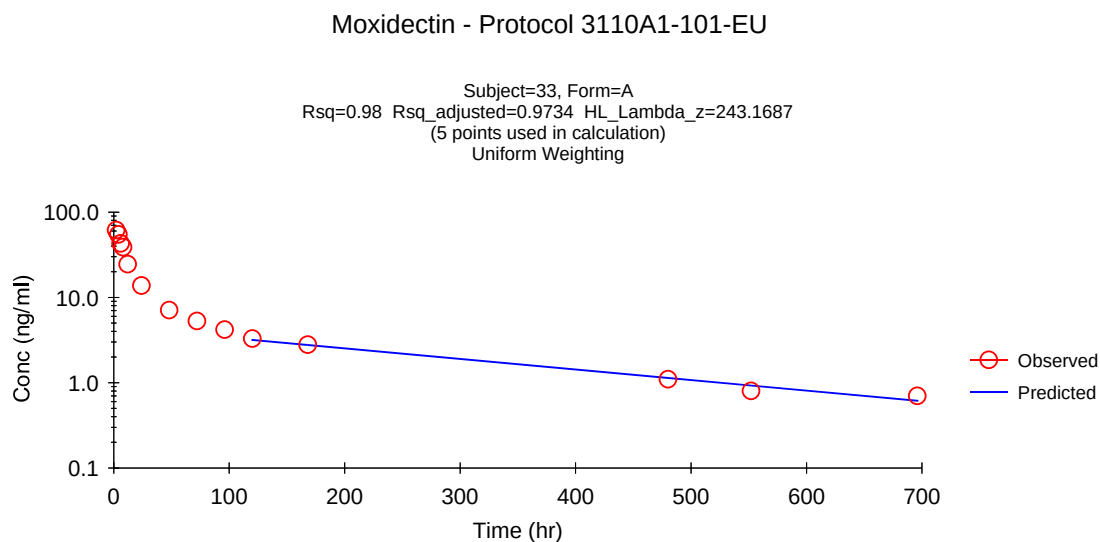
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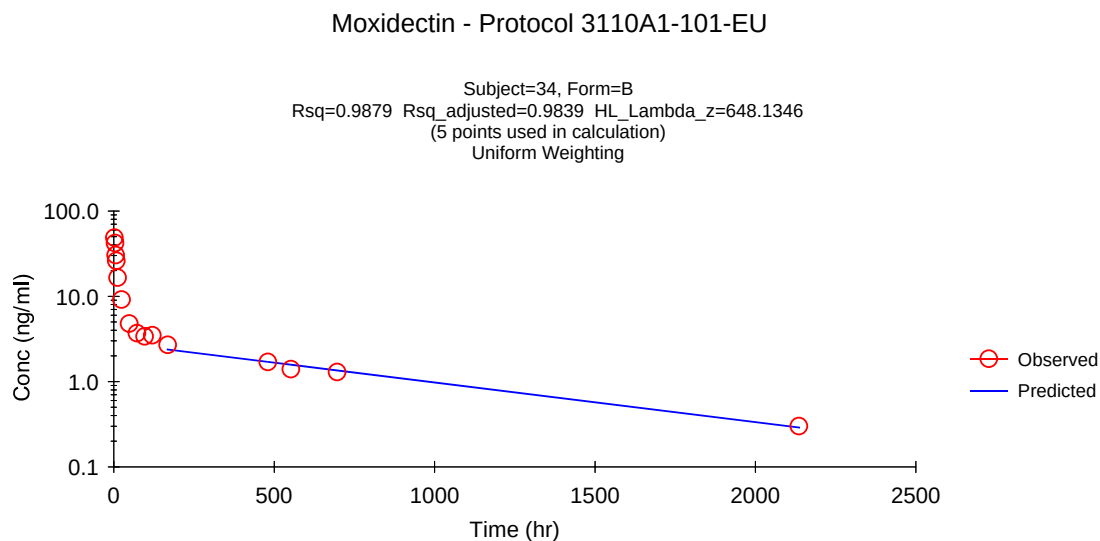
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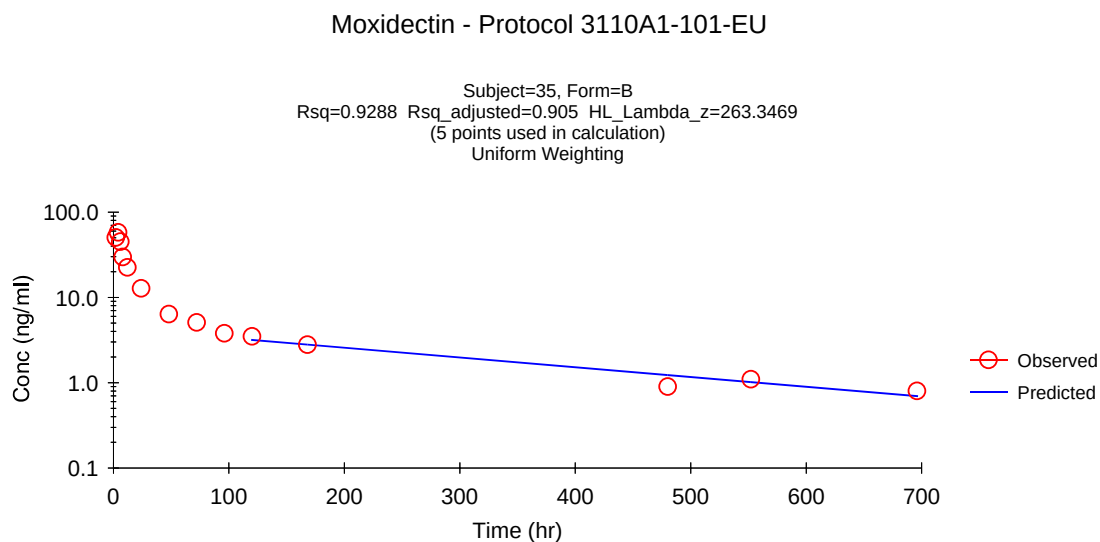
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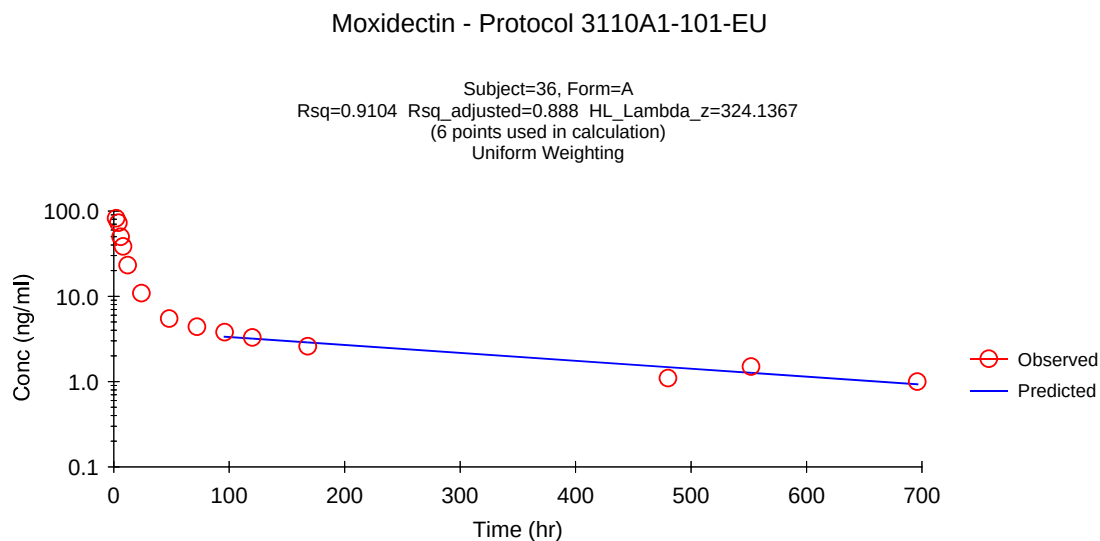
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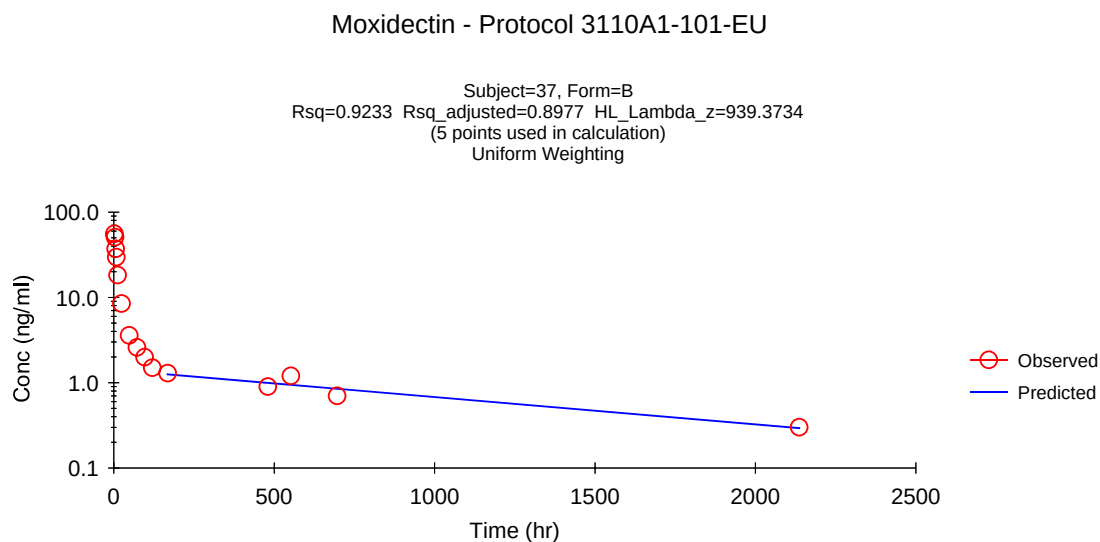
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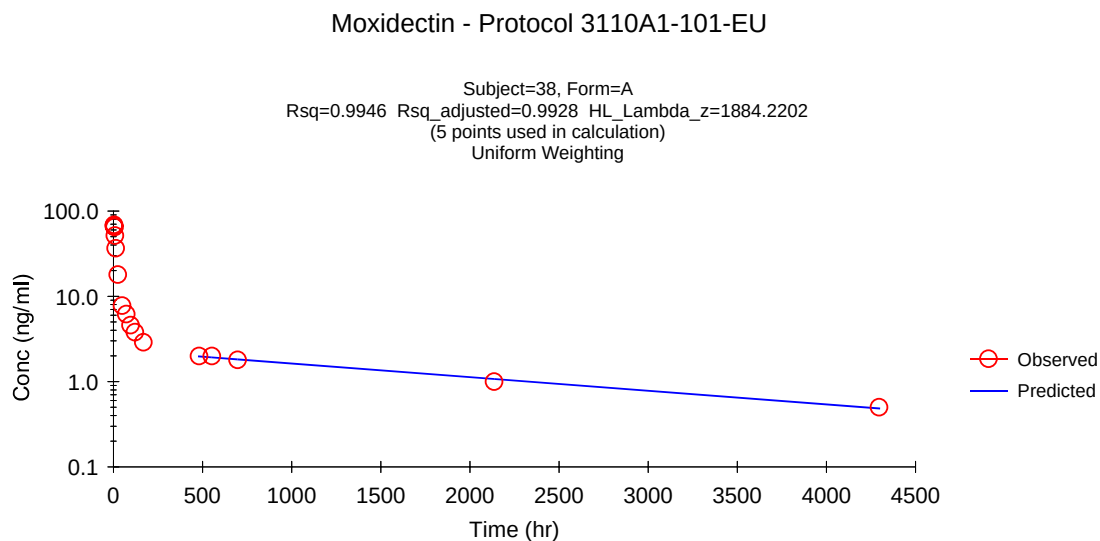
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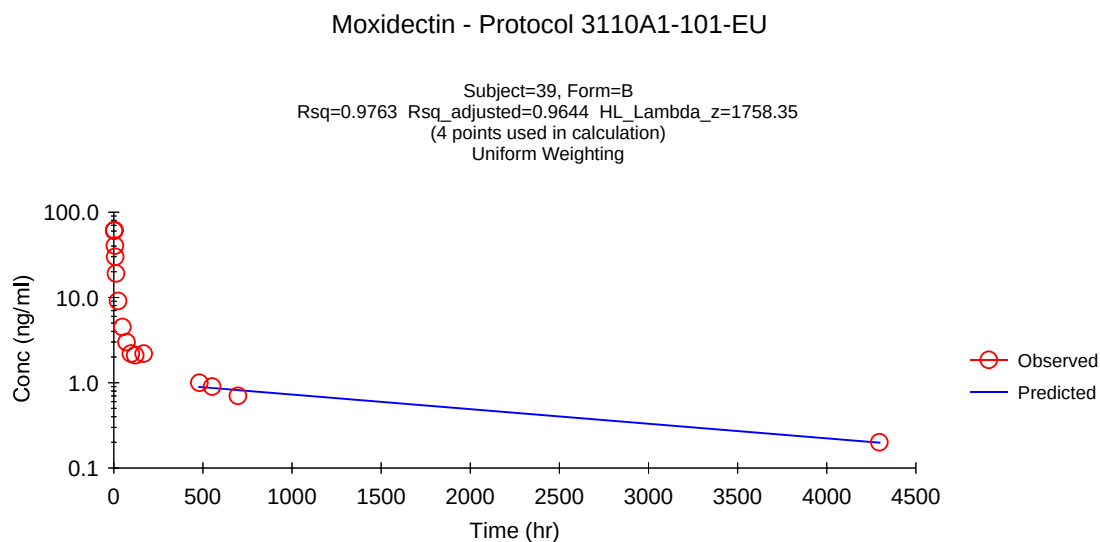
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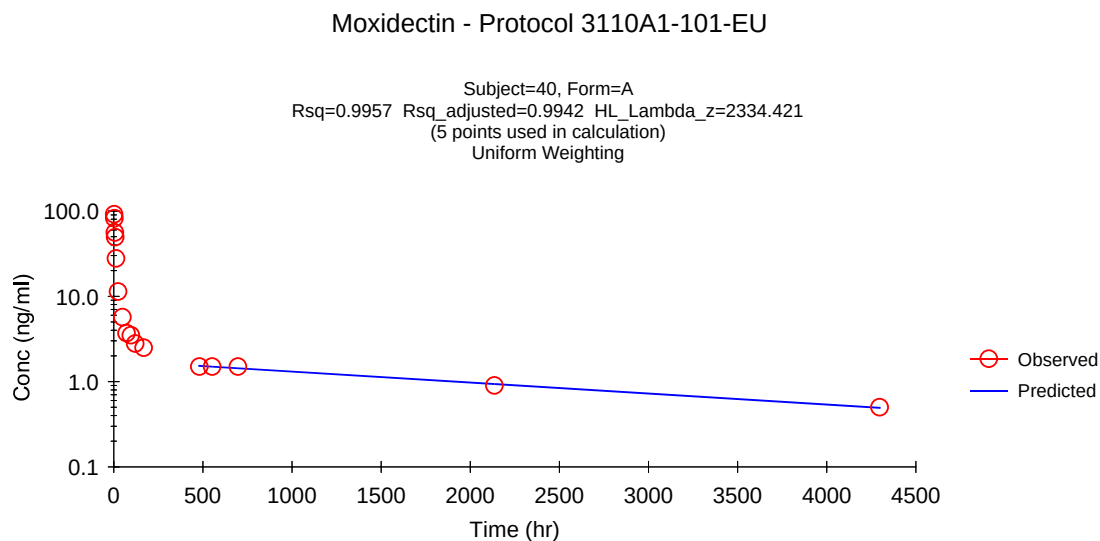
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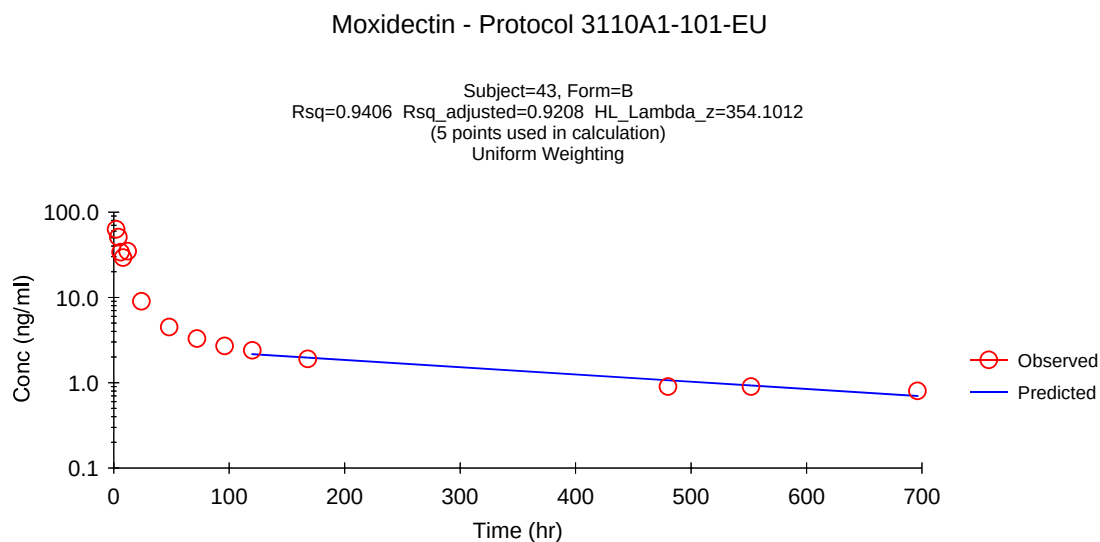
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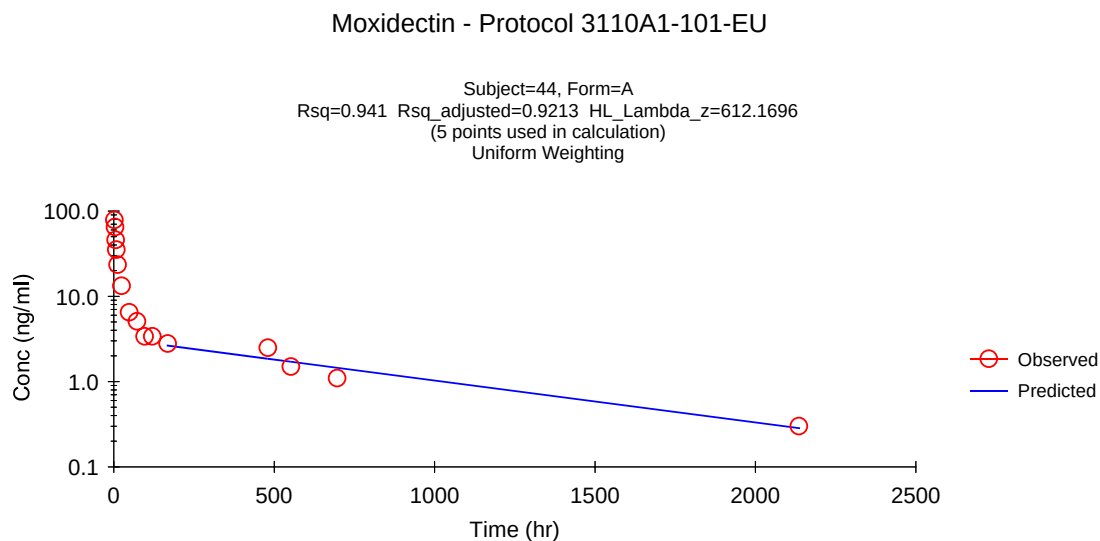
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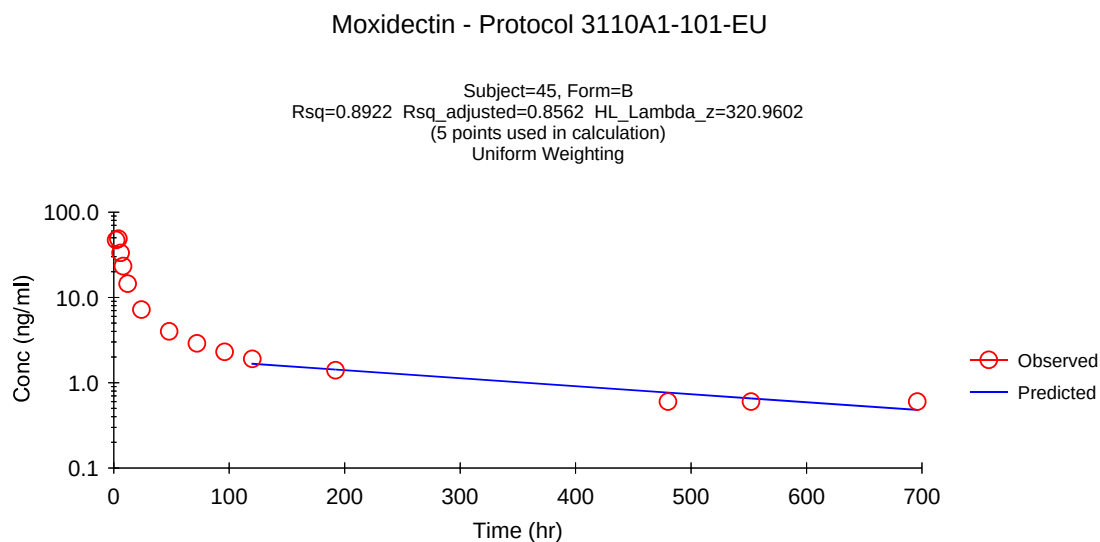
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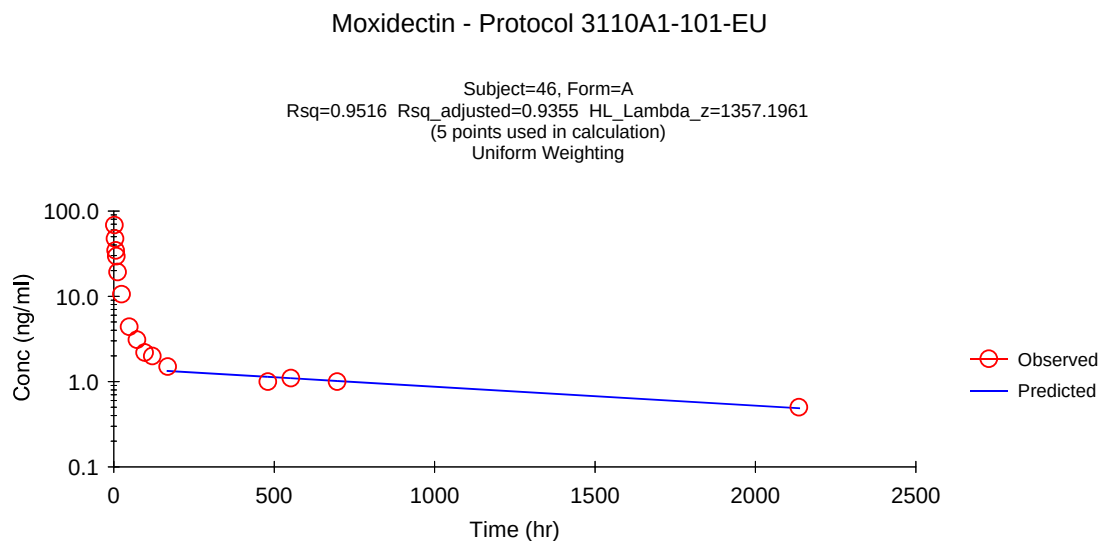
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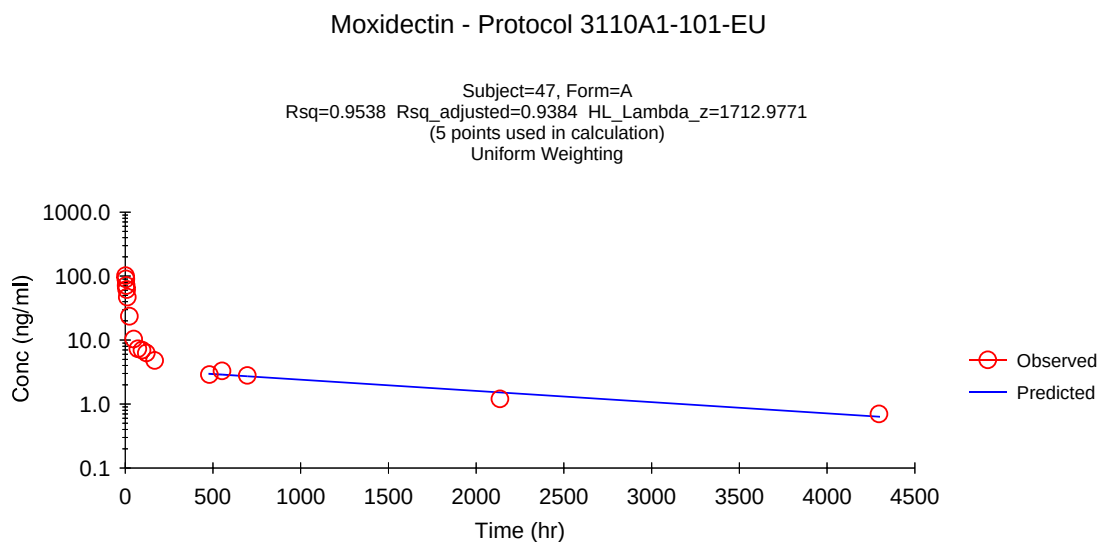
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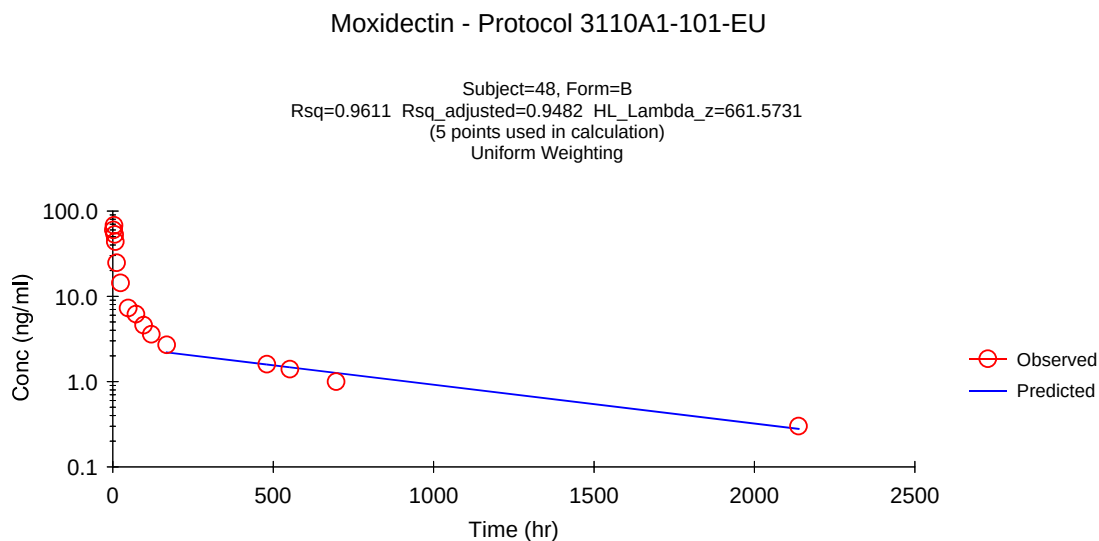
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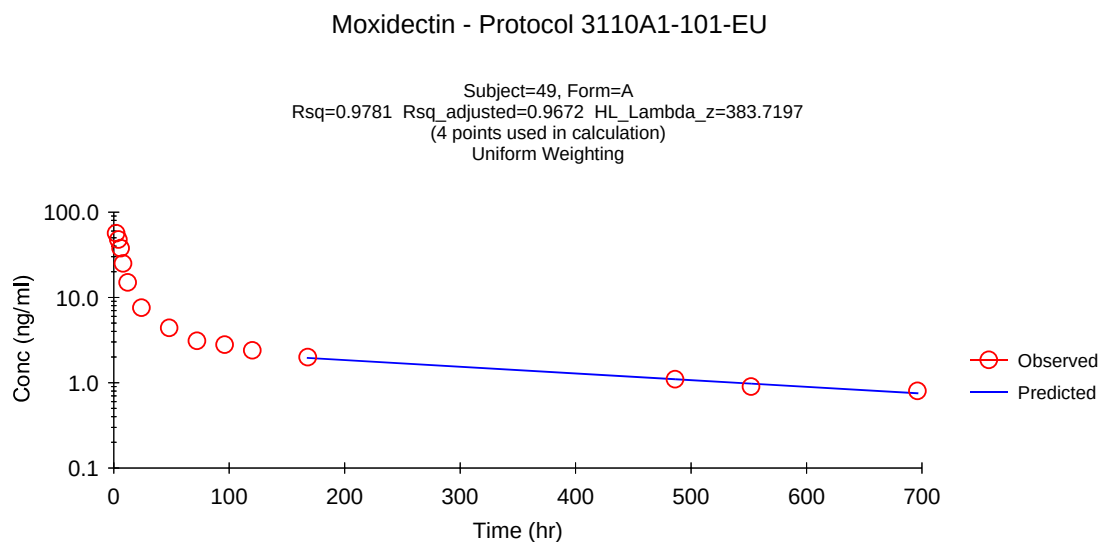
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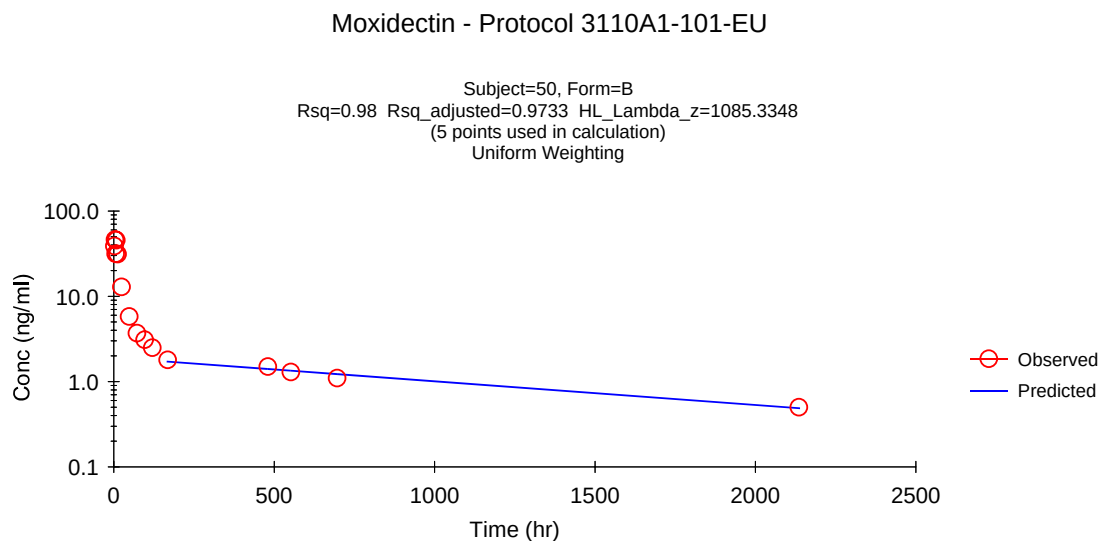
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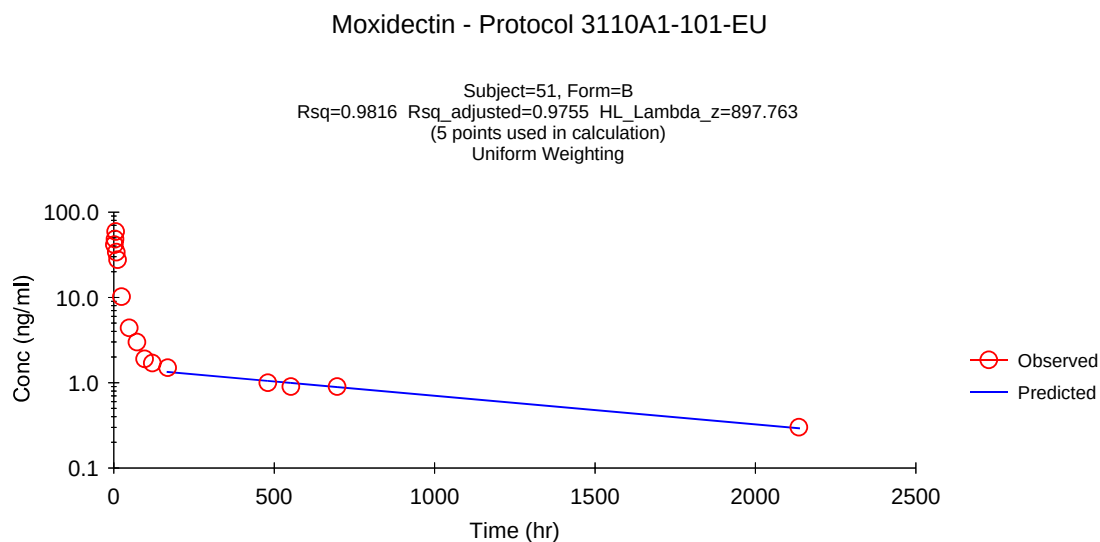
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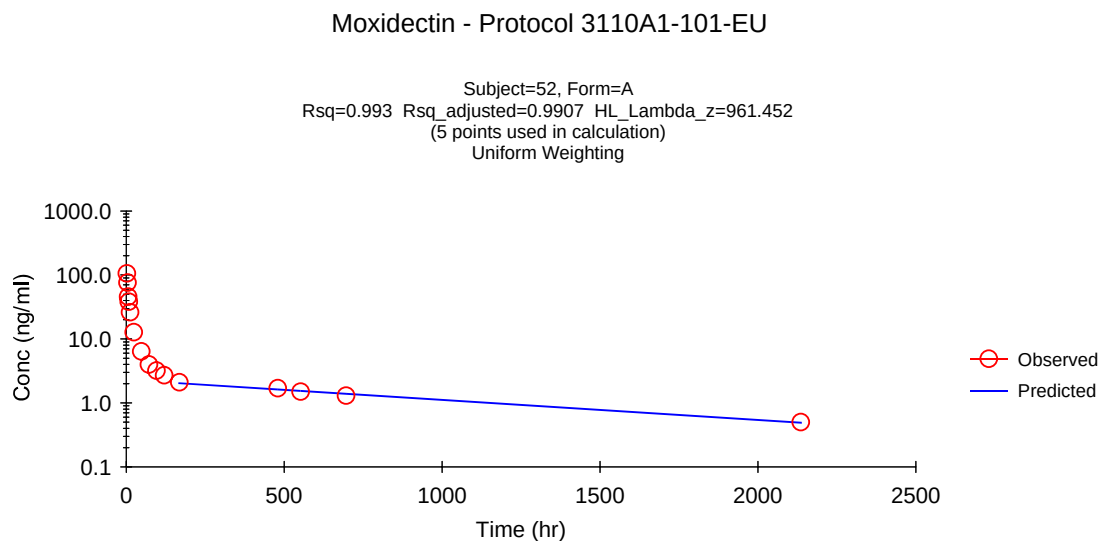
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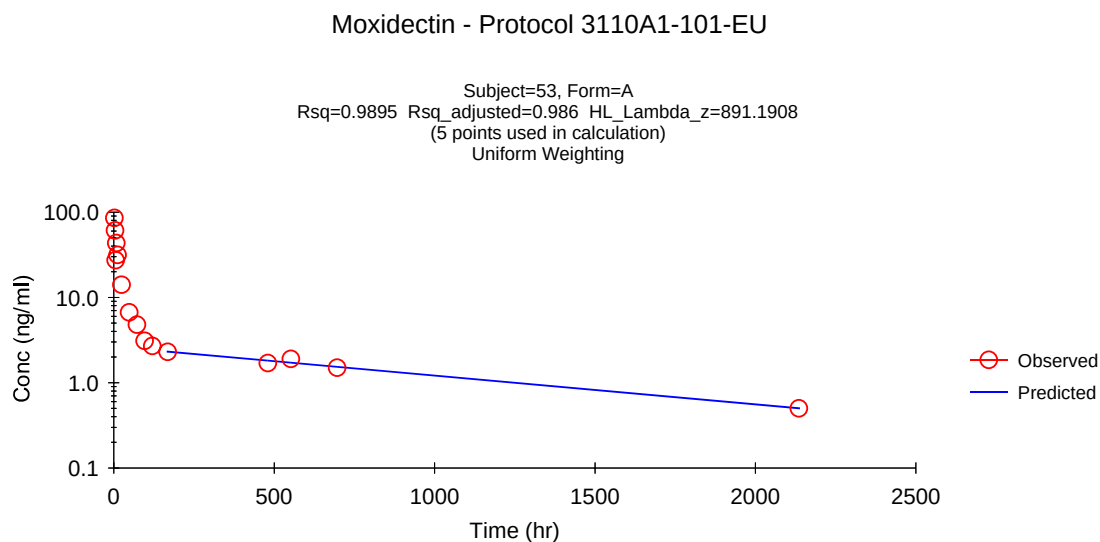
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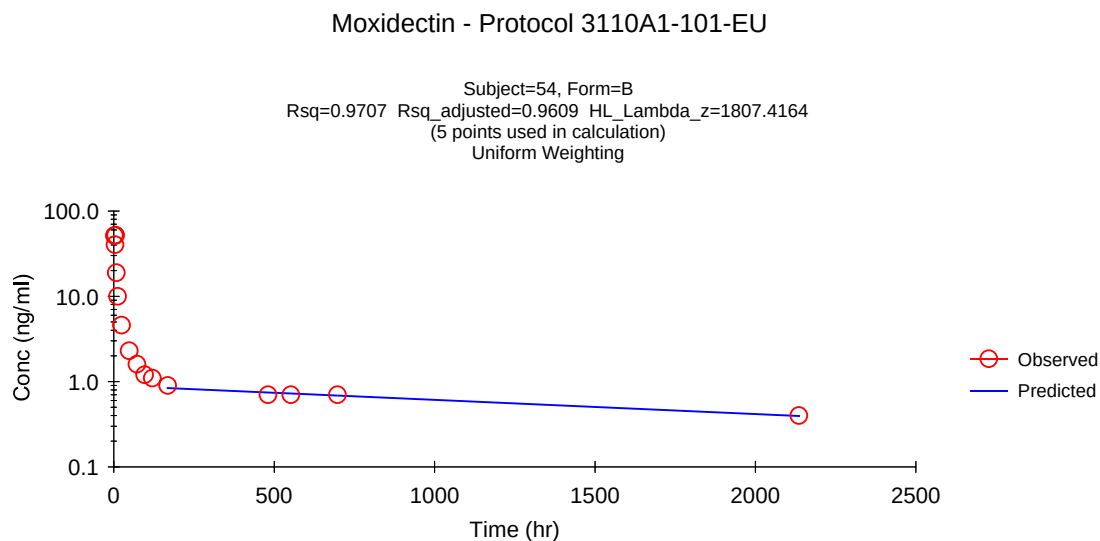
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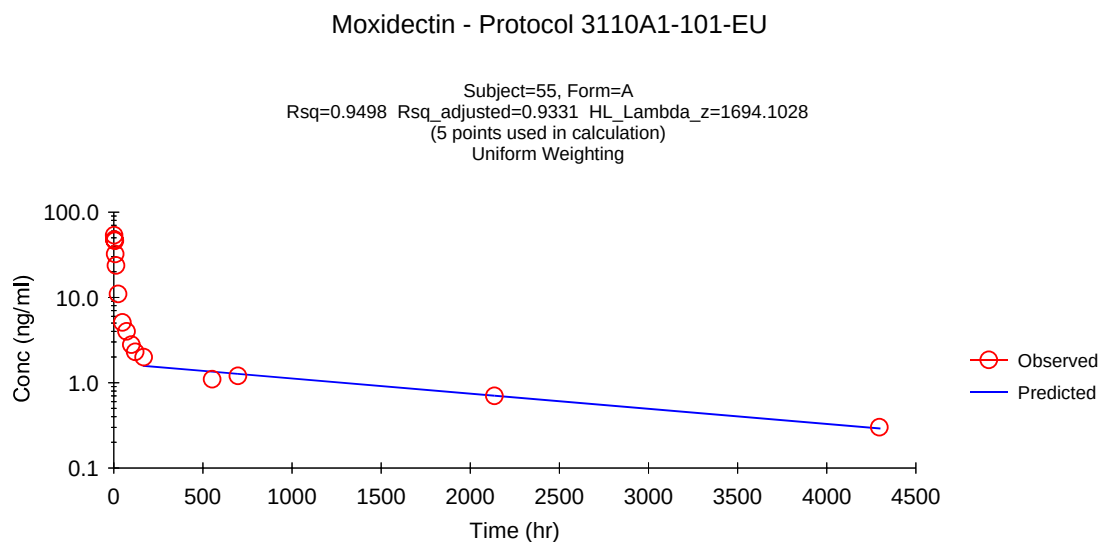
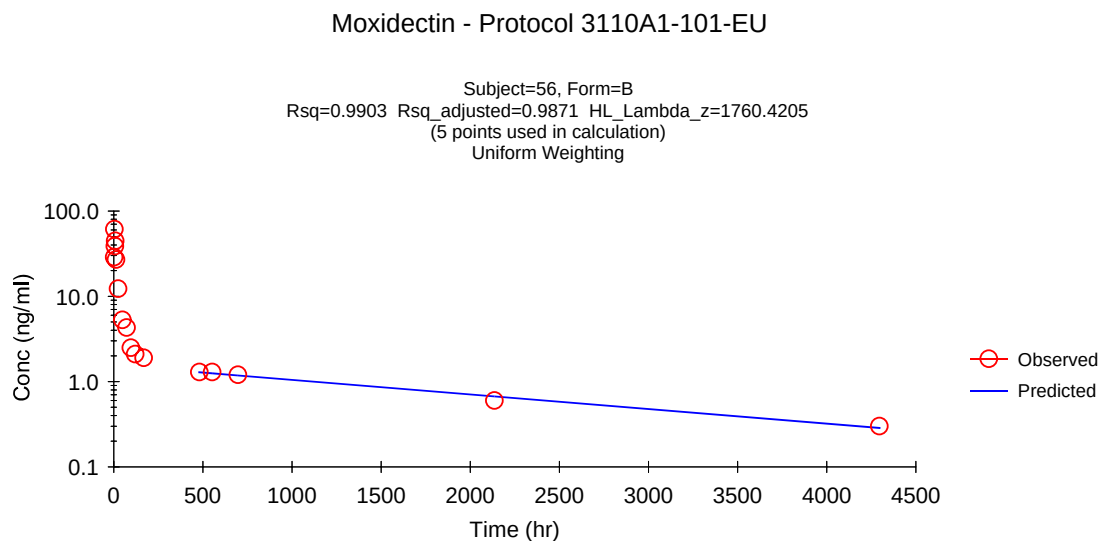


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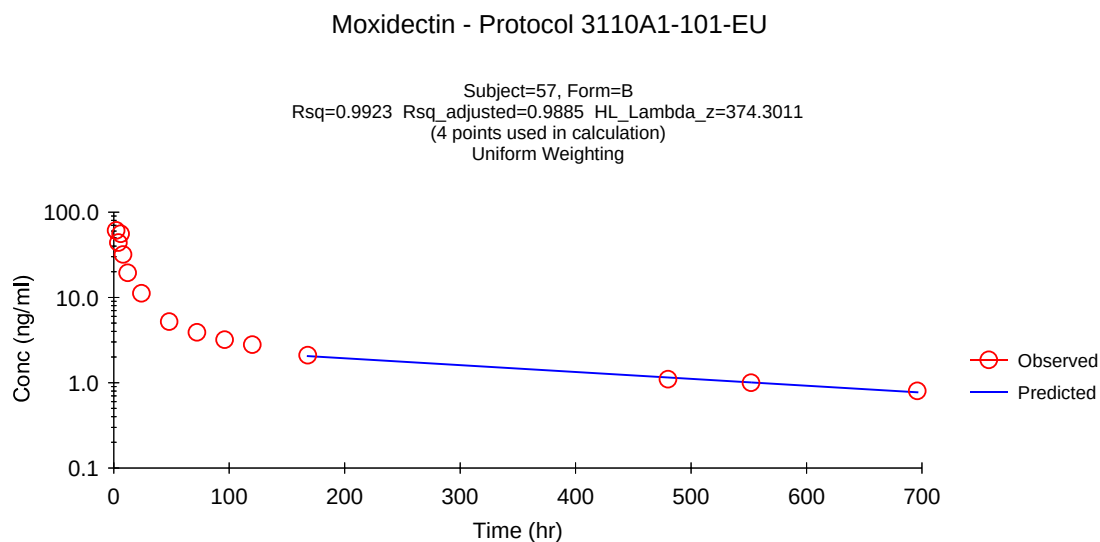


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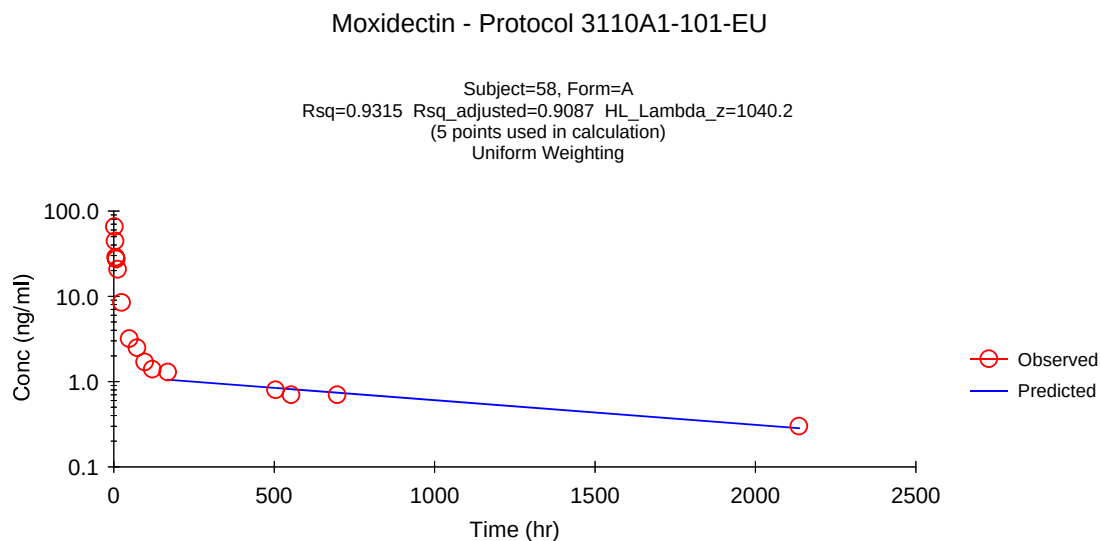


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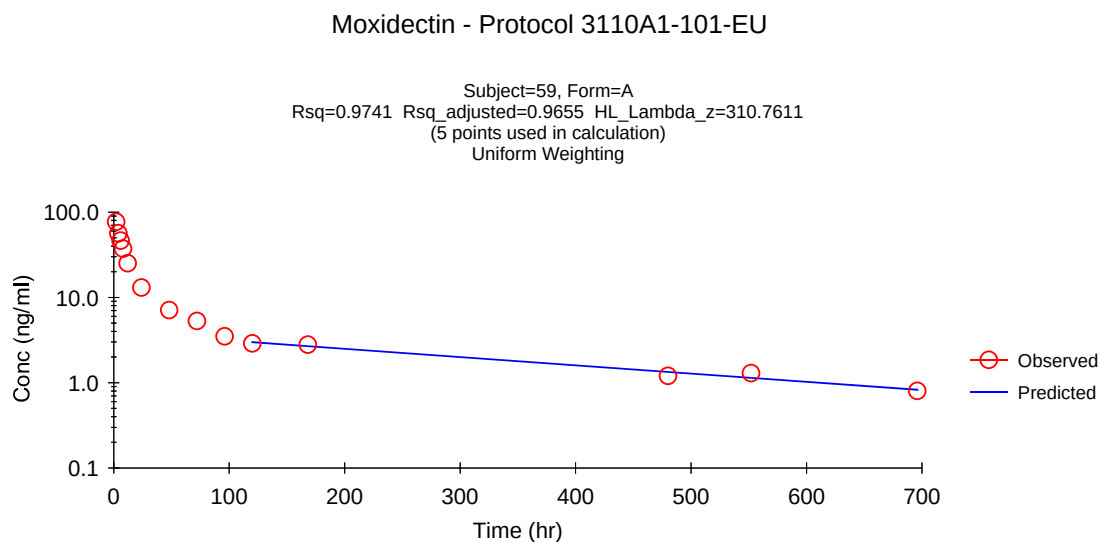
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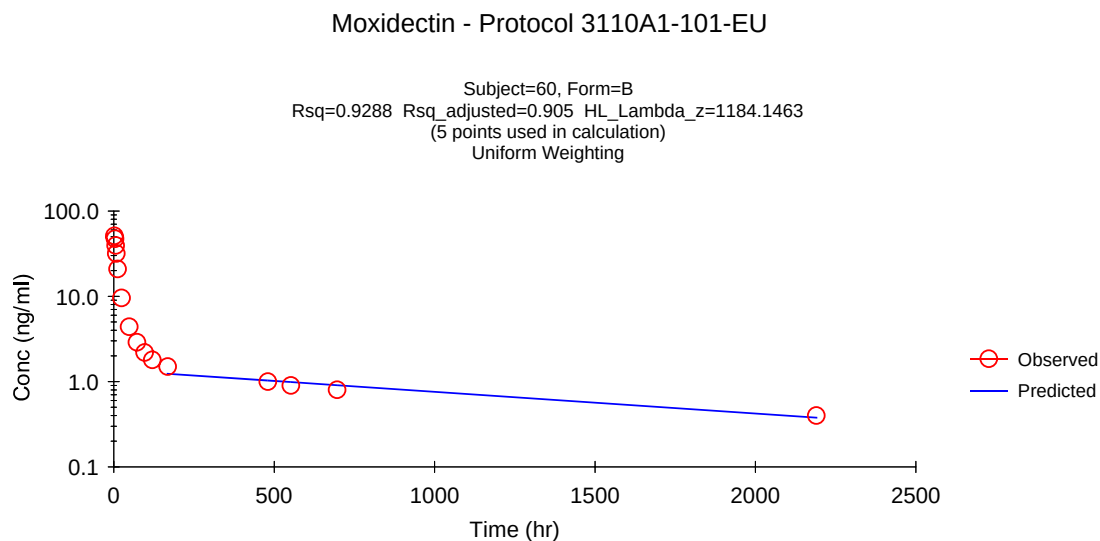
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Summary of data related to recall of Proheart 6 from the US market and FDA advisory committee meeting

(Source documents provided as separate PDF files)

April 2005

Annette C. Kuesel, PhD

WHO/TDR

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1 Abbreviations

AE	Adverse event
FDA	United States Food and Drug Administration
FDAH	Fort Dodge Animal Health, a Wyeth company. Developer, manufacturer and marketer of Proheart 6 as well as other formulations of moxidectin for use in different species of animals
HWP1	Oral heartworm preventative 1
HWP2	Oral heartworm preventative 2
IB	Investigator brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals. Project brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The ICH has issued numerous guidelines on drug development and post marketing evaluation (http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254). Initially the ICH focussed on pharmaceutical for humans. A veterinary project has been added (VICH, http://vich.eudra.org/) .
IMHA	Immune mediated haemolytic anaemia
IMT	Immune mediated thrombocytopenia
NSAID	Nonsteroidal anti-inflammatory drug
PH6	Proheart 6, a sustained release injectable formulation of moxidectin, approved in the US, Canada, Italy, Japan, France, Greece, Portugal, Spain and Korea for the prevention of heartworms in dogs
Q&A	Questions and Answers
SGPT/ALT	Serum glutamic pyruvic transaminase /Alanine Aminotransferase
VICH	International Conference on Harmonization of Technical Requirements for Veterinary Medicinal Products
VM	Veterinary Medicines Division of the FDA
VMAC	Veterinary Medicines Advisory Committee of the FDA

2 Background

Proheart 6 (PH6) is a sustained release injectable formulation of moxidectin, approved in the US, Canada, Italy, Japan, France, Greece, Portugal, Spain and Korea for the prevention of heartworms in dogs for a period of 6 months. PH6 is manufactured and marketed by Fort Dodge Animal Health (FDAH), a Wyeth company, which also developed and markets in the US as well as internationally other formulations of moxidectin for use against parasites in different animal species, including an oral formulation of moxidectin as a heartworm preventative for dogs.

Following the launch of PH6 in June of 2001, the Veterinary Medicines (VM) Division of the United States of America (US) Food and Drug Administration (FDA VM) expressed concern about the number and seriousness of adverse event reports which were submitted by FDAH based on field reports or questions from veterinarians. In October 2004, based on continued FDA concerns, FDAH agreed to voluntarily recall PH6 from the US market. This recall prompted review of the US PH6 adverse event data base as well as local data by the regulatory agencies in Australia, Canada, Japan and Europe. After the review, the agencies of Canada, Japan and Europe confirmed the marketing authorization for PH6 in their countries. Furthermore, the Australian regulatory agency decided that there is no reason to withdraw Proheart 12 from the Australian market. Proheart 12 is a 12-month sustained release formulation of moxidectin which contains three times the dose of Proheart 6. Proheart 12 was developed specifically for Australia where heartworm transmission occurs year round.

The active ingredient in PH6, moxidectin, is being evaluated by WHO/TDR and Wyeth as a drug for the control of onchocerciasis. Based on the data in an extensive animal toxicology study package for moxidectin, Wyeth Research has previously performed two studies in healthy volunteers which indicated that moxidectin, administered orally as a liquid or as a tablet. One conclusion from these studies was that moxidectin the pharmacokinetic and Phase 1 safety profile required for the drug to be evaluated in patients. WHO/TDR and Wyeth concluded a legal agreement for the first study in patients with onchocerciasis and were ready to initiate this study in November 2004.

Following the recall of PH6, this study was put on hold, pending review of the FDA concerns by Wyeth Research Drug Safety and Metabolism experts and the FDA Veterinary Medicine advisory committee (VMAC) review of PH6.

3 FDA VMAC meeting

The agenda included only 1 hour of presentation by the FDA and by FDAH on the safety of Proheart 6, one hour for public hearing and around 3 hours for questions from the panel, prior to the panel having to make their decision.

Prior to the meeting, the participants as well as the public had gotten access to the briefing packages the FDA and FDAH had put together.

3.1 FDA view of post marketing AE data base and AE assessment

The FDA received reports on a total of 21885 clinical manifestations in 6015 dogs. As per FDAH, more than 18 million doses of Proheart 6 were sold during the period in which these clinical manifestations were reported.

The FDA's concerns, as presented at the VMAC meeting, regarding the safety of Proheart 6 are primarily based on:

1. The number of adverse events that the FDA veterinarians classified as possibly or probably drug related. No safety related AEs were classified as 'definitely drug related'. Events classified by the FDA as definitely drug related (32) were all

related to inefficacy reports.

Classification of causality, i.e. relationship of the AE to PH6 by FDA is based on application of the 'modified Kraemer system' by 1 of 7 veterinarians, 6 of whom are working for the FDA on a part time basis. (see Appendix 5.1)

A total of 18939 AEs in 5659 dogs were assessed by the FDA as possibly (15334 AEs, Kraemer score of 0 to 2), probably (4310 AEs, Kraemer score of 3 to 5) or definitively related (32 inefficacy assessments, Kraemer score 6) to PH6, including 9856 AEs with concomitant administration of vaccines or (rarer) other drugs and 6316 AEs without concomitant administration (for the remaining AEs it is unknown whether drugs or vaccines were co-administered).

The number of AEs thus classified by the FDA as possibly drug related or probably drug related was reported to be twice that in the FDA data base for all other (monthly) heart worm preventatives since their approval.¹

2. The fact that reports have not decreased over the approximately three years PH6 has been on the market. **NOTE:** The FDA is considering only absolute numbers, not the numbers of reports relative to the doses sold which were provided by Fort Dodge (see Table 1)
3. The type of AEs reported and assessed by the FDA veterinarians as possibly or probably drug related (see Table 1)
4. The timing of the occurrence of these AEs which co-incides for 15595 Adverse events with the time of increasing or peak (day 0-day 14) moxidectin serum concentration.
5. 485 deaths (with pathology reports reported by the FDA verbally during the meeting available for about 1/3, the FDA had not evaluated whether the pathology reports were consistent with the clinical picture prior to death and whether they indicated a consistent pathology that could be attributed to PH6).
6. The fact that post marketing AEs are underreported.

¹ During the Q&A session it was noted that over the approximately last 12 months, the number of AE reports for oral heart worm preventatives has increased significantly. Because of resource constraints, the FDA has not yet entered those into their data base, thus, they are not included in the comparative AE statistics provided by the FDA. Their inclusion is, however, unlikely to result in a significant change in the relative numbers of AEs reported.

Table 1: Adverse reactions assessed by FDA as probably or possibly related to PH6 as per modified Kraemer system

	Doses sold ¹	Anaphylaxis/ anaphylactoid reactions	Convulsions/ seizures	Liver sign: Elevated SGPT/ALT	Liver signs: Liver lesions	Haematology - Anemias: IMHA	Haematology - Thrombocytopenias
Total number		1828*	405**	222	88	77	135
July 2001-June 2002	Appr. 4.0 Million	704*	110**	34	9	14	26
July 2002-June 2003	Appr. 5.5 Million	544*	126**	52	15	24	28
July 2003-June 2004	Appr. 7.6 Million	487*	118**	92	37	26	52
Probably PH6 related		913*	30**	2	0	1	1
Possibly PH6 related		907*	348**	190	65	66	123
Death FDA assessed as possibly or probably PH6 related		54	61	38	47	34	45
With concomitant vaccine/drug administration		731	215	112	44	34	76
Concomitant Tx unknown		273	76	30	8	14	22
within 3 hours of PH6 administration		80%	16%	6%	3%	Not reported	Not reported
Within 3-24 hours		16%	14%	6%	11%	3% (<24 hrs)	2% (<24 hrs)
within 1-6 days		2%	38%	37%	20%	12%	29%
within 7-30 days		1%	20%	35%	29%	49%	43%
within 1-3 months		0.1%	8%	8%	23%	27%	19%

¹ Number of doses sold derived from figure 4.2.2-2 in FDAH briefing document (see Appendix 5.3).

Bolded: adverse reactions in the label/package insert/prescribing information

IMHA: Immune mediated haematologic anaemia

*, ** total number unclear - see below Notes to Table

Notes to Table:

- Anaphylaxis/anaphylactoid reactions:
total number of reactions not clear since FDA also reports 1837 dogs involved in 1820 episodes assessed as probably or possibly related.
- Convulsions:
total number unclear since FDA also reports 381 dogs involved in 378 episodes assessed as probably or possibly related.
- Other neurologic signs
reported in 484 dogs included ataxia, trembling, nervousness, confusion, paresis.
- Liver signs: Elevated SGPT/ALT levels.
During the Panel Question and Answer session, the FDA reported that in the vast majority of cases there is no information on the enzyme levels prior to PH6 administration or normal values for the testing laboratory.
294 dogs had liver related clinical manifestations determined by the FDA as possibly or probably PH6 related. Among those 222 had elevated SGPT/ALT levels and 88 liver lesions noted on the pathology reports.
- Liver signs: liver lesions
Necrosis or hepatocellular vacuolization was mentioned in some of these pathology reports. FDA as well as FDAH reported that there was no consistent pathology to be seen on the available slides.
- Haematologic signs regarded by FDA as possibly or probably PH6 related were reported in 551 dogs. These included 225 dogs with anaemia classified by the FDA as possibly or probably related to PH6 and 135 episodes of thrombocytopenia.

Conclusions

The FDA concluded that Proheart 6 is not as safe as other heartworm preventatives and given that it is used with the intent of preventing disease and alternatives with fewer reported serious adverse events exist, Proheart 6 should remain off the market.

3.2 FDAH assessment of AEs reported post-marketing and new information provided

The FDAH briefing document includes a summary of the results of moxidectin toxicology studies (see Moxidectin Investigator Brochure), clinical trials conducted with PH6, FDAH's postmarketing surveillance system and analysis of the adverse events FDAH reported to the FDA, a summary of the analysis of adverse events reported in a veterinary clinic association data base and experience with efficacy post marketing. The post-marketing related safety relevant information is summarized here. The remaining information can be read in the briefing document provided.

All data available as of April 2004 relevant for the assessment of the safety of moxidectin in animals as a basis for the decision to evaluate moxidectin in humans are included in the investigator brochure (IB) which is also part of this briefing package.

3.2.1 Fort Dodge Animal Health assessment of post marketing AEs

FDAH complemented the data on the number of AEs reported with an estimate of the AE rate based on the number of doses sold. The total number of doses sold was over 18 Million.

Estimation of event rates is required by the draft STEP 4 International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline 29 for periodic safety reports.

FDAH categorized and reviewed AEs in three categories:

Injection site reports (all regarded as related to PH6)	Average reporting rate from start of marketing to 31 August 2004 reporting rate 0.2 per 10 000 doses sold
Allergy event reports Signs $\leq$ 48 hours and consistent with allergy for species, including as per product label: facial swelling, angioedema and urticaria, alone or in combination with gastrointestinal signs such as vomiting or diarrhea, anaphylaxis or a low percentage of less common signs such as lethargy.	Average reporting rate from start of marketing to 31 August 2004 reporting rate 1.26 per 10 000 doses sold. 37 % of reports included concomitant vaccine administration. For comparison: Vaccine Duramune Max 5/4L has an allergy reporting rate of 0.4/10 000 doses sold, Rabvac a rate of 0.5/10 000 doses sold. >80% of events are self-limiting
Non-Allergy Event Reports (evaluated individually for relationship with PH6)	Average reporting rate from start of marketing to 31 August 2004 reporting rate 1.19 per 10 000 doses sold. 42% if reports included concurrent vaccine administration. For comparison: Vaccine Duramune Max 5/4L has an allergy reporting rate of 0.3/10 000 doses sold, Rabvac a rate of 0.35/10 000 doses sold.

FDAH used the Step 4 draft VICH pharmacovigilance draft guidelines for assessment of causality, i.e. the relationship of an AE to PH6 (see section 5.2). These guidelines were developed by the VICH (which includes veterinary product regulators from Europe, Japan, as well as the US) to provide guidance on global pharmacovigilance harmonization. The criteria are provided in Appendix 5.2.

During their evaluation of drug relationship of the AEs, FDAH assumed initially that all events were possibly related to PH6. This relationship was downgraded to 'unlikely' only for AEs for which sufficient information existed to establish that the event was not likely associated with PH6 use because there were other more plausible explanations for the event.

Remaining 'possible cases' were further reviewed to assess whether there was a 'probable' relationship to PH6 as per VICH guidelines. Those AEs in the possible category for which there was no basis for assigning 'probable' were classified as 'potential' (modification from VICH nomenclature).

For AEs that were regarded as being probably related to PH6, FDAH calculated the frequency of these AEs based on the number of doses sold in the calendar year in which the PH6 dose that was associated with the probably related adverse event was administered.

Table 2: Adverse reactions assessed by FDAH² as probably or possibly related to PH6 as per VICH guidelines

	Doses sold ¹	Allergic reactions	Neurologic AEs	Hepatic Events	Haematologic events	Cardiac Events
Total number		2652	1131	544	782	740
2001	Appr. 4.5 Million		121	48	88	107
2002	Appr. 3.9 Million		427	173	275	269
2003	Appr. 6.6 Million		304	158	220	196
To Aug 2004			279	165	199	168
Probably PH6 related (rate /10000 doses sold) ²		Not assessed	245 (0.12)	156 (0.07)	184 (0.09)	47 (0.02)
Potentially PH6 related		Not assessed	886	388	598	693
Concomitant vaccine/drug administration			47%	38%	49%	49%

¹ Number of doses sold derived from figure 4.2.2-2 in FDAH briefing document (see source documents provided).

² Based on FDAH assessment - the reduction in the number of probable adverse events recommended by the external advisers based on their review of the data is not taken into account.

Bolded: adverse reactions in the label.

3.2.1.1 Neurological events

These included seizures and ataxia as primary clinical signs, all other individual clinical signs each accounted for less than 10% of the total neurological events.

The case summaries of 75% of the 245 AEs assessed by FDAH as probably related to PH6 were reviewed by an outside consultant, a veterinary neurologist from Cornell University. The neurologist noted that seizures were the most common clinical sign reported, which is consistent with general observations in the practice of clinical neurology. The most common cause of seizures in dogs is idiopathic epilepsy. He concluded that '... There is no rational scientific reason to believe that this product [PH6] played any role in the post-injection clinical signs reported in these case summaries'.

Potentially related neurologic events include events classified as allergic and events with non-specific neurological signs (e.g. muscle tremors) seen without other clinical signs and therefore not likely due to a primary neurological disorder.

3.2.1.2 Hematologic events

All data available on the 184 cases determined by FDAH as probably PH6 related were provided to an outside consultant (a clinical pathologist from Purdue University) for review.

He considered only 151 events as *probably* PH6 related, including 79 cases that, based on a conservative case definition, could be immune mediated, even though in many of these cases not enough data were available to establish a definitive diagnosis of Immune mediated hemolytic anemia (IMHA) or immune mediated thrombocytopenia (IMT).

Of these 79 cases, 27 cases occurred too soon following PH6 injection (14 cases, 0-7 days) or too long after PH6 injection (13 cases, >30 days) to be likely to be an event precipitated by PH6.

3 cases of apparent immune mediated bone marrow hypoplasia/aplasia (IMMD) were identified. The timing of all 3 events indicates that they were unlikely to be related to PH6.

3.2.1.3 Hepatic events

The 156 AEs categorized by FDAH as probably PH6 related were reviewed by the outside consultant (the clinical pathologist from Purdue University). He assessed that 56 of these were not probably PH6 related hepatic events. The remaining 100 were reviewed by him in detail.

Among these 100, there were 43 cases of possible primary liver disease and 57 cases which the consultant regarded as probably not primary hepatic events with the mild nonspecific elevations in hepatic enzymes thought to be due to anorexia and/or stress. Given that more than 18 million doses of PH6 were sold it is possible that the 43 cases represent the normal baseline of mild unspecific liver enzyme elevations in the canine population.

Review of the 15 pathology reports available for the 43 cases of possible primary liver disease by a FDAH pathologist showed no pattern of liver pathology indicative of a common toxicological agent in all or a subset of the 15 cases.

3.2.1.4 Cardiac events

60% of AEs occurred within 48 hours of PH6 administration, which is not indicative of a direct cardiac effect. Based on other events reported at the same time an indirect effect associated with an allergic event cannot be ruled out.

Histopathological review by an FDAH pathologist of the slides from 2 cases of cardiac necrosis identified in an FDA presentation revealed cardiac pathology secondary to

uremia in a boxer and chronic heart disease that clearly predated PH6 administration in a Labrador retriever.

3.2.1.5 Deaths

The FDA classified 485 deaths as possibly related to PH6 (77% of all deaths reported) or probably (5% of all deaths reported). FDAH was able to review 353 of the FDA assessment reports. These included deaths which occurred after PH6 administration with concurrent vaccination, deaths due to tumours within less than 6 weeks of PH6 administration. 1/3 of the deaths that FDA assessed as 'possibly related' were assessed by FDAH as 'remotely related'. Two examples presented were:

A dog with a hemorrhagic episode found to have significant levels of rodenticide in the liver. The FDA classified this death as 'possibly related' to PH6.

A dog which presented with pain in the abdomen 4 months post PH6 administration. Upon necropsy following euthanasia a hemangiosarcoma of the liver was diagnosed. The FDA assessed the death as 'probably related'.

The rate of reported death occurring days, weeks of even months after PH6 is around

20 per 1 million dogs per year, assuming that 500 dogs died among an estimated at least 12 million who received PH6 in 2.5 years.

In the general canine population the death rate is

50000 per 1 million dogs per year

Taking into account the limitations of the passive post marketing adverse event reporting system and the estimate of doses administered (12 Million doses administered of the 18 Million sold), the level of deaths reported to have occurred after PH6 administration is less than the expected mortality rate in dogs.

3.2.2 Epidemiological analysis of safety data from veterinary clinics' data base including 735 654 administrations of PH6

A veterinary epidemiologist from Purdue University conducted an analysis of the safety of PH6 in comparison to that of two unidentified monthly oral treatments based on the data of an association of veterinary hospitals from all over the US (Banfield) which included data on the administration of PH6 (i.e. data that are required for calculation of incidences) and two monthly heartworm preventatives as well as administration of vaccines.

This analysis included calculation of the frequency of adverse events occurring within 30 days (period of follow up of clinic with dog owners) after administration of PH6 and two monthly heart worm preventatives (HWP1 and HWP2) in the data base which covers 6.8 million visits of dogs to a clinic, including

- 735 654 visits involving treatment with PH6,
- 411 082 visits involving treatment with HWP1 and
- 18 405 visits involving treatments with HWP2, as well as
- 5 634 016 visits without administration of either of these three heartworm preventatives. (Table 3)

The frequency of the adverse events categorized by

- type of AE the FDA was concerned about when they requested FDAH to stop marketing
- heart worm preventative administered
- administration alone or concomitantly with a vaccine

are provided in Table 4.

Table 3 Overview of number and rate of adverse events recorded by a veterinary clinic association after administration of different heartworm preventatives with and without vaccine

Vaccine	ProHeart6			HW Prev 1			HW Prev 2			No HW Treatment		
	N	N_A	Rate	N	N_A	Rate	N	N_A	Rate	N	N_A	Rate
Yes	483,064	6,292	130.3	246,131	2,804	113.9	11,975	120	100.2	1,489,032	17,406	116.9
No	252,590	2,253	89.2	164,951	1,469	89.1	6,430	45	70.0	4,144,984	120,529	290.8
Total	735,654	8,545	116.1	411,082	4,273	103.9	18,405	165	89.4	5,634,016	137,935	244.8

N = Total Number of Encounters

N_A = Total Number of Adverse Events

Rate = Number Adverse Events Per 10,000 Encounters

Table 4 Number and rate of adverse events per 10000 recorded by a veterinary clinic association after administration of different heartworm preventatives with and without vaccine by type of adverse event

Treatment Category				N	Potentially Associated Adverse Event Type									
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine		Liver Disease		Neurological Disease		Ocular Disease		Immune Mediated Disease		Allergic Reaction	
					N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	25,531	61.6	3,157	7.6	134	0.3	2,948	7.1	6,832	16.5
			Y	1,489,032	5,207	35.0	522	3.5	27	0.2	265	1.8	6,598	44.3
		Y		6,430	14	21.8	4	6.2	0	0.0	1	1.6	12	18.7
		Y	Y	11,975	24	20.0	2	1.7	0	0.0	2	1.7	62	51.8
	Y			164,951	523	31.7	68	4.1	1	0.1	40	2.4	236	14.3
	Y		Y	246,131	671	27.3	94	3.8	2	0.1	22	0.9	1,336	54.3
Y				252,590	880	34.8	123	4.9	4	0.2	59	2.3	485	18.4
Y			Y	483,064	2,011	41.6	178	3.7	7	0.1	98	2.0	2,581	53.4
Any				6,800,061	34,866	51.3	4,149	6.1	175	0.3	3,435	5.1	18,123	26.7

Treatment Category				N	Potentially Associated Adverse Event Type							
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine		Death		Cancer		Cardio Disease		Anaphylaxis	
					N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	74,470	179.7	3,724	9.0	8,089	19.5	139	0.3
			Y	1,489,032	2,690	18.1	562	3.8	1,804	12.1	108	0.7
		Y		6,430	11	17.1	0	0.0	4	6.2	0	0.0
		Y	Y	11,975	17	14.2	2	1.7	10	8.4	2	1.7
	Y			164,951	363	22.0	67	4.1	219	13.3	4	0.2
	Y		Y	246,131	354	14.4	75	3.0	281	10.6	18	0.7
Y				252,590	392	15.5	155	6.1	250	9.9	13	0.5
Y			Y	483,064	709	14.7	205	4.2	635	13.1	34	0.7
Any				6,800,061	79,006	116.2	4,790	7.0	11,274	16.6	318	0.5

In MULTIVARIATE analysis, taking into account confounding factors, in particular age, weight, concomitant administration of vaccines, NSAID, steroids and PH6 dose number,

- vaccines had the greatest effect on allergic reactions,
- PH6 as well as HWP1, NSAIDs and glucocorticoids were also associated with allergic reactions,
- Each additional dose of PH6 did not further increase the risk of allergic reactions,
- HWP1 was associated with an increased risk of death, while PH6 was associated with a decreased risk of death.

The epidemiologist concluded that the safety profile of PH6 is favorable compared to that of the two monthly heartworm preventatives and that there is no scientific rationale for the continued withdrawal of PH6 from the US market.

3.2.3 Conclusions

The animal toxicology data of moxidectin, the analysis of the PH6 adverse events by FDAH and by the external experts who reviewed them, as well as the analysis of the safety profile of PH6 in comparison with those of two monthly heartworm preventatives during use by veterinary clinics show that the safety profile of PH6 is favorable:

- Extensive toxicology studies in mice, rats and dogs support the safety of moxidectin and the regulatory approval of different moxidectin formulations for use in food-producing animals.
- In a 1 year dog toxicology study, there were no significant toxicological findings at a daily dose of moxidectin that resulted in a monthly moxidectin exposure 454 times the exposure of dogs administered the recommended dose of PH6.
- FDAH as well as the external experts who reviewed the post marketing PH6 adverse event data base concluded that the majority of events in the data base are not causally related to PH6 and reflect the normal range of diseases occurring in the dog population.

3.3 Committee recommendations

The committee was asked by FDA to provide answers to two questions:

1. Is PH6 safe for use in dogs?
 - 8 Panel members (including the vast majority of the standing committee members) voted NO. Reasons provided for the NO included:
 - Not enough information is available on the benefit of PH6, so a risk-benefit assessment cannot be done
 - A risk benefit analysis in comparison with other drugs is needed
 - PH6 is a preventive and we have still lots to learn about it
 - Need more clinical trial data - Banfield data base does not have the quality of a clinical trials data base.
 - Need for additional data
 - Frequency of co-administration of PH6 with vaccines
 - 7 Panel members (including the vast majority of the experts called for this particular meeting) voted Yes.
2. In case of remaining safety concerns, what additional avenues of research to mitigate or/and prevent AEs do you recommend.

The proposals came primarily from the consultants who had voted no to question 1.

- Change in the FDA reporting system
- Resolve disparate case definitions between FDA, FDAH and Banfield
- Review available data more closely re number of PH6 administrations, consistency of pathology with clinical picture, moxidectin PK in febrile dogs
- Analyse Banfield data base as a case-control study, review study design with FDA
- Collection and analysis of additional data since Banfield has a conflict of interest
- More analysis of available data - liver enzymes are unlikely to be related to PH6 - analyse in dogs who had a reaction genetic relationship
- Conduct meta-analysis of different studies
- Large scale clinical field trial (e.g. 2000 dogs) and large prospective study agreed upon by FDA and FDAH

In response to these suggestions by some VMAC members, another VMAC member pointed out that the analysis of the frequency of the AEs in the Banfield data base has shown that the adverse events are so rare that a prospective study is unrealistic since it would have to include >500 000 dogs to get meaningful data.

- Look at moxidectin concentrations in animals with AEs
- Sheet for veterinarians to improve the quality of follow up
- Advice to veterinarians not to co-administer with a vaccine
- Training of veterinarians on how to administer the drug
- Conduct prospective study looking at the vehicle and potential user mistakes by the veterinarians
- Experimental investigation of possible causes of immunological reactions to the vehicle
- Evaluate correlation of time to death for L4 and L5 larvae with immunological AEs
- Compare frequency of immune related AEs in endemic and non-endemic areas to see whether microfilaria death is cause of immune related AEs.
- Test whether microspheres are antigen depot, mask them to the immune system (as is done e.g. for contrast agents)
- Consider development of single use vials
- Collect more information on compliance with oral vs. PH6
- More data on risk-benefit in long term studies since PH6 has the potential to reduce the incidence of a terrible disease
- The issues are likely to be the same for all heartworm medications - thus the manufacturers of the different medications should get together.

4 Post meeting FDA actions

The FDA concluded from the Advisory Committee recommendations that further discussions are required. As a consequence, the FDA initiated discussions with Fort Dodge. These discussions will among others try to determine why the FDA interpretation

of the adverse events is so different from that of FDAH and its experts. These discussions are ongoing as of the finalization of this document (15 April 2005).

5 Appendix

5.1 Kraemer system for assessment of causality of AEs used by the FDA VM

The Kraemer system used by FDA is based on the sum of the scores given based on the answer to a set of 7 questions:

1. Previous Experience With Drug:

+1	CM generally recognized to occur in this species at the dosage received.
0	CM is not generally recognized to occur in this species at the dosage received but has been previously reported in veterinary and/or human medicine. Drug has limited accumulated clinical experience (time and/or quantity marketed).
-1	CM previously unreported and drug has substantial accumulated clinical experience (time and/or quantity marketed).

2. Alternative Etiologic Candidates:

+2	There is no good candidate or no change in a candidate which can explain the CM, exclusive of drug administration.
0	An alternative candidate(s) exists, but not a good one(s) which can well explain the CM. CM commonly occurs spontaneously in this type of patient and situation, usually in the absence of any recognizable alternative candidate(s).
-1	There is a good candidate or a change in a candidate which can well explain the CM, exclusive of drug administration.

3. Timing of Events:

+1	Timing was consistent and as expected for this type of CM to this drug.
0	Do not know what timing to expect.
-2	Timing was inconsistent for this type of CM to this drug.

4. Evidence of Overdose:

+1	CM is clearly a dose-related type of manifestation, and there is unequivocal evidence that the amount of drug received was an overdose for this animal.
0	CM is not a dose related type of manifestation or there is no evidence of an overdose.

5. Dechallenge:

+1	CM diminished or disappeared after discontinuation of suspect drug or administration of a specific antidote. CM is known to be dose-related, and CM diminished or disappeared after dosage reduction.
0	Dechallenge difficult, impossible, or inappropriate to assess. A non-specific agent or maneuver (non-antidotal) was administered that was directed against the CM and that usually produces the degree and rate of improvement observed in the case. CM characteristically transient and episodic, and there is no established pattern episodes (regardless of what occurs after discontinuing the drug). CM known to be dose-related, and CM did not diminish or disappear after dosage was reduced.
-1	CM improved without dechallenge and the improvement cannot be attributed to the development of tolerance.

6. Rechallenge:

+1	CM unequivocally recurred or exacerbated after rechallenge.
0	There was no rechallenge attempted. A non-specific agent or maneuver (non-antidotal) was administered that obscured the response of the CM. CM failed to recur or exacerbate on rechallenge, but the dosage or duration of drug administration on rechallenge was substantially less than that suspected of causing the original CM. Recurrence or exacerbation of CM was impossible to assess because it was progressing or was at a level of severity that any further increase would be difficult to appreciate.
-1	CM failed to recur or exacerbate on rechallenge.

The component scores above are then summed to reach a final causal score:

Scores	Category of Association
-9	Not applicable
-8	Information lacking
-7	No conclusion
-1 to -6	Remotely drug-related
0 to 2	Possibly drug-related
3 to 5	Probably drug-related
6 to 7	Definitely drug-related

-1	Ineffectiveness - Remotely drug-related
0 to 1	Ineffectiveness - Possibly drug-related
3	Ineffectiveness - Probably drug-related
6	Ineffectiveness - Definitely drug-related

The Veterinary ICH committee has determined that this system should not become the VICH accepted standard (as per FDAH information provided at the meeting).

A number of the questions in the Kraemer system are not applicable (e.g. dechallenge) or applicable only in a compromised fashion (e.g. rechallenge)

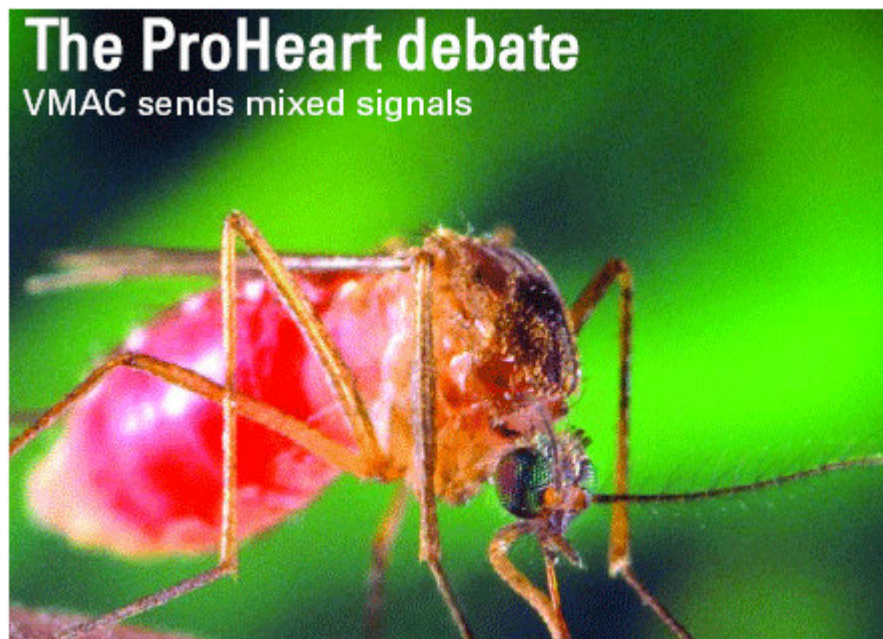
5.2 Veterinary ICH system for assessment of causality used by FDAH

Likelihood of association	Criteria
Probable	All of the following criteria should be met - Reasonable association in time between administration of drug and onset and duration of reported AE - Description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the CMP - No other equally plausible explanation for the AE
Possible	Association of the AE with administration of the drug is one of other possible and equally plausible explanations for the described event
Unlikely	Sufficient information exists to establish that the described event was not likely to have been associated with the drug or other more plausible explanations exist
Unknown	Reliable data are either unavailable or are insufficient to make an assessment.

5.3 American Veterinary Medical Association summary of FDA VMAC meeting

Source: <http://www.avma.org/onlnews/javma/apr05/050415c.asp>

April 15, 2005



As many as 30 species of mosquito can transmit heartworms.

In January, the Food and Drug Administration's Veterinary Medicine Advisory Committee and consultants heard presentations by the FDA Center for Veterinary Medicine and Fort Dodge Animal Health on the safety of ProHeart 6 (sustained release injectable moxidectin).

This past September, Fort Dodge voluntarily issued a recall and ceased production of the drug, until FDA concerns about safety could be resolved. The advisory committee failed to reach consensus.

The VMAC deliberated over two questions. First, based on the presentations and information provided, is ProHeart 6 safe for use in dogs? Second, if there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events? Before voting, the committee heard from a number of presenters.

Background

Dr. Lynn Post, director of the FDA-CVM Division of Surveillance, and Dr. Margarita Brown, a veterinary medical officer with the FDA-CVM, explained the agency's method for analyzing animal drug adverse event reports, and discussed the ProHeart 6 experience.

Several veterinarians with practice experience review adverse event reports. Most reports come to the FDA from manufacturers, which are mandated by the FDA to furnish the voluntary reports of veterinarians and animal owners. Some reports come directly to the FDA from the public. The FDA employees assign points to six components and use an algorithm to interpret whether events are remotely, possibly, probably, or definitely drug-related. The components are previous experience with the drug, alternative explanations of the events, timing of events, any evidence of overdose, whether the problem disappears after withdrawal of the drug, and whether the problem reappears when the drug is reintroduced.

On the basis of the number of reports judged to be possibly related, the FDA concluded that the number of deaths associated with ProHeart 6 was greater than with other heartworm preventives, relative to the market shares of the products. The FDA also believed that ProHeart 6 was associated with a greater number of certain organ system events and allergic reactions. Despite three label changes, the CVM had continued to receive a large number of serious adverse drug event reports. The FDA expressed concern with the timing of reports coinciding with peak serum concentrations of the drug.

With this information in hand, and considering that ProHeart 6 is used in a preventive fashion and alternatives exist, the FDA asked Fort Dodge for the recall. The FDA is of the opinion that a higher standard for safety of preventive drugs should exist as compared with therapeutic drugs.

The debate

Dr. Rami Cobb, vice president of pharmaceutical research and development for Fort Dodge, reviewed the safety data that had been used by the FDA to approve the drug in 2001. Dr. Cobb explained the extensive toxicology database for the active ingredient moxidectin, and the data review and continued marketing of ProHeart drugs in other countries.

Dr. David Hustead, senior director of international technical and regulatory affairs at Fort Dodge, focused on the company's analysis of adverse event reports. He described a method approved by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products. The company used the total number of adverse reports divided by doses of drug sold to achieve a reporting rate. Differentiating reporting rate from incidence, Dr. Hustead indicated that a reporting rate is a useful tool, so long as one is aware of its limitation. Dr. Hustead explained that the firm retained independent experts, and that they and the company concluded that most adverse events were not causally related to ProHeart 6 and reflect the normal range of diseases occurring in the dog population. Fort Dodge Animal Health concluded that ProHeart 6 is a safe and effective product for prevention of heartworm disease.

Dr. Larry Glickman, a professor of epidemiology and environmental medicine at the Purdue University School of Veterinary Medicine, also came to the conclusion that there was no scientific rationale for the continued withdrawal of ProHeart 6 from the market. His evidence came from an unpublished, controlled epidemiologic study that evaluated more than seven million dog encounters at Banfield, The Pet Hospital from 42 states. The study examined the safety profiles of ProHeart 6, which provides six months of protection, and two monthly heartworm preventives in dogs. Because exposure to the drug was known and could serve as a denominator against which adverse event reports are considered, the study was the only source of incidence data. His conclusion was that the safety profile of ProHeart 6 was favorable compared with those of the two monthly heartworm preventives.

Consideration

As the advisory committee and consultants individually considered the question of safety posed to them, it appeared that participants were not operating under a common definition of "safe." Several members wrestled with their own interpretation of the term, as well as what clients might expect, including zero tolerance for risk. Narrower interpretations of safe were generally accompanied by requests for more information.

The VMAC grappled with the data and issues, including how concomitant administration with vaccination may confuse interpretation of the associated adverse event reports following office visits. Some participants pointed out that the risks of an adverse event associated with the drug, while such an event may be severe, appear to be small and, by some accounts, similar to those of other approved drugs widely used for the same purpose. Some pondered the concept of the safety standard for a preventive medication being higher than that for a disease treatment. The lack of risk/benefit information further complicated the evaluation. What is the risk of adverse reaction to the product, compared with the benefit of heartworm prevention, particularly since the sustained-release nature of the product eliminates possible infections caused by poor compliance with monthly dosing?

Many committee members and consultants agreed that the epidemiologic data from Banfield, The Pet Hospital were compelling.

In the end, eight participants did not declare the drug safe and indicated that they needed more information. Seven participants voted that the drug was safe.

Future outlook

Because a clear signal had not emerged from the advisory committee, Dr. Stephen Sundlof, director of the FDA-CVM, said that the FDA would take the comments back to the agency for additional discussion.

Dr. John Gay, as epidemiology representative to the AVMA Council on Biologic and Therapeutic Agents, stated during the public comment period that there is room for improvement in the federal process for collecting, analyzing, and responding to adverse event reports. He emphasized that a strong system would reduce two general types of errors in the areas of sensitivity and specificity. Improving system sensitivity would provide early, clear detection of associations between particular drugs and adverse effects in segments of the patient population. Improving system specificity would reduce the problems with spurious associations between particular drugs and adverse events in animals' lives. Both are required to maintain the profession's confidence in the drugs that veterinarians use, the availability of safe and effective drugs, and clients' confidence in their veterinarians, Dr. Gay said.

At press time, the FDA had not made any further decisions about ProHeart 6.

For more information, including copies of presentations made at the meeting, visit www.fda.gov/cvm/index/vmac/VMACWinter2005.htm.

5.4 FDA and FDAH briefing packages and presentations at the VMAC meeting

Source: <http://www.fda.gov/cvm/VMAC/VMACWinter2005.htm>

See separate pdf documents (filename preceded by 4)

Briefing document for FDA Veterinary Advisory committee

2 FDA presentations at FDA Veterinary Advisory committee

Fort Dodge Briefing document presentations for FDA Veterinary Advisory committee

3 Fort Dodge presentations at FDA Veterinary Advisory committee

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Introduction

The Center for Veterinary Medicine (CVM) has the regulatory responsibility for ensuring the safety of marketed animal drug products. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness under the labeled conditions of use. Many of the common adverse events may become known prior to approval. CVM maintains a post-approval monitoring system to detect adverse events that occur after the new animal drug is approved. After approval, the drug will be used in a larger and more diverse population.

This document describes CVM's method for evaluating adverse drug experience reports associated with animal drugs and provides data on adverse drug events reported for canine heartworm preventives. It demonstrates that the number of reports of serious adverse drug events, such as anaphylaxis, convulsions, liver abnormalities, immune-mediated hemolytic anemia, thrombocytopenia, and death, is substantially higher for ProHeart 6 (moxidectin sustained release) than for other heartworm preventives. The frequency of ProHeart 6 adverse drug event reports, the severity of the clinical manifestations within the reports, and the temporal association with drug administration raise serious questions about the safety of this heartworm prevention product. Fort Dodge, at FDA's request, agreed to immediately cease production and recall Proheart 6 from the market until the safety concerns associated with the product are resolved.

Definitions

Adverse drug experience (ADE): Any adverse event associated with the use of a new animal drug, whether or not considered to be drug related and whether or not the new animal drug was used in accordance with the approved labeling ([CFR 514.3.doc](#)).¹

Adverse drug experience includes, but is not limited to:

- (1) An adverse event occurring in animals in the course of the use of an animal drug product by a veterinarian or by a livestock producer or other animal owner or caretaker.
- (2) Failure of a new animal drug to produce its expected pharmacological or clinical effect (lack of expected effectiveness).

- (3) An adverse event occurring in humans from exposure during manufacture, testing, handling, or use of a new animal drug.

In this document the term “adverse drug event” is used interchangeably with “adverse drug experience.

Serious adverse drug experience: An adverse event that is fatal, or life threatening, or requires professional intervention, or causes an abortion, or stillbirth, or infertility, or congenital anomaly, or prolonged or permanent disability, or disfigurement.

Unexpected adverse drug experience: An adverse event that is not listed in the current labeling for the new drug and includes any event that may be symptomatically and pathophysiologically related to an event listed on the labeling, but differs from the event because of greater severity or specificity.

ADE report: An adverse drug experience report submitted by a sponsor on [Form 1932](#) or by a veterinarian or consumer on [Form 1932a](#).^{2, 11} Nearly all of the reports submitted to CVM by drug sponsors are identified with a unique sponsor case number.

Correspondence date: The date an ADE report is postmarked.

Clinical manifestation: Equivalent to a clinical sign or outcome and can be a primary, secondary, or tertiary clinical sign or outcome. A report may contain several clinical manifestations.

Causality assessment: The evaluation and scoring of a clinical manifestation using the modified Kramer algorithm. There is a causality assessment score for every clinical manifestation in a report. Causality assessment scores are grouped into causality assessment categories:

<u>Causality Assessment</u>	<u>Causality Assessment</u>
<u>Scores</u>	<u>Categories</u>
-9	Not applicable
-8	Information lacking
-7	No conclusion
-1 to -6	Remotely drug-related
0 to 2	Possibly drug-related
3 to 5	Probably drug-related
6 to 7	Definitely drug-related

If clinical manifestations in an ADE report cannot be attributed to a single animal, an assessment could involve more than one animal. For companion animals, there is usually one animal for each assessment.

Episode: The occurrence of one or more clinical manifestations in the smallest number of animals to which the clinical manifestation(s) can be uniquely ascribed. If clinical manifestations in an ADE report cannot be attributed to a single animal, an episode could include more than one animal. For companion animals, there is usually one animal in each episode.

Time of onset: The duration of time between drug administration and onset or detection of a clinical manifestation.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (World Health Organization). ²⁷

Adverse Event Reporting for Animal Drugs

In the United States, the Center for Veterinary Medicine (CVM) approves new animal drugs under Section 512 of the Federal Food, Drug, and Cosmetic Act based on applications that include full reports of investigations which have been made to show whether or not the drug is safe and effective for use. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness. Thus, most of the common adverse events will become known during those pre-approval studies. Post

approval monitoring of adverse drug events is a widely accepted method for monitoring the safety and effectiveness of approved drugs when used in a larger, heterogeneous population.²¹ Goals of CVM's pharmacovigilance program include: (1) providing pertinent safety information for the product label, (2) monitoring for unsafe or defective products, and (3) monitoring for unsafe drug-use practices.⁴

Post approval monitoring is critical to ensuring that drugs approved as safe and effective continue to be so; however, it has some inherent limitations. In the United States, reporting of adverse drug events by physicians and veterinarians is entirely voluntary and accomplished through passive reporting systems. It is well recognized that adverse drug events are substantially under-reported.^{5, 6, 7, 8, 9, 10, 21} When an adverse drug event is reported, accurate assessment of the event depends upon the general quality and completeness of the report. Additional limitations in veterinary pharmacovigilance include the cost and availability of diagnostic tests and the lack of comprehensive post-mortem information. Veterinary clinical care is becoming more sophisticated, and reports currently submitted to CVM are more comprehensive than 10 years ago.²⁰

In most cases, national ADE reporting rates can only be estimated because the population at risk (number of patients exposed to a particular product) is not precisely known. Furthermore, an ADE reporting rate is **not** an incidence rate because ADEs are substantially under-reported (numerator) and accurate data on the number of exposed patients (denominator) is often lacking.²⁸ A reporting rate that is high compared to the background incidence rate may signal a problem with a product. However, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily mean that the product is not associated with an increased risk of an adverse event.

CVM currently receives about 25,000 adverse drug experience reports per year. Approximately 99% of ADE reports are received from drug sponsors. A sponsor of a new animal drug completes [Form 1932](#) when it receives a report (by telephone, mail or e-mail) of an adverse event from a veterinarian or a consumer. Under the mandatory reporting requirement of [CFR 21§514.80](#) (and formerly under CFR 21§510.300), sponsors are required to submit a Form 1932 to FDA within 15 working days for each serious, unexpected ADE. Under CFR 21§514.80, sponsors must report other ADEs in

periodic Drug Experience Reports, which are submitted every 6 months for the first 2 years following product approval and yearly thereafter. Approximately 1% of ADE reports come directly to CVM from pet owners and veterinarians on [Form 1932a](#). Each ADE report contains one or more clinical manifestations, which are coded by CVM according to a standard dictionary of clinical terms.¹²

When an ADE report arrives at CVM, it is logged into the Document Control Unit, assigned a submission number, and forwarded to the Division of Surveillance for processing. CVM safety reviewers, who are experienced clinical veterinarians, then review the individual ADE reports. The safety reviewers enter all relevant information such as age, breed, history, pre-existing problems, and concomitant drugs into an Oracle database called the Submission Tracking and Reporting System (STARS).

The reviewers evaluate each clinical manifestation reported using a scoring system that has been previously described.^{3, 4, 13} This system is a modified version of the Kramer algorithm, a human adverse drug event algorithm.^{14, 25, 26} This scoring system has the following 6 components:

- 1. Previous Experience with the Drug**
- 2. Alternative Etiologic Candidates**
- 3. Timing of Events**
- 4. Evidence of Overdose**
- 5. Dechallenge** (whether the problem disappears after withdrawal of the drug)
- 6. Rechallenge** (whether the problem reappears when the drug is reintroduced)

Consideration is given to information about age, breed, gender, pre-existing conditions, and concomitant drugs. A summary causality assessment score for each clinical manifestation is determined and entered into the STARS database. The summary score corresponds to the strength of the association between the drug and the clinical manifestation and ranges between -9 and +7. Clinical manifestations with summary scores of ≥ 0 are considered possibly, probably, or definitely drug-related. When many ADE reports listing a particular clinical manifestation have accrued for a particular drug, CVM assigns a higher “previous experience” component score for that clinical manifestation in subsequent ADE reports. Therefore, scores for a particular

manifestation may increase over time. Dechallenge and rechallenge components of Kramer score usually don't apply with a sustained release product like ProHeart 6 so the maximum causality assessment score for such products is usually +4 unless there is an overdose, in which case it can be +5. Detailed information about the components of the algorithm used by CVM may be found in [Appendix A](#). Causality assessment scores for ineffectiveness can be as high as +6 because CVM uses a modified version of this algorithm for ineffectiveness complaints.²⁹

Follow-up reports are an important part of pharmacovigilance. 21 CFR 514.80(b)(2)(ii). They generally arrive within a month or two after the initial report. A new record is not created for follow-up reports; the information in a follow-up report is added to that in the initial report. In some cases, there may be more than 3 follow-up reports per original ADE report. Follow-up reports provide significant new information that may either strengthen or weaken the association between an event and use of the drug. In addition, follow-up reports may provide new clinical manifestations or outcomes to previously reported ones. For example, in the absence of a follow-up report, a severe outcome such as death may go unreported.

The severity and frequency of clinical manifestations in the STARS database are continuously monitored by CVM. STARS data summaries may be generated by cumulative experience or by detailed search criteria such as age, time of onset, attending veterinarian opinion, gender, and breed. The cumulative numbers of dogs with reported clinical manifestations that had causality assessment scores of zero or above are placed in the public domain on the [CVM website](#) by active ingredient and route of administration.

When severity or frequency of reported ADEs for a given product are of concern, the Division of Surveillance may request additional information from the drug sponsor or organize an internal CVM product safety meeting to review available data. At the product safety meeting, CVM determines whether a label revision or any other action is indicated.

Canine Heartworm Disease

Heartworm disease is a serious but preventable mosquito-borne parasitic disease that primarily affects dogs and cats. It is caused by the *Dirofilaria immitis* nematode. Dogs are usually asymptomatic until maturation of heartworm larvae in the right atrium

and pulmonary artery causes cardiopulmonary effects. Typically, maturation of the larvae takes about six months. The chances of contracting heartworm disease without prophylaxis depend on exposure to mosquitos. Dogs are more likely to become infected if they live in the Southeast, Gulf Coast, or Mississippi River Valley near fresh or saltwater, are housed outside, and are not receiving heartworm preventives. Dogs can survive a heartworm infection by receiving appropriate treatment. There is a risk of thromboembolism and death following adult heartworm treatment when worms break loose from their location in the right heart, and there can be side effects from the drugs that are commonly used to treat adult heartworms. Additional information about canine heartworm disease can be found through the American Heartworm Society.^{30, 31}

Macrocytic Lactones

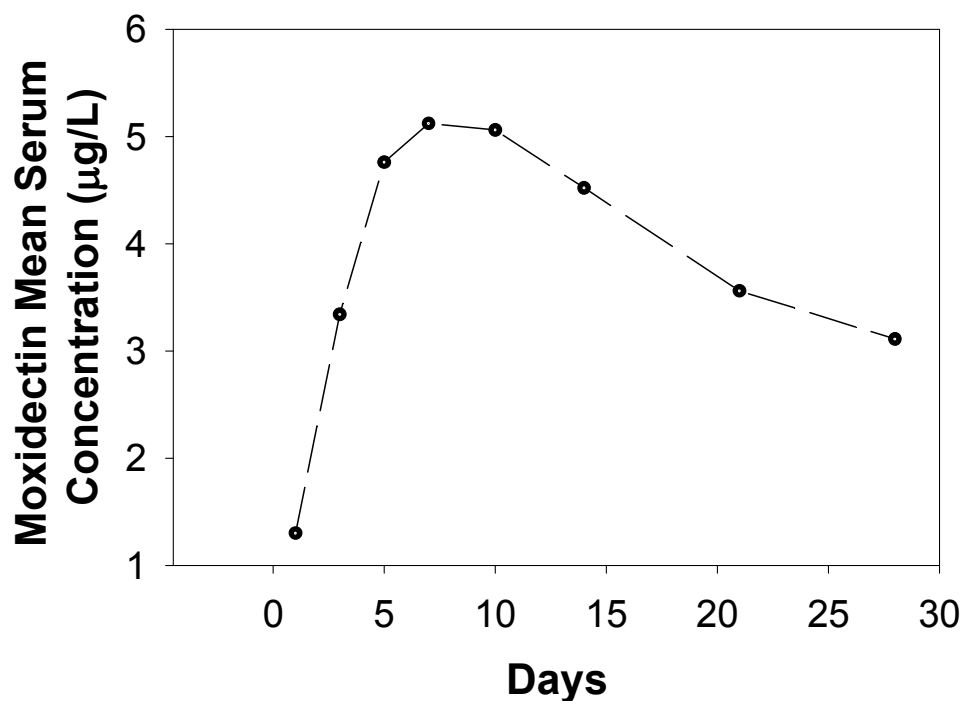
The macrocyclic lactones are natural fermentation products of soil-dwelling bacteria of the genus *Streptomyces*. They have activity against both internal and external parasites, specifically nematodes (including heartworms) and arthropods. Macrocyclic lactones consist of two major groups, the avermectins and the milbemycins. Moxidectin is a member of the milbemycin group. The other macrocyclic lactones approved for use in dogs include ivermectin, milbemycin oxime, and selamectin.³² Known signs of macrocyclic lactone toxicity in mammals include dilated pupils, vomiting, diarrhea, salivation, disorientation, lack of coordination, muscle twitching, tremors, depression, coma, and blindness. Severe reactions can involve other neurologic signs such as seizures which have been added to the post-approval safety information on several macrocyclic lactone labels.³²

ProHeart 6 Product Information

ProHeart 6 is a sustained release microencapsulated preparation of moxidectin. It is indicated for use in dogs at least 6 months of age and older as a 6-month heartworm preventive. It is also approved for treatment of existing larval and adult hookworm infections in dogs. It is manufactured and sold by Fort Dodge Animal Health (FDAH), the veterinary division of Wyeth Pharmaceuticals, under the new animal drug application (NADA) number 141-189. ProHeart 6 is sold in multi-dose vials. The [Freedom of Information Summary](#) describes conditions of approval for this product.¹⁵ A copy of the

current label for ProHeart 6 can be found in [Appendix C](#).¹⁶ ProHeart 6 is the only heartworm prevention product that is approved in the U.S. for parenteral administration in dogs; it is administered subcutaneously (under the skin). Following injection, mean ProHeart 6 blood levels peak 7-14 days post-administration. Figure 1 shows mean moxidectin serum levels following a single injection of ProHeart 6.¹⁵

Figure 1. Mean serum moxidectin concentrations following a single injection of ProHeart 6 in dogs



The other major canine heartworm preventives (ivermectin, milbemycin, and selamectin) are delivered as a monthly dose; ivermectin and milbemycin are administered orally and selamectin is administered topically. ProHeart, a once-a-month moxidectin tablet, is also manufactured and sold by FDAH, but is not commonly used in dogs in the United States. A listing of approved monthly and 6-month heartworm prevention products and their indications can be found in [Appendix B](#).

Regulatory History of ProHeart 6

ProHeart 6 was approved under NADA 141-189 on June 6, 2001 based on pre-approval safety and effectiveness studies. Laboratory studies revealed no serious adverse drug events in healthy dogs. In clinical field studies, the following adverse reactions were reported in approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and increased body temperature. The death of 3 dogs (2 geriatric dogs and 1 dog with a history of health problems) resulted in the following **PRECAUTION** statement on the [label](#): **Use with caution in sick, debilitated or underweight animals.**

Since approval of ProHeart 6, three label revisions have been initiated by the Division of Surveillance at CVM because of serious and unexpected adverse drug reactions. The first label revision, which was approved on June 13, 2002, added the post-approval reported clinical manifestations of anaphylaxis/anaphylactoid reactions, depression/lethargy, urticaria, and head/facial edema. The second revision, which was approved on November 5, 2002, added post-approval reported cardiopulmonary signs associated with administration of the product in heartworm positive dogs. The third revision, which was approved on July 15, 2003, added a [Client Information Sheet \(CIS\)](#) and the phrase “and rare reports of death” to the post-approval adverse reactions section of the label. Two “Dear Doctor” letters describing the label revisions were disseminated by the sponsor to veterinarians. The first letter described the anaphylaxis/anaphylactoid reaction experiences reported and a precaution to test dogs for heartworms before administration. The second “Dear Doctor” letter contained a combined description of the second and third CVM initiated label changes. The current label for ProHeart 6 can be found in [Appendix C](#).

After a clinical manifestation is added to the Adverse Reactions section of the product label, CVM safety reviewers may assign a higher value for the “previous experience” component of a causality assessment score. CVM did not re-evaluate ProHeart 6 ADE reports that were reviewed prior to label changes, but if CVM had re-evaluated them, the causality assessment scores would increase for clinical manifestations added to the product label.

On several occasions, CVM discussed with the sponsor discrepancies in reported adverse drug events and the lack of adequate follow-up information contained in the ProHeart 6 ADE reports, generally through teleconferences.^{22, 23, 24} CVM met with FDAH on January 14, 2004, July, 13, 2004 and September 1, 2004 to discuss the Center's concerns about the frequency and severity of reported ADEs associated with Proheart 6. In addition to safety issues, concerns with the current Good Manufacturing Practices (GMPs) have been noted. In December 2003 FDA issued a [Warning Letter](#) to FDAH for violations occurring in the ProHeart 6 manufacturing facility.¹⁷ An August 2004 inspection found that the GMP violations had been corrected. Two firm-initiated nationwide recalls of ProHeart 6 have been made due to GMP problems. The first recall occurred on [April 27, 2004](#) for failure to meet the 6-month dissolution time point.¹⁸ The second recall was issued on [May 13, 2004](#) because of failure to meet GMPs and concerns about proper sterilization.¹⁹ An August 2004 inspection found the GMP violations had been corrected.

ADE Reports for ProHeart 6 and Other Heartworm Preventives

This section summarizes STARS searches conducted by CVM for ADEs reported for marketed monthly and 6-month heartworm preventives with the active ingredients: ivermectin, milbemycin, selamectin, and moxidectin. Searches were conducted using correspondence dates for 2 time periods: 1) product approval to September 1, 2004 and 2) June 1, 2001 to September 1, 2004. Only ADEs (including death) considered to be possibly, probably, or definitely related to the products are reported.

Table 1 indicates the number of dogs with reported ADEs for monthly and 6-month heartworm preventives and Table 2 shows the number of deaths among the dogs. Table 1 and Table 2 include all ADEs and deaths (possibly, probably, or definitely drug-related), including those related to "ineffect" for heartworms, hookworms, roundworms, fleas, ticks, and mites.

Table 1. Number of dogs with reported ADEs* that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives.

Heartworm Preventive	Year of Initial Approval	Number of Dogs, Approval to September 1, 2004	Number of Dogs, June 1, 2001 to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	5667	4646
Milbemycin and Milbemycin/Lufenuron	1990	3243	2273
Selamectin	1999	9719	7681
Moxidectin Tablets (ProHeart)	1997	12	1
Moxidectin Sustained Release (ProHeart 6)	2001	5659	5659

*including “ineffect” for heartworms, hookworms, roundworms, fleas, ticks, and mites

Table 2. Number of reported dog deaths that are possibly, probably, or definitely related to marketed monthly or 6-month heartworm preventives.

Heartworm Preventive	Year of Initial Approval	Number of Deaths, Approval to September 1, 2004	Number of Deaths, June 1, 2001 to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	133	50
Milbemycin and Milbemycin/Lufenuron	1990	131	59
Selamectin	1999	171	110
Moxidectin Tablets (ProHeart)	1997	0	0
Moxidectin Sustained Release (ProHeart 6)	2001	485	485

Selamectin had the highest number of dogs with ADE reports. Many of these dogs had reports of ineffect for fleas, mites, and ticks and many had mild local reactions or hair loss at the application site. Between 2001 and 2002, CVM worked with the sponsor of the selamectin product to address serious ADEs that were observed in underweight and debilitated animals. CVM collaborated with the sponsor to add a warning on the label: “Do not use in sick, debilitated or underweight animals” and to develop an in-clinic approach to educating prescribing veterinarians and staff members. The reported safety-related ADEs decreased in frequency and severity. Between 2002 and 2004 the sponsor was also asked to conduct post-approval studies to address reports of ineffectiveness with respect to heartworm prevention. In July 2004, the sponsor issued a Dear Doctor Letter to veterinarians about these studies.

During the period of June 1, 2001 and September 1, 2004, there were more than twice as many deaths reported among dogs that received ProHeart 6 than for all other heartworm preventives combined, even though ProHeart 6 sales represent 21-24% of the market (as reported by FDAH to CVM in January and September, 2004).

Ineffectiveness complaints for heartworm prevention claims were reported for all marketed products including ProHeart 6. CVM discussed this issue at a recent national meeting.²⁹ Table 3 shows the number dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of marketed monthly or 6-month heartworm preventives. Table 3 also illustrates the small number of deaths that are possibly, probably, or definitely drug-related among those dogs.

Table 3. Number of dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of marketed monthly or 6-month heartworm preventives and the number of reported deaths possibly, probably, or definitely drug-related among those dogs.

Heartworm Preventive	Year of Initial Approval	Number of Dogs, Approval to September 1, 2004	Number of Deaths, Approval to September 1, 2004
Ivermectin and Ivermectin/Pyrantel (all products)	1987	906	4
Milbemycin and Milbemycin/Lufenuron	1990	1610	0
Selamectin	1999	2815	11
Moxidectin Tablets (ProHeart)	1997	2	0
Moxidectin Sustained Release (ProHeart 6)	2001	411	4

Table 4 and Table 5 show the number of causality assessments for serious clinical manifestations reported among dogs administered monthly or 6-month heartworm preventives from product approval to September 1, 2004 and from June 1, 2001 to September 1, 2004, respectively. The number of assessments for anaphylaxis/anaphylactoid reactions, convulsions, liver lesions, elevations in SGPT/ALT (serum glutamic-pyruvic transaminase/alanine transferase), low platelets

(thrombocytopenia), and immune-mediated hemolytic anemia (IMHA) were considerably higher for ProHeart 6 than for other heartworm preventives. The number of convulsions in dogs receiving selamectin was high between 2001 and 2002 but has been declining since the warning not to use this product in sick, debilitated or underweight animals was placed on the label in 2002. The numbers of hematologic and liver signs also decreased for selamectin.

Table 4. Number of causality assessments for certain reported clinical manifestations that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives, from approval to September 1, 2004.

Heartworm Preventive (year of initial approval)	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT Elevations	Liver Lesions	Low Platelets	IMHA
Ivermectin and Ivermectin/Pyrantel (all products) (1987)	16	131	38	9	10	20
Milbemycin and Milbemycin/Lufenuron (1990)	36	194	38	8	26	16
Selamectin (1999)	45	304	69	13	50	15
Moxidectin Tablets (Proheart) (1997)	0	1	0	0	0	0
Moxidectin Sustained Release (ProHeart 6) (2001)	1820	378	192	65	124	67

Table 5. Number of causality assessments for certain reported clinical manifestations that are possibly, probably, or definitely related to the use of marketed monthly or 6-month heartworm preventives, June 1, 2001 to September 1, 2004.

Heartworm Preventive	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT elevations	Liver lesions	Low Platelets	IMHA
Ivermectin and Ivermectin/Pyrantel (all products)	13	69	10	2	5	8
Milbemycin and Milbemycin/Lufenuron	20	107	26	5	10	9
Selamectin	37	234	45	8	30	8
Moxidectin Tablets (ProHeart)	0	0	0	0	0	0
Moxidectin Sustained Release (ProHeart 6)	1820	378	192	65	124	67

ProHeart 6 ADEs

Between June 6, 2001 and September 1, 2004, ProHeart 6 ADEs were reported for 6015 dogs (all causality assessment categories). There were 21,885 causality assessments conducted for clinical manifestations reported among these dogs.

Table 6 shows the number of assessments by causality assessment category. There were 19,676 assessments for clinical manifestations determined by CVM to be possibly, probably, or definitely related to the administration of ProHeart 6 (Table 6). These assessments were for clinical manifestations in 5659 dogs (Table 1).

There were 637 dog deaths (all causality assessment categories) reported on ProHeart 6 ADE reports and 485 deaths were determined by CVM to be possibly or probably related to ProHeart 6 (Table 2).

Table 6. Number of causality assessments for clinical manifestations reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Definitely drug-related	32*
Probably drug-related	4310
Possibly drug-related	15334
Remotely drug-related	2026
Information Lacking	183
Total	21885

*clinical manifestations that were considered definitely drug-related all had causality assessment scores of +6 for heartworm ineffect

Among dogs with clinical manifestations that were possibly, probably, or definitely related to the administration of ProHeart 6, 2585 had concomitant drugs and/or vaccines and 2034 did not have concomitant vaccines or drugs. The concomitant drug/vaccine status for the remainder of the dogs is not known. There were 5548 episodes for the 5659 dogs with clinical manifestations that were possibly, probably, or definitely drug-related. The health status of these dogs was noted by the reporting veterinarian as good in 4916 episodes, fair in 544 episodes, and poor in 52 episodes. The health status of dogs in 36 episodes was not reported.

Time of onset refers to the duration of time between drug administration and onset or detection of a clinical manifestation. Table 7 shows the number of causality assessments by time of onset and concomitant drug/vaccine status for clinical manifestations that were determined to be possibly, probably, or definitely related to ProHeart 6 administration.

Table 7. Number of causality assessments by time of onset* and concomitant drug/vaccine status for reported clinical manifestations that are possibly, probably or definitely related to the use of ProHeart 6, June 6, 2001 to September 1, 2004.

Time of Onset	Total Causality Assessments[†]	Assessments with Concomitant Drugs and/or Vaccines	Assessments without Concomitant Drugs or Vaccines
<3 hours	6613 (34.9%)	2710 (27.5%)	3043 (48.2%)
3 to < 24 hours	2546 (13.4%)	1291 (13.1%)	877 (13.9%)
1 to <3 days	2296 (12.1%)	1279 (13.0%)	660 (10.4%)
3 to <7 days	2178 (11.5%)	1399 (14.2%)	515 (8.2%)
7 to <14 days	1962 (10.4%)	1301 (12.2%)	370 (5.9%)
14 to <30 days	1395 (7.4%)	839 (8.5%)	332 (5.3%)
1 to <3 months	1291 (6.8%)	715 (7.3%)	354 (5.6%)
≥3 months	658 (3.5%)	322 (3.3%)	165 (2.6%)
Total*	18939	9856	6316

*For those with known time of onset

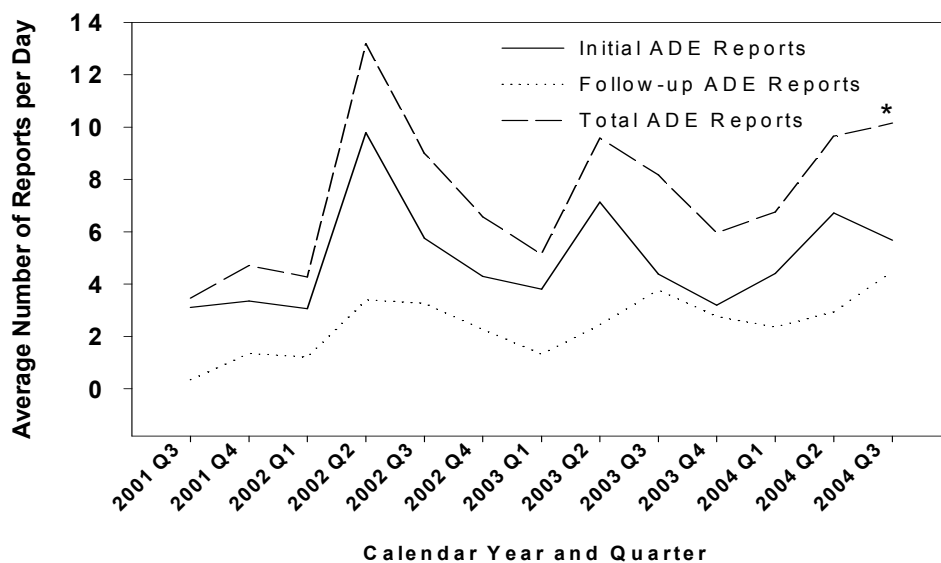
[†] Includes causality assessments for dogs that had concomitant drugs and/or vaccines, dogs that did not have concomitant drugs or vaccines, and dogs with unknown concomitant drug/vaccine status

The majority of clinical manifestations occurred between 0 and 14 days, when there were rising or peak serum moxidectin levels. Some dogs had no adverse events on initial dosing but did after subsequent doses. CVM encouraged the sponsor to investigate whether the drug could be causing hypersensitivity reactions. Hypersensitivity reactions occur when there is an exaggerated immune response to a foreign substance. Anaphylaxis is one type of hypersensitivity reaction. Preliminary results from studies investigating the possible association between ProHeart 6 and hypersensitivity reactions were discussed at a meeting on January 14, 2004. FDAH postulated that reactions might be due to direct mast cell degranulation.

Trends in ProHeart 6 ADE Reporting

CVM tracks the number of incoming original and follow-up ADE reports as well as severity of reported ADE's. Often, severe ADE's will have follow-up reports. Figure 2 shows the mean number of initial and follow-up ProHeart 6 ADE reports received per day at CVM by calendar quarter (90 to 92 day quarter). Data for the third quarter of 2004 represents the mean number of ADE reports per day across the first 62 days of the quarter. The reporting pattern has remained similar each year, with a peak in the second quarter, coinciding with start of heartworm prevention season (Figure 2).

Figure 2. Mean number of initial and follow-up ProHeart 6 reports received by CVM day, by calendar quarter*.



*Data for the third quarter of 2004 represents the mean number of reports per day across the first 62 days of the quarter

The annual reporting period for a product is based on its approval date, not the calendar year. Table 8 shows the annual number of initial and follow-up ProHeart 6 ADE reports received by CVM from July 1, 2001 to June 30, 2004. The table shows that the annual number of initial ProHeart 6 ADE reports has not decreased over time.

Table 8. Number of ProHeart 6 ADE reports received by CVM, by year (July 1, 2001 to June 30, 2004).

Period	Initial reports	Follow-up reports	Total reports
July 1, 2001-June 30, 2002	1719	546	2265
July 1, 2002-June 30, 2003	1905	838	2743
July 1, 2003-June 30, 2004	1763	1076	2839

Table 9 shows the number of assessments over time for anaphylaxis/anaphylactoid reactions, convulsions, elevated SGPT/ALT, liver lesions, low platelets, and immune-mediated hemolytic anemias (IMHA) that were possibly or probably related to ProHeart 6 administration. The annual number of assessments for anaphylaxis/anaphylactoid reactions decreased, but still remained relatively high in 2003-2004. The number of assessments for convulsions ranged between 110 and 126 annually. Assessments for the other clinical manifestations shown in Table 10 have increased over time. The clinical manifestations shown in Table 9 are described in more detail in the next section.

Table 9. Number of causality assessments for certain reported clinical manifestations that are possibly or probably related to the use of ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Anaphylaxis/ Anaphylactoid Reactions	Convulsions	SGPT/ALT Elevation	Liver Lesions	Low Platelets	IMHA
July 1, 2001 - June 30, 2002	704	110	34	9	26	14
July 1, 2002 - June 30, 2003	544	126	52	15	28	24
July 1, 2003 - June 30, 2004	487	118	92	37	52	26

Table 10 shows by year the number of dogs with ADEs that were possibly, probably, or definitely related to ProHeart 6 and the number of dog deaths that were possibly or probably related to ProHeart 6 by year. A label revision, which was approved on July 15, 2003, required the sponsor to add “and rare reports of death” to the post approval experience section of the product label and to send a Dear Doctor Letter. Despite these changes, the number of reported deaths, possibly or probably related to ProHeart, 6 increased each year since the product was marketed (Table 10). In addition, the number of dogs with heartworm infections that were possibly, probably, or definitely related to the ineffectiveness of ProHeart 6 also increased (Table 11).

Table 10. Number of dogs with reported ADEs that are possibly, probably, or definitely related to ProHeart 6 and number of reported dog deaths that are possibly or probably related to ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Number of Dogs	Number of Deaths
July 1, 2001 - June 30, 2002	1896	112
July 1 2002 - June 30, 2003	1814	148
July 1 2003 - June 30, 2004	1640	185

Table 11. Number of dogs with reported heartworm infections that are possibly, probably, or definitely related to the ineffectiveness of ProHeart 6, by year (July 1, 2001 to June 30, 2004).

Period	Number of Dogs
July 1, 2001 - June 30, 2002	8
July 1 2002 - June 30, 2003	164
July 1 2003 - June 30, 2004	208

Clinical Manifestations

This section provides additional information on anaphylaxis/anaphylactoid reactions, convulsions, SGPT/ALT elevations, liver lesions, thrombocytopenia, and immune-mediated hemolytic anemia reported as ProHeart 6 ADEs. STARS searches were done using correspondence dates of June 6, 2001 (date of ProHeart 6 approval) to September 1, 2004. Because only one clinical manifestation is addressed within each subsection, the number of assessments is equal to the number of episodes. Case examples for each clinical manifestation can be found in [Appendix D](#).

Anaphylaxis/Anaphylactoid Reactions

Table 12 shows causality assessment categories for 1828 reported episodes of anaphylaxis/anaphylactoid reactions in dogs that received ProHeart 6. CVM determined that approximately one-half of the anaphylaxis/anaphylactoid reactions were probably drug-related and approximately one-half were possibly drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the episodes were: high (1338), medium (374), low (94), and unknown (22).

Table 12. Number of assessments for anaphylaxis/anaphylactoid reactions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	913
Possibly drug-related	907
Remotely drug-related	5
Information Lacking	3
Total	1828

For the 1820 episodes of anaphylaxis/anaphylactoid reactions determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (1741), fair (69), and

poor (3). The health status of dogs in the remaining 7 episodes is not known. In 816 episodes, dogs did not have concomitant drugs or vaccines and in 731 episodes, dogs had concomitant drugs and/or vaccines. The concomitant status for dogs in 273 episodes is not known.

Table 13 shows the number of anaphylaxis/anaphylactoid reaction assessments by time of onset. Eighty (80) percent of the episodes occurred within 3 hours of ProHeart 6 administration. Among the 1837 dogs involved in the 1820 episodes, there were at least 54 deaths that were possibly or probably related to ProHeart 6.

Table 13. Number of assessments by time of onset for anaphylaxis/ anaphylactoid reactions possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
< 15 minutes	374 (20.5%)
15 minutes to <1 hour	575 (31.6%)
1 to <3 hours	508 (27.9%)
3 to < 24 hours	296 (16.3%)
1 to <3 days	37 (2.0%)
3 to <7 days	8 (0.4%)
7 to <14 days	14 (0.8%)
14 to <30 days	3 (0.2%)
≥1 month	1 (0.1%)
Unknown	4 (0.2%)
Total	1820

The first ProHeart 6 label revision, which was approved on June 13, 2002, added to the product label the post-approval reported clinical manifestations of anaphylaxis/anaphylactoid reactions, depression/lethargy, urticaria, and head/facial edema. Although anaphylaxis/anaphylactoid reactions have declined (Table 9), they remain an ongoing problem with ProHeart 6. For the single marketing year of July 1, 2003 to June 30, 2004, there were 487 reported episodes with anaphylaxis/anaphylactoid reactions that were possibly or probably related to ProHeart 6 (Table 9). In contrast, there were only 97 reported episodes with anaphylaxis/anaphylactoid reactions that were possibly, probably, or definitely related to all monthly heartworm preventives combined for all marketing years (Table 4).

On January 14, 2004, the sponsor stated that anaphylactic reactions may be due in part to minimum residue solvents and that the elimination of these solvents might reduce these reactions. However, CVM continued to receive ADE reports for anaphylaxis/anaphylactoid reactions with zero residual solvent lots.

Convulsions

Seizures¹ were listed on the original ProHeart 6 product label because one dog in the clinical field trial experienced an increase in seizure frequency post-injection. Table 14 shows causality assessment categories for 405 reported episodes of convulsions in dogs following the administration of ProHeart 6. CVM determined that the majority of the convulsions were possibly (348) or probably (30) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the episodes were: high (88), medium (156), low (142), and unknown (19).

¹ Seizures are coded as “convulsions” in the CVM database.

Table 14. Number of assessments for convulsions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	30
Possibly drug-related	348
Remotely drug-related	23
Information Lacking	4
Total	405

For the 378 episodes of convulsions determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (302), fair (64), and poor (7). The health status of dogs in the remaining 5 episodes is not known. In 87 episodes, dogs did not have concomitant drugs or vaccines and in 215 episodes, dogs had concomitant drugs and/or vaccines. The concomitant status for dogs in 76 episodes is not known.

Table 15 shows the number of convulsion assessments by time of onset. Approximately one-half of the convulsion episodes occurred within 3 days after the administration of ProHeart 6. Among the 381 dogs involved in the 378 episodes, there were at least 61 deaths that were possibly or probably related to ProHeart 6.

Table 15. Number of assessments by time of onset for convulsions possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	62 (16.4%)
3 to <24 hours	51 (13.5%)
1 to <3 days	74 (19.6%)
3 to <7 days	66 (17.5%)
7 to <14 days	43 (11.4%)
14 to <30 days	31 (8.2%)
1 to <3 months	29 (7.7%)
≥3 months	13 (3.4%)
Unknown	9 (2.4%)
Total	378

There were more episodes with convulsions during the period of June 1, 2001 to September 1, 2004 for ProHeart 6 (Table 5) than for ivermectin products, for milbemycin products, or for selamectin products since their approvals (Table 4). The clinical manifestation “convulsions” was the most commonly reported neurologic sign among dogs treated with ProHeart 6. However, there were an additional 484 dogs with other types of neurologic signs that were possibly or probably related to ProHeart 6. Other neurologic signs reported include, but are not limited to ataxia, trembling, nervousness, confusion, and paresis.

Liver Signs

Between June 6, 2001 and September 1, 2004, there were more than 294 dogs reported to have liver-related clinical manifestations that were determined to be possibly

or probably related to ProHeart 6. Elevated SGPT/ALT and liver lesions noted on pathology reports were the most commonly reported liver-related clinical manifestations and will be the focus of this discussion.

SGPT/ALT Elevations

Table 16 shows the number of assessments, by causality assessment category, for SGPT/ALT elevations reported in 222 dogs following the administration of ProHeart 6. CVM determined that the majority of SGPT/ALT elevations were possibly (190) or probably (2) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the elevations were: high (49), medium (97), low (71), and unknown (5).

Table 16. Number of assessments for SGPT/ALT elevations reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	2
Possibly drug-related	190
Remotely drug-related	30
Information Lacking	0
Total	222

For the 192 SGPT/ALT elevations determined to be possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (149), fair (36), and poor (6). The health status of 1 dog is not known. Fifty (50) dogs did not receive concomitant drugs or vaccines and 112 dogs received concomitant drugs and/or vaccines. The concomitant status for 30 dogs is not known. Table 17 shows the number of assessments for SGPT/ALT elevations by time of onset. Approximately 58% of SGPT/ALT elevations occurred between 1 and 14 days after the administration of ProHeart 6. The 192 SGPT/ALT elevations occurred

in 192 dogs. There were at least 38 deaths among the dogs that were possibly or probably related to ProHeart 6.

Table 17. Number of assessments by time of onset for SGPT/ALT elevations possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	11 (5.7%)
3 to <24 hours	11 (5.7%)
1 to <3 days	31 (16.1%)
3 to <7 days	40 (20.8%)
7 to <14 days	41 (21.4%)
14 to <30 days	26 (13.5%)
1 to <3 months	16 (8.3%)
≥3 months	13 (6.8%)
Unknown	3 (1.6%)
Total	192

Liver Lesions

Table 18 shows the number of assessments, by causality assessment category, for liver lesions reported in dogs following the administration of ProHeart 6. CVM determined that the majority of liver lesions (65) were possibly drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the elevations were: high (16), medium (30), low (39), and unknown (3).

Table 18. Number of assessments for liver lesions reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	0
Possibly drug-related	65
Remotely drug-related	23
Information Lacking	0
Total	88

For the dogs with liver lesions determined to be possibly drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (50) and fair (13). The health status of 2 dogs is not known. Thirteen (13) dogs did not have concomitant drugs or vaccines and 44 dogs had concomitant drugs and/or vaccines. The concomitant status for 8 dogs is not known.

Table 19 shows the time of onset for liver lesions possibly related to ProHeart 6 administration. Among the 65 dogs with liver lesions, at least 47 deaths were possibly or probably related to ProHeart 6. Necrosis or hepatocellular vacuolization was mentioned in some of these pathology reports.^{d47}

Table 19. Number of assessments by time of onset for liver lesions possibly related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<3 hours	2 (3.1%)
3 to <24 hours	7 (10.8%)
1 to <3 days	8 (12.3%)
3 to <7 days	5 (7.7%)
7 to <14 days	10 (15.4%)
14 to <30 days	9 (13.8%)
1 to <3 months	15 (23.1%)
≥3 months	8 (12.3%)
Unknown	1 (1.5%)
Total	65

There were more assessments for SGPT/ALT elevations and liver lesions for ProHeart 6 in the period June 1, 2001 to September 1, 2004 (Table 5) than there were for all monthly heartworm preventives combined for all marketing years (Table 4). Furthermore, Table 9 shows that the number of assessments for these two signs have increased over time for ProHeart 6.

Hematologic Signs

Several hematologic signs (clinical manifestations) were reported as ADEs for ProHeart 6. There were 551 dogs with hematologic signs possibly or probably related to ProHeart 6. Anemia (low red blood cell count) and thrombocytopenia (low platelet count) were among the most commonly reported hematologic signs. A number of dogs had both thrombocytopenia and hemolytic anemia.

Immune-Mediated Hemolytic Anemia

There were 225 dogs with anemia that was possibly or probably related to ProHeart 6. Some of these dogs were reported to have immune-mediated hemolytic anemia (IMHA), a life-threatening condition that occurs when an immune response causes the destruction of red blood cells.³³

Table 20 shows the number of assessments, by causality assessment category, for IMHA reported in dogs following the administration of ProHeart 6. CVM determined that the majority of IMHAs were possibly (66) or probably (1) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the anemias were: high (20), medium (28), low (19), and unknown (3).

Table 20. Number of assessments for IMHAs reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	1
Possibly drug-related	66
Remotely drug-related	2
Information Lacking	1
Total	70

For the 67 dogs with IMHA that was possibly or probably drug-related, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (56), fair (10), and poor (1). Nineteen (19) dogs did not have concomitant drugs or vaccines and 34 dogs had concomitant drugs and/or vaccines. The concomitant drug/vaccine status for 14 dogs is not known. Table 21 shows the time of onset for IMHAs possibly or probably related to ProHeart 6 administration. Approximately one-half the IMHAs occurred between 1 week and 1 month following the administration of ProHeart 6. Among the 67 dogs with IMHA, there were at least 34 deaths that were possibly or probably related to ProHeart 6.

Table 21. Number of assessments by time of onset for IMHAs possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<24 hours	2 (3.0%)
1 to <3 days	2 (3.0%)
3 to <7 days	6 (9.0%)
7 to <14 days	15 (22.4%)
14 to <30 days	18 (26.9%)
1 to <3 months	18 (26.9%)
≥3 months	6 (9.0%)
Unknown	0
Total	67

Thrombocytopenia

Thrombocytopenia refers to a low platelet count. In dogs, thrombocytopenia is frequently caused by the destruction of platelets by an immune response (immune-mediated thrombocytopenia). ³³

Table 22 shows the number of assessments, by causality assessment category, for thrombocytopenia reported in dogs following the administration of ProHeart 6. There were 135 reported episodes with thrombocytopenia following ProHeart 6 administration. CVM determined that the majority were possibly (123) or probably (1) drug-related. The opinion of reporting veterinarians that ProHeart 6 caused the low platelet counts were: high (21), medium (61), low (48), and unknown (5).

Table 22. Number of assessments for thrombocytopenias reported as ProHeart 6 ADEs, by causality assessment category, June 6, 2001 to September 1, 2004.

Causality Assessment Category	Number of Assessments
Probably drug-related	1
Possibly drug-related	123
Remotely drug-related	10
Information Lacking	1
Total	135

For the 124 thrombocytopenia episodes possibly or probably related to ProHeart 6, the reporting veterinarians indicated that at the time of ProHeart 6 administration, the health status of the dogs was: good (91), fair (28), and poor (4). The health status for the dog(s) in one episode is not known. In 26 episodes, the dogs did not have concomitant drugs or vaccines and in 76 episodes, the dogs had concomitant drugs and/or vaccines. The concomitant drug/vaccine status for dogs in 22 episodes is not known.

Table 23 shows the time of onset for thrombocytopenia possibly or probably related to ProHeart 6 administration. The times of onset for thrombocytopenia are similar to those for IMHA. Forty-three (43) percent of thrombocytopenias occurred between 1 week and 1 month following ProHeart 6 administration. The 124 thrombocytopenia episodes involved 125 dogs. There were at least 45 deaths among these dogs that were possibly or probably related to ProHeart 6.

Table 23. Number of assessments by time of onset for thrombocytopenia possibly or probably related to ProHeart 6 administration, June 6, 2001 to September 1, 2004.

Time of Onset	Number of Assessments
<24 hours	2 (1.6%)
1 to <3 days	11 (8.9%)
3 to <7 days	25 (20.2%)
7 to <14 days	29 (23.4%)
14 to <30 days	24 (19.4%)
1 to <3 months	23 (18.5%)
≥3 months	8 (6.5%)
Unknown	2 (1.6%)
Total	124

There were more assessments for IMHA and thrombocytopenia for ProHeart 6 in the period June 1, 2001 to September 1, 2004 (Table 6) than there were for all monthly heartworm preventives combined for all marketing years (Table 5). Table 9 shows that the number of assessments for low platelets has increased over time for ProHeart 6.

Conclusions

CVM has the responsibility for ensuring the safety of animal drugs. The sponsor of an animal drug product has the responsibility to demonstrate that the product is safe and effective prior to approval. Prior to their approval, new animal drugs are subject to studies to establish their safety and effectiveness under the labeled conditions of use. Most of the common adverse events may become known prior to approval. CVM has a post-approval monitoring system to detect adverse drug events that occur after marketing, i.e., when an animal drug is used in a larger and more diverse population.

If CVM determines that a marketed animal drug product is likely to be causing serious adverse effects, it must evaluate what steps are necessary to address the issues

raised by the adverse event reports. ProHeart 6 is used primarily to prevent heartworm infections in dogs. There are alternative products that are approved for use in dogs to prevent heartworm infections. The frequency of ProHeart 6 adverse drug events, the severity of the events, which include death, and the temporal association with administration of ProHeart 6 raise serious questions about the safety of this heartworm preventive product. These adverse drug events are particularly striking when compared to other marketed heartworm preventive products, including Fort Dodge Animal Health's monthly heartworm preventive. In working with FDAH to address the adverse events associated with ProHeart 6, CVM has requested three label revisions. Despite these changes, the agency has continued to receive a large number of serious adverse drug events related to ProHeart 6. Therefore, CVM has concluded that there are serious questions regarding the continued safety of ProHeart 6. Fort Dodge, at FDA's request, agreed to immediately cease production and recall Proheart 6 from the market until the safety concerns associated with the product are resolved.

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Appendix A. Causality Assessment Algorithm for Adverse Drug Events

1. Previous Experience With Drug:

+1 CM generally recognized to occur in this species at the dosage received.

0 CM is not generally recognized to occur in this species at the dosage received but has been previously reported in veterinary and/or human medicine.

Drug has limited accumulated clinical experience (time and/or quantity marketed).

-1 CM previously unreported and drug has substantial accumulated clinical experience (time and/or quantity marketed).

2. Alternative Etiologic Candidates:

+2 There is **no** good candidate or no change in a candidate which can explain the CM, exclusive of drug administration.

0 An alternative candidate(s) exists, but not a good one(s) which can **well** explain the CM.

CM commonly occurs spontaneously in this type of patient and situation, usually in the absence of any recognizable alternative candidate(s).

-1 There **is** a good candidate or a change in a candidate which can well explain the CM, exclusive of drug administration.

3. Timing of Events:

+1 Timing was consistent and as expected for this type of CM to this drug.

0 Do not know what timing to expect.

-2 Timing was inconsistent for this type of CM to this drug.

4. Evidence of Overdose:

- +1 CM is clearly a dose-related type of manifestation, **and** there is unequivocal evidence that the amount of drug received was an overdose for this animal.
- 0 CM is not a dose related type of manifestation **or** there is no evidence of an overdose.

5. Dechallenge:

- +1 CM diminished or disappeared after discontinuation of suspect drug or administration of a **specific** antidote.

CM is known to be dose-related, and CM diminished or disappeared after dosage reduction.

- 0 Dechallenge difficult, impossible, or inappropriate to assess.

A non-specific agent or maneuver (non-antidotal) was administered that was directed against the CM and that usually produces the degree and rate of improvement observed in the case.

CM characteristically transient and episodic, and there is no established pattern episodes (regardless of what occurs after discontinuing the drug).

CM known to be dose-related, and CM did not diminish or disappear after dosage was reduced.

- 1 CM did **not** diminish or disappear after discontinuation of suspect drug.

CM improved without dechallenge **and** the improvement **cannot** be attributed to the development of tolerance.

6. Rechallenge:

- +1 CM unequivocally recurred or exacerbated after rechallenge.

- 0 There was no rechallenge attempted.

A non-specific agent or maneuver (non-antidotal) was administered that obscured the response of the CM.

CM failed to recur or exacerbate on rechallenge, **but** the dosage or duration of drug administration on rechallenge was substantially less than that suspected of causing the original CM.

Recurrence or exacerbation of CM was impossible to assess because it was progressing or was at a level of severity that any further increase would be difficult to appreciate.

- 1 CM failed to recur or exacerbate on rechallenge.

The component scores above are then summed to reach a final causal score:

<u>Scores</u>	<u>Category of Association</u>
-9	Not applicable
-8	Information lacking
-7	No conclusion
-1 to -6	Remotely drug-related
0 to 2	Possibly drug-related
3 to 5	Probably drug-related
6 to 7	Definitely drug-related
-1	Ineffectiveness - Remotely drug-related
0 to 1	Ineffectiveness - Possibly drug-related
3	Ineffectiveness - Probably drug-related
6	Ineffectiveness - Definitely drug-related

Appendix B. Approved Monthly and 6-Month Heartworm Preventives

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ANADA	Approval Date
Heartgard	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease. Heartgard® prevents heartworm disease by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for a month (30 days) after infection.	138-412	4/7/1987
Heartgard Chewables	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for one month (30 days) after infection .	140-886	8/9/1989
Heartgard Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for one month (30 days) after infection andfor the treatment and control of ascarids (<i>Toxocara canis</i> , <i>Toxascaris leonina</i>) and hookworms (<i>Ancylostoma caninum</i> , <i>Uncinaria stenocephala</i> , <i>Ancylostoma braziliense</i>).	140-971	1/15/1993
Advantage Duo	Ivermectin and Imidacloprid	Oral	Advantage DUO (imidacloprid/ivermectin) is indicated for the prevention of heartworm disease caused by <i>Dirofilaria immitis</i> , kills adult fleas and is indicated for the treatment of flea infestations (<i>Ctenocephalides felis</i>). Advantqge DUO is recommended for dogs eight weeks of age or older.	141-208	9/27/2002
Iverhart	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease. IVERHART tablets prevent heartworm disease by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for one month (30 days) after infection.	200-270	11/30/2001
Ivermectin Chewable Tablets	Ivermectin	Oral	For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for a month (30 days) after infection.	200-297	6/18/2004

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ANADA	Approval Date
Iverhart Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm diseases by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for a month (30 days) after infection and for the treatment and control of ascarids (<i>Toxocara canis</i> , <i>Toxascaris leonina</i>) and hookworms (<i>Ancylostoma caninum</i> , <i>Uncinaria stenocephala</i> , <i>Ancylostoma braziliense</i>).	200-302	5/30/2001
Tri-Heart Plus	Ivermectin and Pyrantel Pamoate	Oral	For use in dogs to prevent canine heartworm diseases by eliminating the tissue stage of heartworm larvae (<i>Dirofilaria immitis</i>) for a month (30 days) after infection and for the treatment and control of ascarids (<i>Toxocara canis</i> , <i>Toxascaris leonine</i>) and hookworms (<i>Ancylostoma caninum</i> , <i>Uncinaria stenocephala</i> , <i>Ancylostoma braziliense</i>).	200-338	8/13/2003
Interceptor	Milbemycin Oxime	Oral	INTERCEPTOR Flavor Tabs are indicated for use in the prevention of heartworm disease caused by <i>Dirofilaria immitis</i> , the control of adult <i>Ancylostoma caninum</i> (hookworm), and the removal and control of adult <i>Toxocara canis</i> and <i>Toxascaris leonina</i> (roundworms) and <i>Trichuris vulpis</i> (whipworm) infections in dogs and puppies four weeks of age or greater and two pounds of body weight or greater.	140-915	6/14/1990
Sentinel	Milbemycin Oxime and Lufenuron	Oral	SENTINEL Flavor Tabs are indicated for use in dogs and puppies, four weeks of age or older, and two pounds of body weight or greater for the prevention of heartworm disease caused by <i>Dirofilaria immitis</i> , for the prevention and control of flea populations, the control of adult <i>Ancylostoma caninum</i> (hookworm), and the removal and control of adult <i>Toxocara canis</i> , and <i>Toxascaris leonina</i> (roundworm) and <i>Trichuris vulpis</i> (whipworm) infections. Lufenuron controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.	141-084	4/10/1997

Product Name	Active Ingredient(s)	Route of Administration	Indications for Dogs	NADA/ANADA	Approval Date
ProHeart	Moxidectin (Tablets)	Oral	ProHeart (moxidectin) heartworm prevention tablets are indicated for once-a-month use in dogs to prevent infections by the canine heartworm, <i>Dirofilaria immitis</i> , and the subsequent development of canine heartworm disease.	141-051	5/27/1997
ProHeart 6	Moxidectin (Sustained Release)	Subcutaneous Injection	ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by <i>Dirofilaria immitis</i> . ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (<i>Ancylostoma caninum</i> and <i>Uncinaria stenocephala</i>) infections.	141-189	6/6/2001
Revolution	Selamectin	Topical	Revolution is recommended for use in dogs six weeks of age or older for the following parasites and indications: Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (<i>Ctenocephalides felis</i>), prevention of heartworm disease caused by <i>Dirofilaria immitis</i> , and the treatment and control of ear mite (<i>Otodectes cynotis</i>) infestations. Revolution is also indicated for the treatment and control of sarcoptic mange (<i>Sarcoptes scabiei</i>) and for the control of tick infestations due to <i>Dermacentor variabilis</i> .	141-152	5/26/1999

Appendix C. ProHeart 6 Label, May 2003

(note, if difficulty viewing click “view” on the tools menu and then click “print layout”.)

NADA 141-189, Approved by FDA



ProHeart® 6 (moxidectin)

Sustained Release Injectable for Dogs

CAUTION

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

ProHeart 6 (moxidectin) Sustained Release Injectable consists of two separate vials. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH.

PHARMACOLOGY

Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of *Streptomyces cyaneogriseus* subsp *noncyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 0.17 mg moxidectin/kg body weight is the tissue larval stage. The larval and adult stages of the canine hookworms, *Ancylostoma caninum* and *Uncinaria stenocephala*, are susceptible.

Following injection with ProHeart 6, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the six month dosing interval, residual drug concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

INDICATIONS

ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis*.

ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

DOSAGE AND ADMINISTRATION

Frequency of Treatment: ProHeart 6 prevents infection by *D. immitis* for six months. It should be administered within one month of the dog's first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes. When replacing another heartworm preventive product, ProHeart 6 should be given within one month of the last dose of the former medication.

ProHeart 6 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. However, persistent effectiveness has not been established for this indication. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 6 months.

Dose: The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.0227 mL/lb.). This amount of suspension will provide 0.17 mg moxidectin/kg bodyweight (0.0773 mg/lb.). To ensure accurate dosing, calculate each dose based on the dog's weight at the time of treatment. Do not overdose growing puppies in anticipation of their expected adult weight. The following dosage chart may be used as a guide.

Dog Wt.			Dose Volume		
lb	kg		mL/Dog	lb	kg
11	5		0.25	77	35
22	10		0.50	88	40
33	15		0.75	99	45
44	20		1.00	110	50
55	25		1.25	121	55
66	30		1.50	132	60

Injection Technique: The two-part sustained release product must be mixed at least 30 minutes prior to the intended time of use (See **CONSTITUTION PROCEDURES** for initial mixing instructions). Once constituted, swirl the bottle gently before every use to uniformly re-suspend the microspheres. Withdraw 0.05 mL of suspension/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 mL should be administered in a single site. The location(s) of each injection (left or right side) should be noted so that prior injection sites can be identified and the next injection can be administered on the opposite side.

CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

HUMAN WARNINGS

Not for human use. Keep this and all drugs out of the reach of children.

May be slightly irritating to the eyes. May cause slight irritation to the upper respiratory tract if inhaled. May be harmful if swallowed. If contact with the eyes occurs, rinse thoroughly with water for 15 minutes and seek medical attention immediately. If accidental ingestion occurs, contact a Poison Control Center or a physician immediately. The material safety data sheet (MSDS) contains more detailed occupational safety information.

PRECAUTIONS

Use with caution in sick, debilitated or underweight animals (see SAFETY).

ProHeart 6 should not be used more frequently than every 6 months.

The safety and effectiveness of ProHeart 6 has not been evaluated in dogs less than 6 months of age.

Prior to administration of ProHeart 6, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, ProHeart 6 is not effective for microfilariae clearance.

ADVERSE REACTIONS

In field studies, the following adverse reactions were observed in approximately 1% of 280 dogs treated with ProHeart 6: vomiting, diarrhea, listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature.

Post-Approval Experience: Although not all adverse reactions are reported, the following reactions are based on voluntary post-approval drug experience reporting: anaphylaxis/toxic reactions, depression/lethargy, urticaria, head/facial edema, and rare reports of death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products. Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

ANIMAL SAFETY

General Safety: ProHeart 6 has been safely administered to a wide variety of healthy dogs six months of age and older, including a wide variety of breeds, pregnant and lactating females, breeding males, and ivermectin-sensitive collies. However, in clinical studies, two geriatric dogs with a history of weight loss after the initial ProHeart 6 injection died within a month of the second 6 month injection. A third dog who was underweight for its age and breed and who had a history of congenital problems experienced lethargy following the initial injection of ProHeart 6. The dog never recovered and died 3 months later (see **PRECAUTIONS**).

ProHeart 6 administered at 3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in ivermectin-sensitive collies did not cause any adverse reactions. ProHeart 6 administered at 3 times the recommended dose did not adversely effect the reproductive performance of male or female dogs. ProHeart 6 administered up to 5 times the recommended dose in 7-8 month old puppies did not cause any systemic adverse effects.

In well controlled clinical field studies, ProHeart 6 was safely used in conjunction with a variety of veterinary products including vaccines, anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics and flea control products.

Injection Site Reactions: Injection site observations were recorded during effectiveness and safety studies. In clinical studies, ProHeart 6 was administered at six-month intervals to client-owned dogs under field conditions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

In a laboratory safety study, ProHeart 6 was administered at 1, 3 and 5 times the recommended dose to 7-8 month old puppies. Injection sites were clipped to facilitate observation. Slight swelling/edema at the injection site was observed in some dogs from all treated groups. These injection site reactions appeared as quickly as 8 hours post injection and lasted up to 3 weeks. A three-year repeated injection study was conducted to evaluate the safety of up to 6 injections of ProHeart 6 administered at the recommended dose (0.17 mg/kg) every 6 months. Mild erythema and localized deep subcuticular thickening were seen in dogs that received four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous panniculitis with microvacuolation. The only adverse reaction seen that was not related to the injection site was weight loss in one dog.

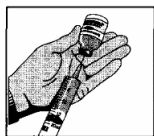
Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 5 months after injection.

CONSTITUTION PROCEDURES

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use.

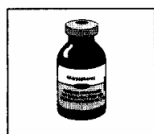
Items needed to constitute ProHeart 6:

- Microspheres (vial 1)
- Enclosed vent needle (25G)
- Vehicle (vial 2)
- Sterile 20 mL syringe for transfer
- Transfer needle (18G or 20G)



Constitution of the 20 mL vial product.

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the unique vehicle from the vial. **There is more vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
7. Record the time and date of mixing on the microsphere vial.
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before every use, gently swirl the mixture to achieve uniform suspension. The microspheres and vehicle will gradually separate on standing.
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.
11. Refrigerate the unused product. The constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.



STORAGE INFORMATION

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 4 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 6 is available in the following two package sizes.

1. 5-Pack

NDC 0856-3670-25 – 20 mL vial product:
5 - 10% moxidectin sterile microspheres - 598 mg/vial
5 - Sterile vehicle - 17 mL/vial

2. 10-Pack

NDC 0856-3670-29 – 20 mL vial product:
10 - 10% moxidectin sterile microspheres - 598 mg/vial
10 - Sterile vehicle - 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 685-5656.

U.S. Patent No. 4,916,154 and 6,340,671

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Appendix D. Case Studies

Anaphylaxis/Anaphylactoid Reactions

The following examples represent dogs with anaphylaxis or anaphylactoid reactions that are possibly or probably associated with ProHeart 6.

1. [Case 200202319](#)

Signalment:

- Age: 8 months
- Breed: Mexican Hairless
- Gender: Neutered male
- Weight: 21 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Neutered on 4/16/02
- Date of Injection: 4/17/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: ketamine, Valium, isoflurane
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Probably drug-related

The dog recovered from surgery and received a ProHeart® 6 injection the next day in the hospital. He collapsed within 20 minutes and was transferred to an emergency clinic.

Radiographs revealed no significant findings. He was treated supportively with intravenous fluids. The attending veterinarian was unable to stabilize his blood pressure, and the owners elected euthanasia.

2. [Case 200306896](#)

Signalment:

- Age: 3 years
- Breed: Schnauzer
- Gender: Spayed female

- Weight: 12.5 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/17/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Probably drug-related

The dog began to vomit within 20 minutes of the injection. She became depressed and collapsed shortly after injection. She was treated with epinephrine, Benadryl, dexamethasone, and intravenous fluids. She recovered initially, but died during the night.

3. [Case 200400552](#)

Signalment:

- Age: 7 years
- Breed: Wire Haired Fox Terrier
- Gender: Spayed female
- Weight: 24.6 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 1/22/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Progressed to severe condition, survived**
- Necropsy: Not applicable

Causality Assessment Category: Probably drug-related

The dog was depressed and lethargic for 48 hours after the injection and was taken to Tufts University Teaching Hospital. The attending veterinarian at Tufts found facial edema and swollen lymph nodes and diagnosed a delayed hypersensitivity adverse event to ProHeart® 6. The dog's condition progressed in 12 days to a more generalized adverse event including thrombocytopenia, prolonged partial thromboplastin time (PTT), painful abdomen, and elevated bilirubin. She was treated with tapering doses of Benadryl. The dog was discharged on 2/10/04.

4. [Case 200403348](#)

Signalment:

- Age: 8.5 years
- Breed: Alaskan Malamute
- Gender: Spayed female
- Weight: 104 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/29/04
- Dose: Underdosed by 0.16 mL
- Concomitant Vaccinations or Drugs: None
- Outcome: **Acute death**
- Necropsy: Acute anaphylactic shock

Causality Assessment Category: Possibly drug-related
The dog was found dead 12 hours post-injection. A post-mortem revealed venous congestion of the lungs and liver consistent with acute anaphylactic shock.

5. [Case 200403885](#)

Signalment:

- Age: 3 years
- Breed: Staffordshire Bull Terrier
- Gender: Female
- Weight: 62 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 6/18/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Probably drug-related

The dog began vomiting within 30 minutes of the injection. She became recumbent with pale membranes within 1 hour. She was given Benadryl and dexamethasone and recovered.

CVM also had concern about anaphylaxis/toxic events reported among dogs that received ProHeart® 6 concurrently with a vaccine or another drug. The following examples represent a sample of cases with causality assessment scores of zero or above for anaphylaxis/anaphylactoid reactions in the concomitant drug and vaccine subgroup.

6. [Case 200200791](#)

Signalment:

- Age: 4 years
- Breed: Miniature Schnauzer
- Gender: Female spayed
- Weight: 19 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 2/11/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper vaccination
- Outcome: **Progressed with multiple clinical signs, recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog collapsed within 2 hours of injection, was treated with fluids, steroids and diphenhydramine, and released. She presented later that evening to the emergency clinic at Michigan State University (MSU) with a seizure. She recovered, but presented to her regular veterinarian the next day with a papular skin eruption on the neck and back and wheals on the head. She was referred to MSU for a skin biopsy. No biopsy results were submitted to CVM, but the dog was progressing well clinically on 4/16/02 re-evaluation.

7. [Case 200203569](#)

Signalment:

- Age: 3 years
- Breed: Pug
- Gender: Neutered male
- Weight: 25.6 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Overweight, arthritis
- Date of Injection: 6/5/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Carprofen

- Outcome: **Acute death**
- Necropsy: Acute anaphylaxis

Causality Assessment Category: Possibly drug related
The dog became agitated during a nail trim following the injection. He vomited, collapsed, arrested and died within 25 minutes. His body was transported to the University of Minnesota Veterinary Teaching Hospital for a post mortem examination; findings were consistent with acute anaphylaxis. The nail trim may have exacerbated the anaphylactic response due to endogenous epinephrine release.

Convulsions

The following examples represent cases involving convulsions that are possibly related to ProHeart® 6 injections in the absence of concomitant vaccinations or drugs.

1. [Case 200103398](#)

Signalment:

- Age: 2 years
- Breed: Yorkshire Terrier
- Gender: Male
- Weight: 3.2 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 7/21/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: Progressive neurological signs
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related (convulsion)

Remotely drug-related (encephalitis)

The dog developed convulsions and periorbital pruritus within 2 hours of ProHeart 6 injection. He was diagnosed with encephalitis of unknown origin. The cause of small dog encephalitis is not known; drugs are one etiologic explanation.³⁴

2. [Case 200104935](#)

Signalment:

- Age: 7 years
- Breed: German Shepherd Mix
- Gender: male
- Weight: 100 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/15/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered, ongoing treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog presented with seizures 30 hours after injection. He was treated with phenobarbital and Valium. The dose of phenobarbital was decreased in late October. As of late November, no additional seizures were reported. The veterinarian listed differential diagnoses of idiosyncratic drug reaction or epilepsy.

3. [Case 200202452](#)

Signalment:

- Age: 18 months
- Breed: Pit Bull Terrier
- Gender: Neutered male
- Weight: 47.5 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/19/02

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered, ongoing treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

Vomiting, diarrhea, and inappetence began an hour after the injection and were ongoing for 3 days. He was examined on 4/22/02 and treated with Baytril, dexamethasone, and cimetidine. The dog began having seizures 9 days after injection. Blood tests showed elevated liver enzymes. He was treated with Valium and phenobarbital. On 5/5/02 (14 days after injection) the dog was trembling and had severe pain when he opened his mouth. A magnetic resonance imaging (MRI) test and a cerebrospinal fluid (CSF) tap identified no cause for the seizures.

4. [Case 200207752](#)

Signalment:

- Age: 3 years
- Breed: Golden Retriever
- Gender: Male
- Weight: 107 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/27/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered, ongoing treatment**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog had a seizure 10 hours after injection. He had two more seizures over the next 24 hours and was treated with phenobarbital and Valium. He developed bloody diarrhea and vomiting at 2 weeks post injection and lost 5 pounds. The veterinarian tried to

discontinue phenobarbital in February 2003, but the dog had another seizure and was started on the phenobarbital again. No additional seizures were noted at a 2 month follow-up visit.

5. [Case 200301322](#)

Signalment:

- Age: 10 years
- Breed: Miniature Schnauzer
- Gender: Spayed female
- Weight: 30 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/1/03 (3rd dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had a seizure 4 days after she was given her third dose of ProHeart® 6 and developed elevated liver enzymes 7 days later. A veterinary neurologist developed a differential diagnosis that included a forebrain lesion due to encephalitis, neoplasia, or a cerebral vascular incident. The dog was euthanized without a necropsy 25 days following her injection.

6. [Case 200301797](#)

Signalment:

- Age: 2.5 years
- Breed: Weimaraner
- Gender: Spayed female

- Weight: Not provided

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/21/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Progressive neurological disease and visual impairment, survived**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

Twenty-four hours after injection, the dog developed bloody diarrhea, vomiting, ataxia and a head tilt. She progressed to a prancing gait and partial blindness and was referred to the Louisiana State University (LSU) veterinary school. Fungal and tick titers were negative. MRI revealed dilated optic vessels and subtle changes in the occipital area of the cerebrum, thalamus, and optic radiation. CSF tap revealed mild lymphocytic inflammation. Distemper titers were 1:80 indicating vaccination, infection, or exposure. No diagnosis was made and the dog was sent home on tapering doses of prednisone. When the owner tried to wean her off her medication, clinical signs returned.

7. [Case 200302409](#)

Signalment:

- Age: 18 months
- Breed: Papillon
- Gender: Neutered male
- Weight: 6.7 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/14/03 (2nd dose)

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Meningoencephalitis; cardiac lesions

Causality Assessment Category: Possibly drug-related (seizure)

Remotely drug-related (encephalitis, cardiac lesions)

This dog began to have seizures 48 hours after his second injection of ProHeart 6. He had two seizures one hour apart. On 4/29/03 he was started on phenobarbital. He had a seizure and died 16 days after the ProHeart®6 injection. Necropsy revealed severe necrotizing granulomatous and eosinophilic meningoencephalitis. Moxidectin levels in the brain were run and were not found at the limits of detection. In the heart, the right ventricle was dilated and flabby with dark red foci of the epicardium. Turk's procedure (a special histopathology stain) indicated right ventricular hypertrophy.

8. [Case 200404520](#)

Signalment:

- Age: 4 years
- Breed: Chihuahua
- Gender: Spayed female
- Weight: 7.4 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/14/04 (2nd dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had one previous ProHeart® 6 injection two years prior. Three days after her second injection she presented for anorexia and lethargy. Bloodwork was normal. She was treated with hydroxyzine and Pet-Tinic vitamins. Four days after that (or 7 days post injection) she had a seizure. She was treated with diazepam and phenobarbital. She had a seizure and died two days later (9 days following injection).

The following examples represent cases involving convulsions that were possibly related to ProHeart® 6 injections in dogs that had received concomitant vaccines or drugs.

9. [Case 200105179](#)

Signalment:

- Age: 6 years
- Breed: Pug
- Gender: Female
- Weight: 25 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/29/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper and rabies vaccinations
- Outcome: **Died**
- Necropsy: Inconclusive (body was frozen)

Causality Assessment Category: Possibly drug-related

This dog had a seizure within 10 minutes of the ProHeart® 6 injection and vaccine administration. She was treated with fluids, Benadryl, and steroids. She recovered and went home, but later that evening she presented to an emergency clinic with difficulty breathing. She had another seizure and died. At necropsy, chronic cardiac changes were noted. Other organ changes were suggestive of shock but the necropsy was inconclusive because the body had been frozen.

10. [Case 200201651](#)

Signalment:

- Age: 3 years
- Breed: Mixed
- Gender: Neutered male
- Weight: Not recorded

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 3/11/02
- Dose: Not provided
- Concomitant Vaccinations or Drugs: Distemper, rabies, and Lyme vaccinations
- Outcome: **Euthanasia**
- Necropsy: Multifocal ischemia of the brain

Causality Assessment Category: Possibly drug-related

This dog had a seizure 6 days after the ProHeart® 6 and vaccine administration. He was euthanized 11 days after the injections when he failed to respond to treatment. A veterinary neurologist at Cornell University examined the brain, noting multifocal ischemic lesions which may have been secondary to the seizures. No evidence of inflammation was found to support a diagnosis of infectious disease or a post-vaccinal condition.

11. [Case 200103297](#)

Signalment:

- Age: 1.5 years
- Breed: Miniature Pinscher
- Gender: Male
- Weight: 13.5 lb

History:

- Heartworm Status: Negative
- Health Status: Good

- Concomitant Medical Conditions: None
- Date of Injection: 6/27/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Monthly imidacloprid for fleas
- Outcome: **Progressive neurological disease, survived**
- Necropsy: Not provided

Causality Assessment Category: Possibly drug-related

The dog's signs started with ataxia and incoordination 12 hours after ProHeart 6 injection and progressed to dysmetria, tremors, abnormal reflexes, and stiffness by 18 days. He was treated successfully through September and weaned off prednisone. A progress review in December 2001 indicated that he still had tremors when excited.

12. [Case 200207622](#)

Signalment:

- Age: 2 years
- Breed: Pit Bull Terrier
- Gender: Neutered male
- Weight: 66.4 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 12/13/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper, rabies, and Lyme vaccinations
- Outcome: **Ongoing seizure disorder**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog started to vomit and have diarrhea within an hour of the ProHeart® 6 injection and vaccination. He had a seizure 1 day post –injections. The seizures returned in March and he has continued to see a neurologist for repetitive seizures. At the last follow-up, he

was on potassium bromide, Valium, and phenobarbital and was having seizures approximately every two weeks.

Liver Signs

The following examples represent cases involving liver lesions noted on biopsy or necropsy (PR-Liver) or SGPT/ALT elevations that were possibly related to ProHeart 6.

1. Case 200202432

Signalment:

- Age: 3 years
- Breed: Labrador Retriever
- Gender: Spayed female
- Weight: 71 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Mild atopy (skin allergies)
- Date of Injection: 1/5/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Benadryl as needed for atopy
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog began vomiting and collapsed 3 days after the injection. She was taken to an emergency clinic where she was found to be anemic and tachycardic. She also had elevated liver enzymes. She was treated with fluids and steroids. She improved and was re-examined the next day by her regular veterinarian who ruled out toxins and Addison's disease. No alternative etiologic candidate was found that explained her clinical manifestations.

2. Case 200206333

Signalment:

- Age: 4 years

- Breed: Pit Bull Terrier
- Gender: Male
- Weight: 58 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 10/8/02
- Dose: Underdosed by 0.20 mL
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

The dog had bloody diarrhea and began vomiting within 10 minutes of the injection. By 2 hours his condition had progressed to collapse, cyanosis, and pulmonary congestion. He was sent to an emergency referral clinic where he was treated with crystalloids, cefazolin, enrofloxacin, famotidine, and sucralfate. He failed to improve, became oliguric, and was referred to a specialist. His SGPT/ALT was as high as 20,773. He died by day 3 following the injection. He was included in both the anaphylaxis/anaphylactoid reaction category and the liver category.

3. Case 200303279

Signalment:

- Age: 10 years
- Breed: Labrador Retriever
- Gender: Spayed female
- Weight: 72 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/20/03

- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Survived**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog was lethargic and anorexic on the evening of her first injection. By the third day following injection, she was jaundiced and diagnosed with elevated liver enzymes. Liver biopsy revealed chronic active hepatitis.

4. [Case 200401208](#)

Signalment:

- Age: 3 years
- Breed: Jack Russell Terrier
- Gender: Spayed female
- Weight: 17 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 8/14/04
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered after several months**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog presented 2 weeks after injection with vomiting, anorexia, and depression. She was diagnosed at an emergency veterinary center with elevated liver enzymes and a heart murmur. She was extensively evaluated by two veterinarians and a specialist and her workups included radiographs and ultrasound examination. No other cause for her condition was found. She was treated supportively with fluids, amoxicillin, and metronidazole and gradually improved over 60 days.

5. Case 200303623

Signalment:

- Age: 11 years
- Breed: Australian Cattle Dog
- Gender: Neutered male
- Weight: 32 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 6/3/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Multiple organ failure secondary to acute myocardial degeneration

Causality Assessment Category: Possibly drug-related

This dog showed signs of vomiting and lethargy 4 days after injection. His blood work revealed elevated creatinine and elevated liver enzymes and he was treated supportively with intravenous fluids and antibiotics. He tested negative for antifreeze poisoning and leptospirosis. He failed to improve and was euthanized at 2 weeks. At necropsy he was noted to have myocarditis, pneumonia, kidney tubular mineralization, ulceration of the stomach, endocardiosis, and mild multifocal hemorrhages of the brain. A veterinary cardiac pathologist reviewed the cardiac slides and diagnosed acute myocardial degeneration not thought to be related to hypoxia or epinephrine. The cause of the acute myocarditis could not be determined. Multiple organ failure was thought to be secondary to the cardiac condition.

6. Case 200202608

Signalment:

- Age: 6 years
- Breed: Maltese
- Gender: Spayed female

- Weight: 11.5 lb

History:

- Heartworm Status: Not provided
- Health Status: Fair
- Concomitant Medical Conditions: Mass in bladder, urinary tract infection
- Date of Injection: 4/26/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Baytril
- Outcome: **Euthanasia**
- Necropsy: Hepatocellular degeneration, encephalomalacia

Causality Assessment Category: Possibly drug-related

This dog presented for a urinary tract infection. The attending veterinarian diagnosed a bladder mass by palpation and ultrasound and prescribed Baytril. It is not clear exactly when the Baytril was started, but two hours after the ProHeart 6 injection, she was noted to be lethargic. Forty-eight hours later she had a seizure. She was treated with Valium and phenobarbital and the seizures stopped. She was transferred the next day to her regular veterinarian who noted elevated bile acids and elevated bilirubin. An MRI indicated diffuse infiltrative disease of the cerebral cortex. The dog was euthanized. A necropsy indicated a leiomyoma of the bladder which was pre-existing according to the history. The liver lesion was described as hepatocellular degeneration. The brain lesion was described as laminar cortical necrosis of the grey matter; most likely due to hypoxia. This dog had strong temporal drug association for neurologic and hepatic signs as well as neurologic signs that were consistent with what has been observed in other small breeds such as Yorkshire Terriers and Pugs (discussed previously under convulsions).

Hematologic Signs

The following examples represent cases of immune-mediated hemolytic anemia (IMHA) and/or thrombocytopenia possibly related to ProHeart 6.

1. [Case 200103479](#)

Signalment:

- Age: 5 years
- Breed: Australian/Border Collie Mix

- Gender: Neutered male
- Weight: 52 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 7/5/01
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog presented for lethargy and depression 14 days post-injection and was diagnosed with immune-mediated hemolytic anemia the next day. He was treated with Oxyglobin® (artificial hemoglobin), steroids, and antibiotics but did not respond. He was euthanized 12 weeks after his ProHeart 6 injection.

2. [Case 2002007721](#)

Signalment:

- Age: 12 years
- Breed: Yorkshire Terrier
- Gender: Spayed female
- Weight: 12 lb

History:

- Heartworm Status: Not mentioned
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 1/11/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog was diagnosed with immune-mediated hemolytic anemia 27 days after injection. She had a packed cell volume of 10% and died overnight at the local veterinary emergency clinic.

3. [Case 200201234](#)

Signalment:

- Age: 1 year
- Breed: Labrador Retriever Mix
- Gender: Neutered male
- Weight: 67 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 2/26/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog vomited and was depressed 6 hours after injection and was treated with dexamethasone, Benadryl, and fluids. Eight days later, he was diagnosed with immune-mediated hemolytic anemia. He tested negative for Lyme and Ehrlichia. He was treated with prednisone and Immuran and recovered.

4. [Case 200203935I](#)

Signalment:

- Age: 5 year
- Breed: Golden Retriever
- Gender: Neutered male
- Weight: 77 lb

History:

- Heartworm Status: Not provided

- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/13/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Unknown**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related (IMHA and low platelets)

This dog presented with exercise intolerance 5 weeks after ProHeart 6 injection. Blood tests showed a Coombs' Positive hemolytic anemia and thrombocytopenia. He was treated with cyclosporine and prednisone. The outcome of the case was not provided.

5. Case 200303433

Signalment:

- Age: 2 years
- Breed: Dachshund
- Gender: Neutered male
- Weight: 40 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: Obesity; narcolepsy
- Date of Injection: 5/26/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Centrilobular hepatic necrosis; pulmonary vascular thrombosis

Causality Assessment Category: Possibly drug-related

This dog presented 34 days after his ProHeart 6 injection with anorexia and lethargy. His hematocrit on presentation was 11%. He had a positive slide agglutination test and elevated serum bilirubin. He was treated with prednisone, but died two days later. Necropsy revealed centrilobular hepatic necrosis

due to severe anemia. He also had cholestasis, hemosiderosis of the spleen, and pulmonary vascular thrombosis.

6. [Case 200305624](#)

Signalment:

- Age: 3 years
- Breed: Poodle
- Gender: Spayed female
- Weight: 15 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/22/03
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog was diagnosed with immune-mediated hemolytic anemia 7 days after ProHeart 6 injection. Her tick panel was negative. She was treated with azathiaprine, prednisone, doxycycline, and cyclosporine and two whole blood transfusions. She gradually improved and by six months post-injection, was off all medications.

7. [Case 200200725 I](#)

Signalment:

- Age: 11 years
- Breed: Pit Bull
- Gender: Spayed female
- Weight: 21 lb

History:

- Heartworm Status: Not provided
- Health Status: Good

- Concomitant Medical Conditions: Grade 3 heart murmur
- Date of Injection: 1/29/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper Vaccination
- Outcome: **Euthanasia**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related

This dog presented to an emergency clinic 8 days after her injections with pale mucous membranes. Her packed cell volume was 8.5%, and she was diagnosed with immune-mediated hemolytic anemia. She was Coombs', Lyme, and Ehrlichia negative and was treated with a blood transfusion and prednisone. She was euthanized at day 33 post-injection.

8. [Case 200307034](#)

Signalment:

- Age: 6 years
- Breed: Beagle mix
- Gender: Neutered male
- Weight: 50 lb

History:

- Heartworm Status: Negative
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 9/27/03 (4th dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

The dog developed a hot spot (pyoderma of the skin) at the tail base 2 hrs after his fourth ProHeart 6 injection and was treated successfully with gentamycin spray. He returned to the veterinarian 7 weeks later with a history of anorexia which started an unknown

number of days prior. He was febrile and weak and was diagnosed with immune-mediated hemolytic anemia (IMHA). Coombs test and tick panels were negative. His chemical profile was normal. He began a course of doxycycline, metronidazole, and increasing doses of prednisone. By 4 months, signs progressed to include elevated liver enzymes, bloody diarrhea, and vomiting. This dog was transferred to Purdue University and was further treated for blood in the stool. An endoscopic exam revealed ulceration of the gastrointestinal tract. Biopsy indicated mild suppurative inflammation of the gastric mucosa. No further follow-up information was provided.

9. Case 200202652 I

Signalment:

- Age: 3 years
- Breed: Rottweiler
- Gender: Spayed female
- Weight: 85 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 4/1/02
- Dose: Labeled
- Concomitant Vaccinations or Drugs: Distemper-Corona and Rabies Vaccinations
- Outcome: **Recovered**
- Necropsy: Not applicable

Causality Assessment Category: Possibly drug-related

This dog presented 26 days after ProHeart 6 injection and vaccination to a local emergency clinic for lethargy and depression of unknown duration. On physical examination, she was icteric. Her packed cell volume was 8%, and she had a positive slide agglutination test. She was treated with a blood transfusion, prednisone, and antibiotics.

10. Case 200205461

Signalment:

- Age: 8 years
- Breed: Keeshond
- Gender: Neutered male
- Weight: 45 lb

History:

- Heartworm Status: Not provided
- Health Status: Good
- Concomitant Medical Conditions: None
- Date of Injection: 5/9/02 (2nd dose)
- Dose: Labeled
- Concomitant Vaccinations or Drugs: None
- Outcome: **Died**
- Necropsy: Not performed

Causality Assessment Category: Possibly drug-related (IMHA and low platelets)

There were no reported problems after the initial dose of ProHeart 6 on 11/2/01. This dog presented with depression and lethargy 14 weeks after the second injection. His PCV was 11% with agglutinating red cells. Platelets were estimated at 22,000. He was treated with two blood transfusions, prednisone, and cytoxin but died in 3 days.





Components of Modified Kramer System

- 1. Previous Experience (-1, 0, +1)**
- 2. Alternative Etiologic Candidate (-1, 0, +2)**
- 3. Timing (-2, 0, +1)**
- 4. Overdose (0, +1)**
- 5. Dechallenge (-1, 0, +1)**
- 6. Rechallenge (-1, 0, +1)**

Interpretation of Range



❖ -6 to -1

Remotely drug related

❖ 0 to +2

Possibly drug related

❖ +3 to +5

Probably drug related

❖ +6 to +7

Definitely drug related

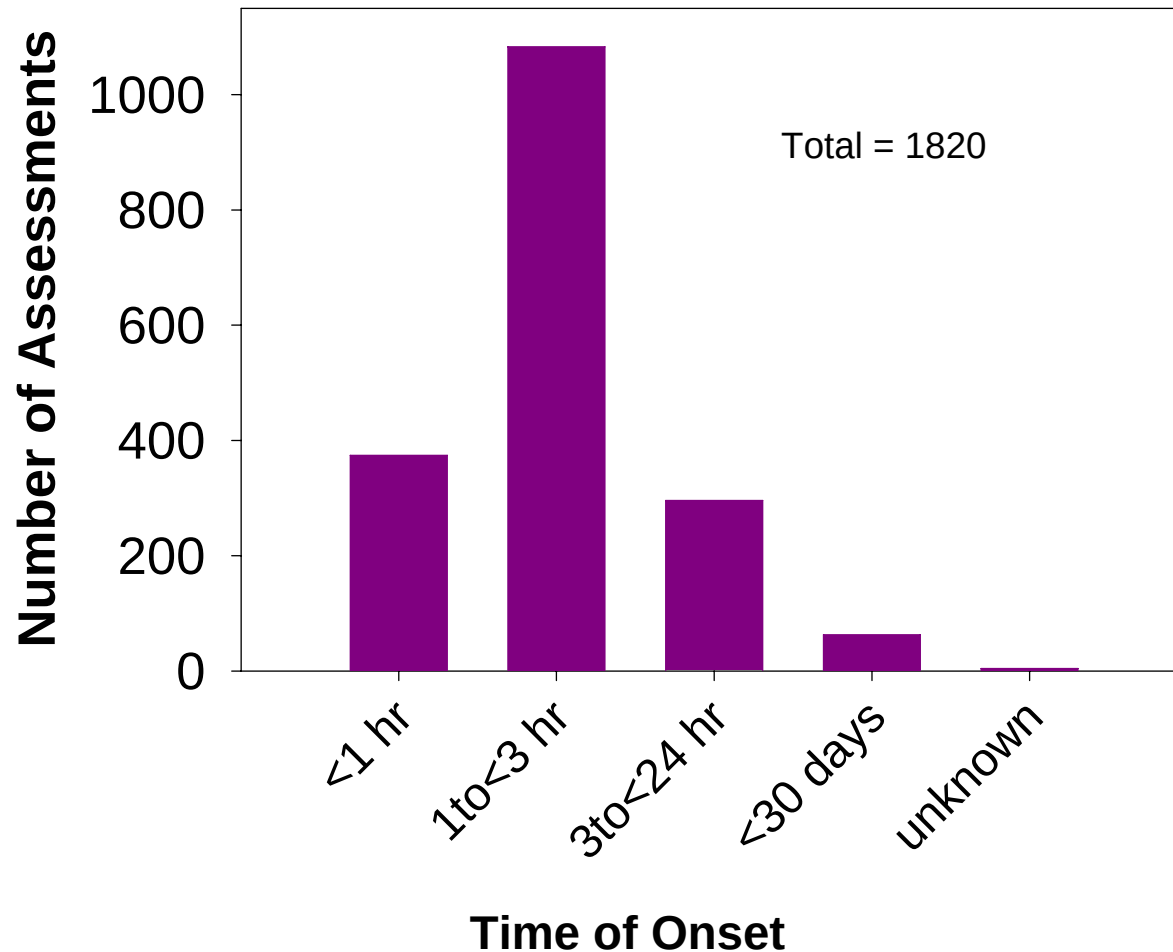
Number of Reported Dog Deaths

Heartworm Preventive	Year of Initial Approval	Number of Deaths, Approval to 9/1/04	Number of Deaths, 6/1/01 to 9/1/04
Ivermectin Products	1987	133	50
Milbemycin Products	1990	131	59
Selamectin	1999	171	110
Moxidectin Tablets (ProHeart)	1997	0	0
Subtotal			219
Moxidectin Sustained Release (ProHeart 6)	2001	485	485

Anaphylaxis / Anaphylactoid Reactions

Heartworm Preventive (year of initial approval)	Assessments Approval to 9/1/04
Ivermectin Products (1987)	16
Milbemycin Products (1990)	36
Selamectin (1999)	45
Moxidectin Tablets (Proheart)(1997)	0
Subtotal	97
Moxidectin Sustained Release (ProHeart 6) (2001)	1820

Onset Times of Anaphylaxis/ Anaphylactoid Reactions (ProHeart 6)



Health Status of Dogs with Anaphylaxis / Anaphylactoid Reactions at Time of ProHeart 6 Administration

■ GOOD	1,741
■ Fair	69
■ Poor	3
■ Unknown	7

Deaths: 54

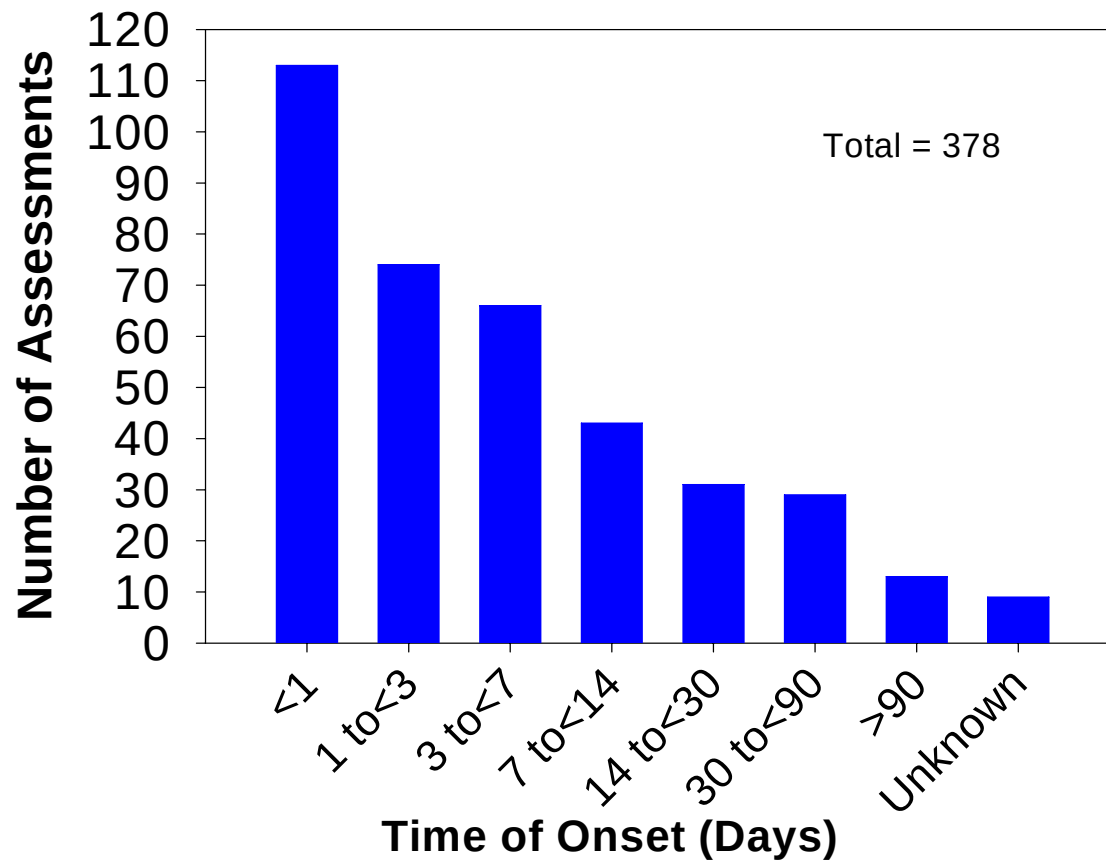
Concomitant Status of Dogs with Anaphylaxis/Anaphylactoid Reactions at Time of ProHeart 6 Administration

■ No concomitant	816
■ Concomitant	731
■ Unknown	273

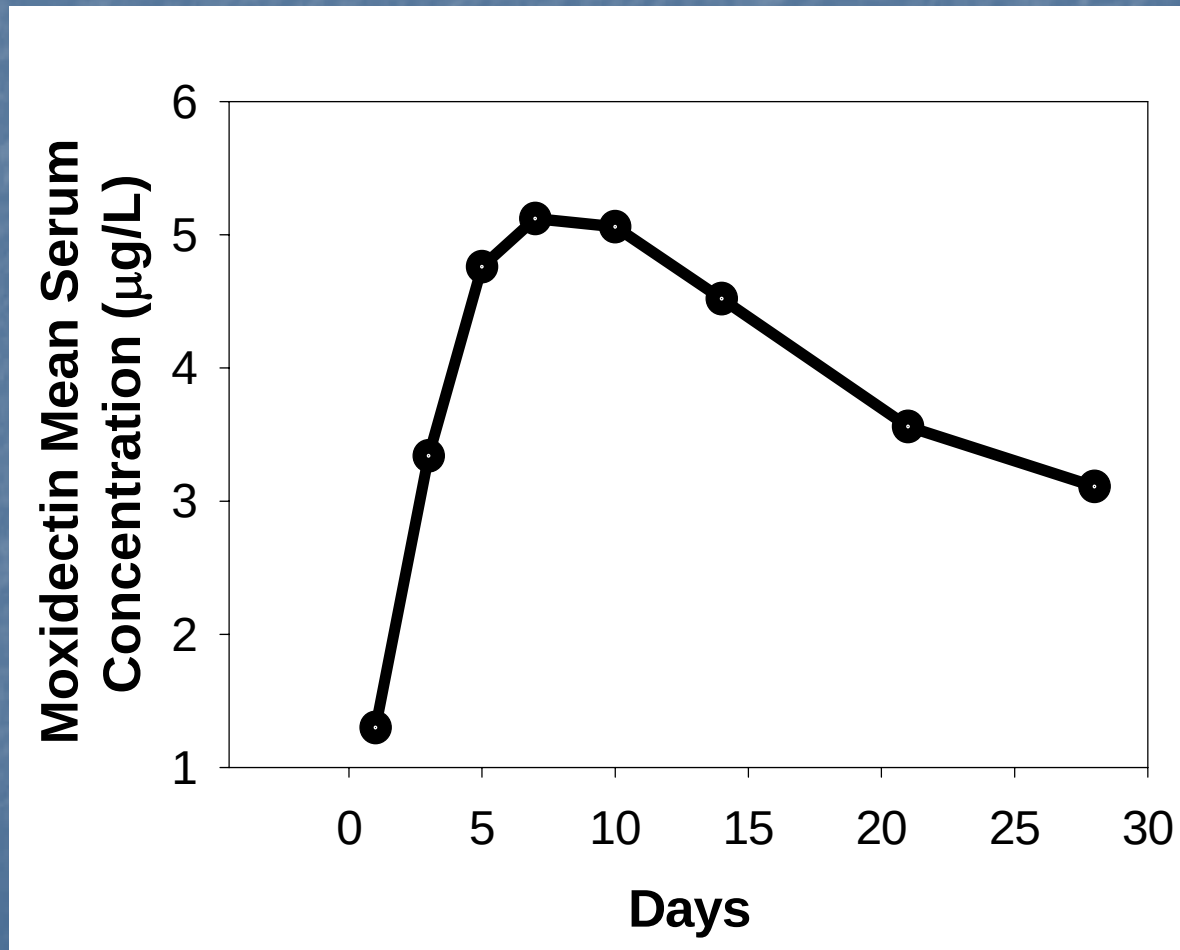
Convulsions

Heartworm Preventive (year of initial approval)	Assessments Approval to 9/1/04
Ivermectin Products (1987)	131
Milbemycin Products (1990)	194
Selamectin (1999)	304
Moxidectin Tablets (ProHeart)(1997)	1
Subtotal	630
Moxidectin Sustained Release (ProHeart 6) (2001)	378

Onset Times of Convulsions (ProHeart 6)



Mean Serum Moxidectin Levels Following a Single Injection



Health Status of Dogs with Convulsions Following ProHeart 6 Administration

■ GOOD	302
■ Fair	64
■ Poor	7
■ Unknown	5

Deaths: 61

Concomitant Status of Dogs with Convulsions Following ProHeart 6 Administration

■ No concomitant	87
■ Concomitant	215
■ Unknown	76

Liver Problem Assessments

Approval to 9/1/04

Heartworm Preventive (year of initial approval)	SGPT/ALT Elevations	Liver Lesions
Ivermectin Products (1987)	38	9
Milbemycin Products (1990)	38	8
Selamectin (1999)	69	13
Moxidectin Tablets (ProHeart) (1997)	0	0
Subtotal	145	30
Moxidectin Sustained Release (ProHeart 6)(2001)	192	65

Health Status at Time of ProHeart 6 Injection for Dogs with Subsequent SGPT/ALT Elevations or Liver Lesions

SGPT/ALT Elevations

■ GOOD	149
■ Fair	36
■ Poor	6
■ Unknown	1

Deaths: 38

Liver Lesions

■ GOOD	50
■ Fair	13
■ Unknown	2

Deaths: 47

Concomitant Status of Dogs with Elevated SGPT/ALT or Liver Lesions Following ProHeart 6 Administration

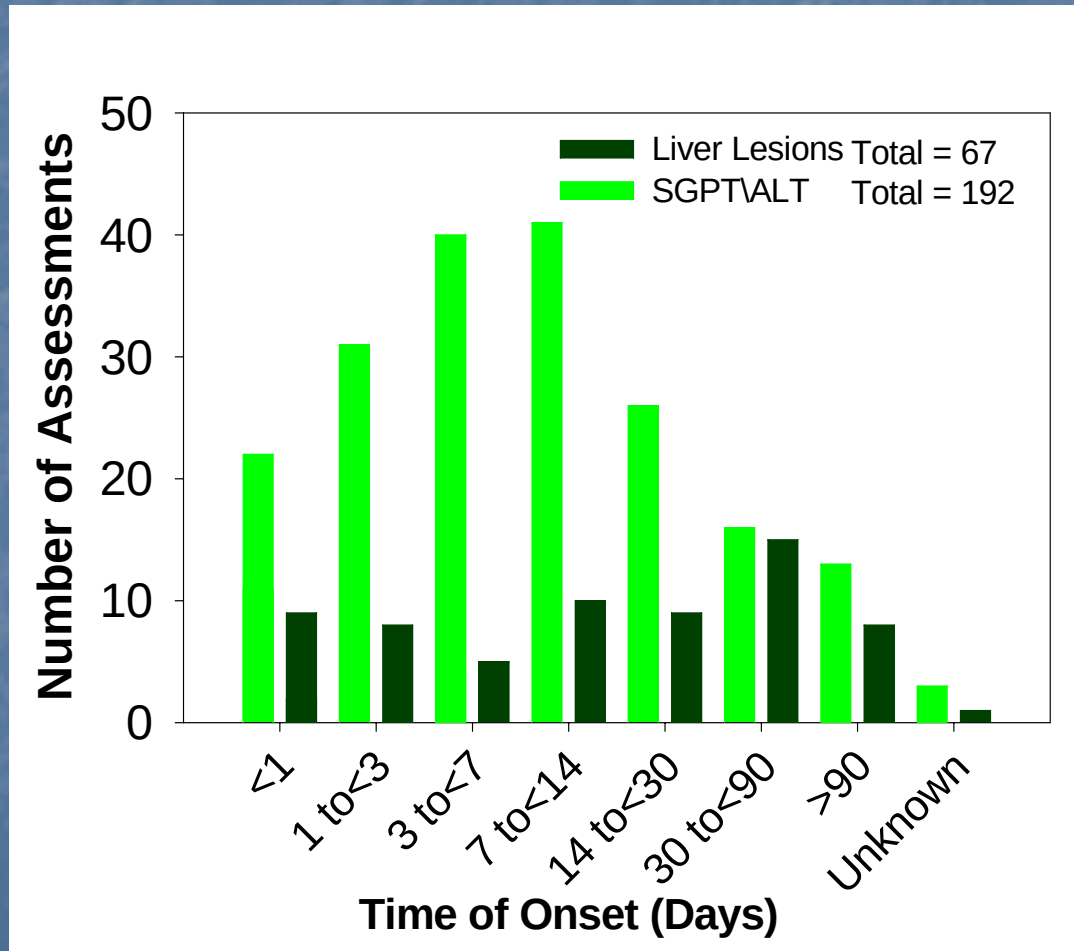
SGPT/ALT Elevation

- No concomitant 50
- Concomitant 112
- Unknown 30

Liver Lesions

- No concomitant 13
- Concomitant 44
- Unknown 8

Onset Times of Elevated SGPT/ALT and Liver Lesions (ProHeart 6)

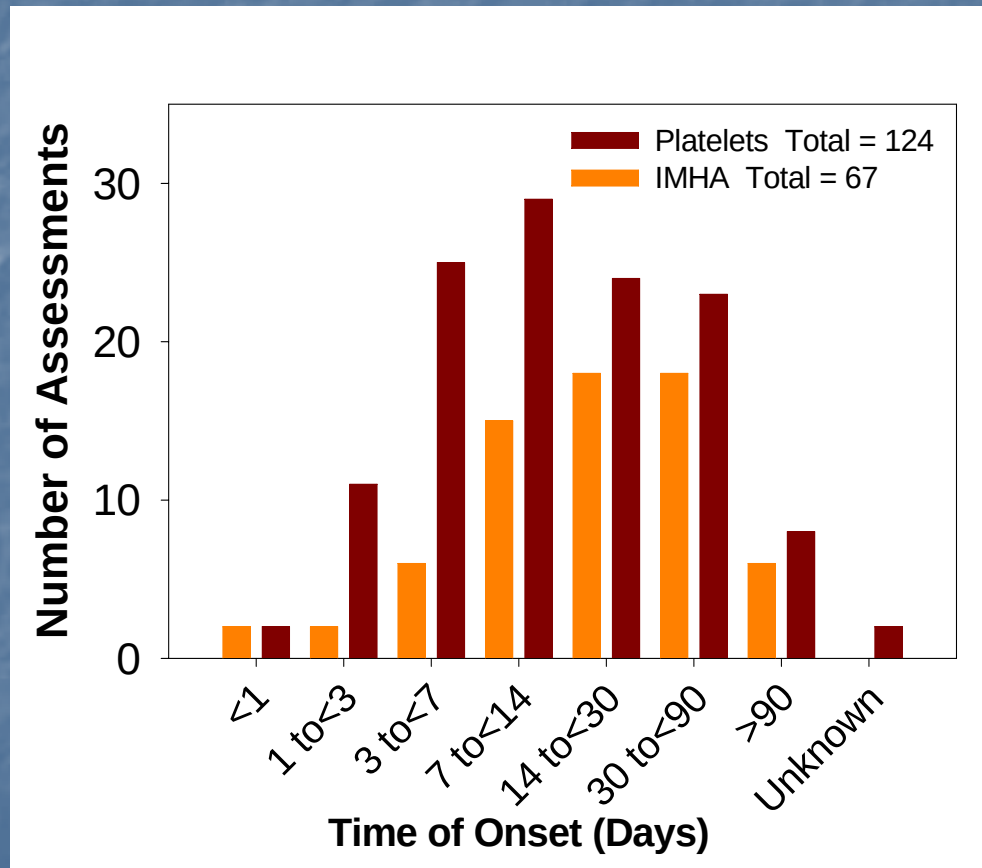


Hematologic Assessments

Approval to 9/1/04

Heartworm Preventive (year of initial approval)	Low Platelets	IMHA
Ivermectin Products (1987)	10	20
Milbemyacin Products (1990)	26	16
Selamectin (1999)	50	15
Moxidectin Tablets (Proheart) (1997)	0	0
Subtotal	86	51
Moxidectin Sustained Release (ProHeart 6) (2001)	124	67

Onset Times for Low Platelets and IMHA (ProHeart 6)



Health Status at Time of ProHeart 6 Injection for Dogs with Low Platelets or IMHA

LOW PLATELETS

■ GOOD	91
■ Fair	28
■ Poor	4
■ Unknown	1

Deaths: 45

IMHA

■ GOOD	56
■ Fair	10
■ Poor	1

Deaths: 34

Concomitant Status of Dogs with Low Platelets or IMHA Following ProHeart 6 Administration

LOW PLATELETS

■ No concomitant	26
■ Concomitant	76
■ Unknown	22

IMHA

■ No concomitant	19
■ Concomitant	34
■ Unknown	14



Number of ProHeart 6 ADE Reports Received by CVM, by Year (July 1, 2001 to June 30, 2004)

Period	Initial Reports	Follow Up Reports	Total Reports
7/1/01 to 6/30/02	1719	546	2265
7/1/02 to 6/30/03	1905	838	2743
7/1/03 to 6/30/04	1763	1076	2839

**Number of Dogs with Reported ADEs and
Number of Reported Dog Deaths
ProHeart 6, by Year
(July 1, 2001 to June 30, 2004)**

Period	Number of Dogs	Number of Deaths
7/1/01 to 6/30/02	1896	112
7/1/02 to 6/30/03	1814	148
7/1/03 to 6/30/04	1640	185

Number of Causality Assessments for Certain Reported Clinical Manifestations, ProHeart 6, by Year (July 1, 2001 to June 30, 2004)

Period	Anaphylactoid Reactions	Convulsion	SGPT/ALT Elevation	Liver Lesions	Low Platelets	IMHA
7/1/01 to 6/30/02	704	110	23	9	26	14
7/1/02 to 6/30/03	544	126	52	15	28	24
7/1/03 to 6/30/04	487	118	92	37	52	26

Reasons for Post-Marketing Surveillance

PRE-MARKETING

- Limited size
- Controlled population

POST-MARKETING

- Larger size
- More diverse population

Post-Approval Concerns for Drug Safety

- Frequency of events
- Severity of events
- Temporal association with administration
- Correlation with rising or peak serum levels
- Ongoing serious events despite regulatory measures

Additional Considerations

- ProHeart 6 is used with the intent of preventing disease
- Other alternatives exist
 - fewer reported serious adverse effects



Analysis of ProHeart 6 Adverse Events by Fort Dodge Animal Health

“Approximately 18 million doses of ProHeart 6 have been sold with more than 12 million doses administered”

-Fort Dodge Animal Health (page 31)

FDAH Allergy Event Reports per 10,000 doses sold (pages 37-38)

- ProHeart 6: 1.26
- Duramune Max 5/4L vaccine: 0.4
- Rabvac 3 vaccine: 0.5

Allergy event reporting rate for ProHeart 6 is 2.5 to 3.1 times higher than for Fort Dodge vaccines

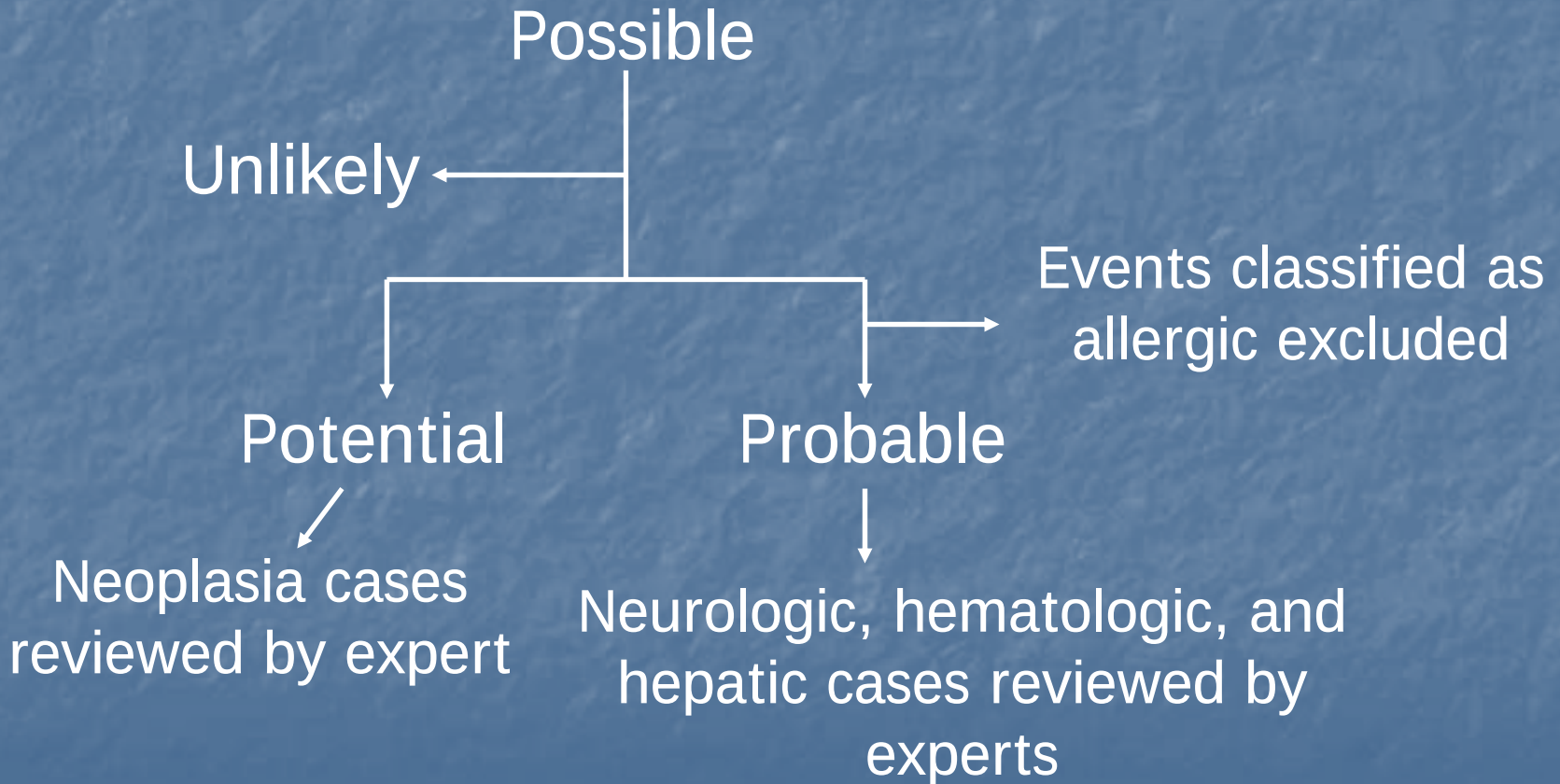
FDAH Non-Allergy Event Reports per 10,000 doses sold (pages 38-39)

■ ProHeart 6:	1.19
■ Duramune Max 5/4L vaccine:	0.3
■ Rabvac 3 vaccine:	0.35

Non-allergy event reporting rate for ProHeart 6
is 3.4 to 4.0 times higher than for Fort
Dodge vaccines

“The adverse event case fatality rate associated with ProHeart 6 reports is lower than many FDAH pharmaceuticals and similar to case fatality rates for the FDAH canine vaccine product lines including Duramune Max 5/4L. Thus the incidence of death does not appear to be causally related to ProHeart 6 usage.”

Fort Dodge's Causality Analysis of Medical Events by Selected Body Systems (page 39)



Analysis of Banfield Data

Limitations

- Selection bias
- Information bias

Table 4.4.2-1. Rate per 10,000 of Any Adverse Event by Treatment Category

Vaccine	ProHeart 6			HW Prev 1			HW Prev 2			No HW Treatment		
	N	N _A	Rate	N	N _A	Rate	N	N _A	Rate	N	N _A	Rate
Yes	483,064	6,292	130.3	246,131	2,804	113.9	11,975	120	100.2	1,489,032	17,406	116.9
No	252,590	2,253	89.2	164,951	1,469	89.1	6,430	45	70.0	4,144,984	120,529	290.8
Total	735,654	8,545	116.1	411,082	4,273	103.9	18,405	165	89.4	5,634,016	137,935	244.8

ProHeart[®] 6 (moxidectin)

January 2005

ProHeart 6 (moxidectin)

**Fort Dodge Animal Health
A Division of Wyeth**

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EXECUTIVE SUMMARY

Canine heartworm infection (*Dirofilaria immitis*) occurs in many parts of the world, including all 50 states in the US. Despite widespread availability of monthly heartworm preventatives, the infection rate in the US increased in the 1990s, and use of heartworm preventatives declined. Surveys have shown that compliance (i.e., reliable monthly treatments by owners) is problematical and a limiting factor in the control of heartworm in the dog population.

The active ingredient in ProHeart® 6 is moxidectin, a macrocyclic lactone. Moxidectin has been thoroughly evaluated to determine its toxicological and metabolic properties in multiple animal species and is approved as an anthelmintic agent for use in cattle, sheep, swine, dogs, and horses, in 70 countries. ProHeart 6 has been carefully evaluated for the treatment of heartworms and hookworms in dogs. In registration studies sponsored by Fort Dodge Animal Health (FDAH) (a Division of Wyeth), the product has been demonstrated to be safe and efficacious. Further, it appears to be well tolerated in canine breeds that do not tolerate some of the monthly products.

In June 2001, Proheart 6 (moxidectin) was approved and launched in the US by FDAH to prevent canine heartworm disease for 6 months, and to treat existing larval and adult stages of the canine hookworm. Since then, the product has also been registered in Italy, Canada, Japan, France, Greece, Portugal, Spain, and Korea. A similar product, ProHeart SR12, which contains approximately 3 times the amount of moxidectin as ProHeart 6, is registered and marketed in Australia since October 2000.

Among heartworm preventative medications for dogs, ProHeart 6 is an innovative product. Unlike conventional products that require monthly dosing for a minimum of 1 month prior to mosquito exposure through 1 month after mosquito exposure, in order to achieve protection against heartworm infection over a mosquito-infestation season, 1 injection of ProHeart 6 (moxidectin) sustained-release product provides 6 months of protection. ProHeart 6 was specifically developed to overcome field efficacy problems that result from poor compliance with monthly treatments. The introduction of ProHeart 6 provided an avenue for continuous protection against heartworm infection.

Shortly after launch of ProHeart 6, FDAH received a number of reports of allergic-type reactions after administration. The reactions ranged from mild and self-limiting to severe anaphylactoid reactions. Product analysis of minor component profiles between batches of ProHeart 6 revealed a trend to lower reactions for lots with no detectable residual solvents. At this time, FDAH was continuing to optimize the manufacturing process. As part of this process, the decision was made that all ProHeart products would be produced from moxidectin technical material with no detectable solvents. After the manufacturing change was implemented, there was a decline in the adverse-event reporting rate from all markets.

Since the launch of the product, FDA expressed concern about the number and seriousness of adverse event reports (AERs). The vast majority of the AERs were submitted by FDAH based on field reports from veterinarians and dog owners. The reports were submitted under mandatory reporting regulations without assessment of the likelihood of association of the AER with Proheart 6 administration. As a result of FDA's concern, FDAH has made revisions to the product label and issued "Dear Doctor" letters. On September 3, 2004, based on continued FDA concerns, FDAH agreed to voluntarily recall the product from the U.S. market. The recall prompted regulatory authorities in Canada, Australia, Japan and Europe to further review the safety of ProHeart 6. These authorities have allowed continued marketing of all FDAH moxidectin products for canine heartworm control.

FDAH's postmarketing surveillance and analysis of AERs from June 2001 through August 2004 show the number of these AERs were generally decreasing. The peak of AERs in the second quarter of each year corresponds to peak-use periods and also appear to be decreasing over time. Analysis of AERs for ProHeart 6 by category show that the occurrence of injection-site reports remained low and consistent with other injectable products in the FDAH database. Allergy AERs trended down over time at 1.26 per 10,000 doses. Non-allergy AERs were low and consistent over time at 1.19 per 10,000 doses (neurologic at 0.12 per 10,000 doses; hematologic at 0.09 per 10,000 doses; hepatic 0.07 per 10,000 doses; cardiac at 0.02 per 10,000 doses; neoplasia at 0.06 per 10,000 doses). When taken in context with usage, the overall rate for AERs was low and trending down over time, up to the point of the recall.

FDAH recently sponsored a study of the safety of ProHeart 6 use in general veterinary practice and a comparison to the monthly oral products. The study utilized a database covering 403 full-service veterinary hospitals in 42 states and did not rely on voluntary reporting. The review evaluated approximately 7 million canine office visits with an emphasis on comparison of heartworm product safety with and without concomitant vaccine administration. Overall, the safety profile of ProHeart was similar to that of 2 commonly used monthly oral products. Many of the adverse events could be attributed to concomitant vaccine administration. The results of the study provide no support for the withdrawal of ProHeart 6 from the market.

In conclusion, FDAH has performed additional research and further evaluation of the ProHeart 6 database to add to the extensive safety and toxicology database for moxidectin and formulated products. These evaluations provide additional support for the safety and efficacy of the product and were conducted to address questions raised by FDA.

1.0 INTRODUCTION

Moxidectin is a semi-synthetic methoxime derivative of nemadectin that is a fermentation product of *Streptomyces cyaneogriseus* subspecies *noncyanogenus*. It is a pentacyclic 16-membered lactone macrolide. Moxidectin is licensed and marketed worldwide by Fort Dodge Animal Health (FDAH) (a Division of Wyeth) as an anthelmintic agent that causes the paralysis and death of affected parasites in cattle, sheep, swine, horses, and dogs. It is currently being developed in a collaboration between Wyeth and the World Health Organization (WHO) for humans with onchocerciasis (river blindness), a disease caused by infection with the tissue filarial nematode *Onchocerca volvulus*.

ProHeart® 6 (moxidectin) was approved in the US and launched by FDAH in June 2001, to prevent canine heartworm (*Dirofilaria immitis*) disease for 6 months, and to treat existing larval and adult stages of the canine hookworms (*Ancylostoma caninum* and *Uncinaria stenocephala*). Since then, this product has also been registered in Italy, Canada, Japan, France, Greece, Portugal, Spain, and Korea. A similar product, ProHeart® SR 12, which contains approximately 3 times the amount of moxidectin as ProHeart 6 and provides 12 months of protection is registered and marketed in Australia since October 2000.

Among heartworm preventative medications for dogs, ProHeart 6 is an innovative product. Unlike conventional oral tablets or topical applications that require monthly dosing for a minimum of 1 month prior to mosquito exposure through 1 month after mosquito exposure, in order to achieve protection against heartworm infection over a mosquito-infestation season, 1 subcutaneous (SC) injection of ProHeart 6 (moxidectin) sustained-release product provides sustained 6-month protection. The single administration of ProHeart 6 for a 6-month period of protection eliminates the possibility of the pet owner missing 1 or more monthly doses, which is the primary cause of lack of efficacy associated with these heartworm medications.

ProHeart 6 has been well received by veterinary professionals and dog owners as evidenced by its increasing market share in major markets since launch. By the third quarter of 2004, ProHeart 6 was the number two product in the US with a 24% market share. In Italy, it is expected to

achieve a 35% share by the end of 2004. ProHeart SR 12 is the market leader in Australia, presently with a 47% share.

Subsequent to the product approval in June 2001, the FDA Center for Veterinary Medicine (CVM) raised concerns over the number of reports of adverse events associated with ProHeart 6.¹ Further concern was raised that “many of the reports received have involved serious, life-threatening adverse events such as anaphylaxis, convulsions, hematopoietic disorders, hepatopathies” and also “neurologic problems and unusual cardiac signs.” It was also stated that “Pet owners should be advised on appropriate alternative heartworm preventatives for their dogs.” FDA requested “that the firm continue to conduct research to determine the cause of related adverse reactions...before the product is marketed again.”

On September 3, 2004, FDAH announced that it was voluntarily ceasing production for the US market and recalling ProHeart 6 from the US market until resolution of FDA safety concerns, based on reports of adverse events. Despite the voluntary recall, FDAH maintains that ProHeart 6 is safe and efficacious with acceptable field performance. Regulatory authorities in Canada, Australia, Japan, and Europe have allowed continued marketing of the FDAH moxidectin products for heartworm. FDAH supports the FDA formation of an independent Advisory Panel to review safety data on ProHeart 6. In order to provide the Advisory Panel with extensive analyses of available scientific data on ProHeart 6, FDAH sought assistance from independent experts. As requested by the FDA, additional research has been conducted to better define the adverse reactions. FDAH anticipates that comprehensive review of available ProHeart 6 data by the Advisory Panel will satisfactorily resolve FDA safety concerns.

Careful evaluation of the nature and timing of the AERs identified that allergy-based signs could be attributed to treatment and occurred shortly after treatment. The true incidence of allergic events to ProHeart6 is confounded because many dogs receive concurrent vaccinations. These are recognized to trigger allergic manifestations. A range of commonly occurring disease conditions that affect dogs is also seen in the AERs. These appear to represent baseline occurrence of these conditions in the canine population.

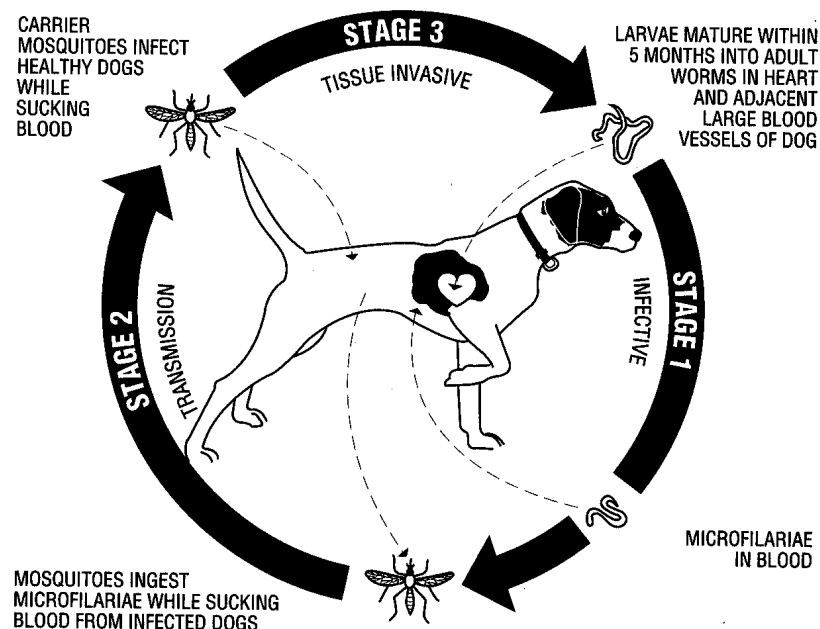
The purpose of this document is to present an overview of moxidectin and ProHeart 6 information from non-clinical studies, clinical trials, adverse event reporting, and analysis of safety and efficacy data for review by the Advisory Panel. This information includes new data on pharmacokinetics, new pharmacological investigations, new evaluation of adverse event findings, and epidemiological information from 7.0 million canine visits to veterinary clinics. FDAH is confident that the new research and re-evaluation of previous data support the safety and efficacy of ProHeart 6 and looks forward to returning this product to the market.

2.0 REVIEW OF HEARTWORM IN DOGS

2.1 Life Cycle of Dog Heartworm (*Dirofilaria immitis*)

The life cycle of the dog heartworm can be described in 3 stages as shown.

Figure 2.1-1. Life Cycle of Dog Heartworm



Stage 1: Adult female worms release tiny immature heartworms called microfilariae into the bloodstream of the infected dog. Adult worms are reported to live for 2 to 7 years.

Stage 2: The infection is spread from dog to dog by mosquitoes. When a mosquito bites an infected dog and feeds on blood, it takes in some of these microfilariae. Within 2 to 3 weeks, these microfilariae will develop into a stage which can infect other dogs when they are bitten by the same mosquito as it feeds.^{2,3}

Stage 3: Following infection, the immature stages grow and develop over 2 to 3 months in the subcutaneous (SC) tissues, muscle, and fatty tissues of the dog. They then migrate, and from 70 to 120 days post infection, stages of heartworm may be found in the heart or pulmonary artery. These develop into adult heartworms which are long slender roundworms, normally living in the right side of the heart and nearby blood vessels. The worms may be up to 35 cm in length when mature.^{2,3}

Mature female *Dirofilaria immitis* begin releasing microfilariae into the blood stream some 6 to 7 months after infection, thus completing the lifecycle.

Heartworm preventative products exert their effect at Stage 3, the tissue migrating stage.

Heartworm tests rely on detection of the parasite either at Stage 2, by detection of circulating microfilariae, or at Stage 3, by detection of female heartworm antigen. Heartworm antigen tests are not positive until the infection is at least 5 months old, they are inconsistently positive at 5 to 7 months, and are not considered to be reliably diagnostic until the infection (with female worms present) is at least 8 months old. These tests are highly sensitive and specific. If clinical signs raise any doubt about the accuracy of the particular test result, the test should be repeated, preferably with a different test kit or laboratory.⁴

2.2 Heartworm Disease in Dogs

Many dogs may be infected for several months with *Dirofilaria immitis* without showing clinical signs. This is particularly true for inactive dogs. However, immature worms in the pulmonary artery can initiate disease as early as 3 months after infection.⁵ Adult worms in the heart cause inflammation of the heart lining and valves, and can eventually lead to heart failure. The effect on blood flow can lead to problems in other organs, particularly lungs and kidneys.

It can be difficult to know that a dog is affected in all stages of the disease because symptoms may be slight. The dog may only be listless and tire easily. Performance in working dogs may be affected. As the disease progresses, there may be cough, loss of condition, and build-up of fluid in the abdomen. Severely affected dogs may die.

Treatment of the disease can be risky, and early detection before chronic damage occurs to heart and lungs is important. This is because thromboembolic complications may occur, particularly in heavily infected dogs with pulmonary arterial vascular obstruction, and especially if congestive heart failure is present. The approved adulticide treatment is melarsomine, trade name Immiticide, an arsenical compound. While melarsomine is less toxic and more effective than its predecessor, thiacetarsamide, it is administered as a deep intramuscular injection into the lumbar muscles to reduce swelling and soreness at the injection site. Pulmonary thromboembolism and/or shock may occur following adulticide treatment even in symptomless dogs. Exercise restriction during the recovery period (weeks) is essential to minimize cardiopulmonary complications. Off label use of ivermectin for this purpose has been reported, but is not recommended because of progression of heartworm disease in the treated dogs.⁶

2.3 Canine Heartworm Epidemiology in the US

Heartworm infection in dogs has been diagnosed in many parts of the world, including all 50 states of the United States. While heartworm is considered endemic in the 48 contiguous states and Hawaii, transmission has not been documented in Alaska, even though there has been importation of infected dogs. It is likely that the climate is not conducive to the maturation of infective larvae. Adequate temperature and humidity are required both to support a suitable mosquito population and also to provide sufficient heat for maturation to the infective larval stage (L₃). Laboratory studies indicate that at 80°F, 10 to 14 days are required for maturation to infective stage, this period is longer at lower temperatures or where significant diurnal temperature fluctuation occurs.^{2,3}

Therefore, the length of the heartworm transmission season varies with geographical location and climatic factors. The peak months for heartworm transmission in the northern hemisphere are July and August. Estimates of the duration of the transmission season vary from less than 4 months in Southern Canada to essentially all year in sub-tropical areas such as Florida and the Gulf Coast. It is believed that transmission occurs for 6 months or less above the 37th parallel.

The prevalence of heartworm in dogs varies from state to state, with higher infection rates in southern states, and particularly higher along the Mississippi and Ohio rivers. The number of adult heartworms present in infected dogs has been reported to be lower in the North (Michigan) than in the South.⁷ A survey undertaken by the American Heartworm Society in 2001, published

in 2002, reported the highest infection rates in Texas, followed by Florida, Louisiana, North Carolina, Georgia, Mississippi, Tennessee, South Carolina, Alabama, and Indiana. Of significant veterinary concern, the survey reported that despite the widespread availability of monthly heartworm preventatives, the rates of infection with heartworm had not decreased over the previous 10 years.^{2,8,9} For further information see Section 4.5.

For the past 2 decades, heartworm prevention relied on monthly administration of macrocyclic lactones, sometimes in combination with other active ingredients to treat other parasites. Commonly used products include ivermectin, milbemycin oxime, and selamectin. Combination products include ivermectin plus pyrantel (for roundworm control) and generics, and milbemycin oxime plus lufenuron (for flea control). For dogs that suffered toxic effects from these compounds, the only alternative available was daily treatment with diethyl carbamazine.

The introduction of ProHeart 6 in the US in the second half of 2001 provided 6 months of continuous protection against heartworm infection without having to rely on monthly treatment by the dogs' owners, a major source of lack of efficacy.

3.0 MOXIDECTIN OVERVIEW

3.1 Pharmacology – Mechanism of Action

Moxidectin has been shown to have activity at the γ -aminobutyric acid (GABA)-A receptor-chloride channel complex resulting in an influx of chloride ions and hyperpolarization of cell membranes. Hyperpolarization causes the nerve fibers to be less excitatory and results in paralysis and death of the parasitic organism. Another proposed mechanism of action for moxidectin is through activity at glutamate-gated chloride ion channels. The specificity of moxidectin for the parasite versus the mammalian host results from 1) a low affinity for mammalian GABA-gated chloride channels, and 2) GABA-containing neurons and receptors are found in mammals in the central nervous system, whereas in arthropods and nematodes these are found in the neuromuscular junctions of the peripheral nervous system and thus are more accessible to a blood-borne therapeutic.

In dogs, the approved oral monthly dosage of moxidectin for prevention of heartworm is 3 µg/kg; the approved SC dosage of moxidectin as ProHeart 6 is 0.17 mg/kg administered every 6 months. In this and the sections that follow, dosages of ProHeart 6 or moxidectin expressed as mg/kg refer to mg of moxidectin per kg of animal body weight.

3.2 Pharmacokinetics and Drug Metabolism

Studies were conducted in various animal species to characterize the absorption, distribution, metabolism, and excretion of moxidectin after oral administration. Moxidectin was moderately absorbed with a bioavailability of 19% in rats, and had a long serum half-life of 23 to 45 hours in rats and 8.1 days in dogs after oral gavage administration. A single SC injection of the approved dosage of 0.17 mg/kg as ProHeart 6 to beagle dogs resulted in peak concentration in serum ($C_{\max}$) of 5.1 ng/mL, a time to peak concentration ($t_{\max}$) of 7 to 10 days, an area under the concentration-versus-time curve ($AUC_{0-\infty}$) of 217 ng•days/mL, and an apparent elimination half-life ($t_{1/2}$) of approximately 35 days. After SC injection of ProHeart 6 once every six months for a total of 6 injections, there was no evidence of alterations in pharmacokinetic parameters or indication of accumulation. A recent study of the single administration of moxidectin in the diet to female dogs at 45 ppm (corresponding to approximately 1 mg/kg used in the 1-year toxicology study) resulted in a $C_{\max}$, $AUC_{0-\infty}$, and $t_{1/2}$ values of 290 ng/mL, 678 ng•day/mL and 8.3 days, respectively. These recent studies in the dog, and an ongoing 28-day pharmacokinetic study in rats were designed to further evaluate the systemic exposure to moxidectin under the conditions of the previously conducted toxicology studies.

After oral administration, the major site of moxidectin distribution was in fat in rats, cattle, sheep, and horses. It was eliminated largely unmetabolized in the feces. The $t_{1/2}$ in fat in the rat was 11.5 days, much longer than in serum. Limited metabolism was noted in all species and minor metabolites were identified as predominantly mono- and di-hydroxylated moxidectin.

Moxidectin did not result in significant in vitro inhibition of cytochrome P450 isozymes, indicating that drug-drug interactions mediated through cytochrome P450 are unlikely to occur.

P-glycoproteins (P-gps) are transmembrane proteins that transport a wide variety of endogenous and exogenous molecules across cell membranes. Moxidectin, similar to other macrocyclic lactones, is a substrate for P-gps. This relationship is of clinical importance in the development of nematode resistance to ivermectin and plays a significant role in breed sensitivity. A mutation in the P-gp gene of ivermectin-sensitive Collie dogs has been shown to be responsible for ivermectin-induced CNS toxicity. Moxidectin, however, was well-tolerated by these ivermectin-sensitive dogs (see Section 4.1.3.2). Thus, moxidectin transport is less dependent on P-gp and subsequent toxicity is less likely manifest due to factors which alter P-gp activity.¹⁰

3.3 Toxicology

The toxicologic profile of moxidectin administered by the oral route has been well established. This profile is relevant to other routes of administration because of limited metabolism of moxidectin in the body and the long terminal half-life regardless of the route of administration. A more detailed discussion of the pharmacokinetics and toxicity assessment of moxidectin is presented in Appendix 6.1.

3.3.1 In Vitro Side-Effect Profiling

Moxidectin and moxidectin microspheres (as present in ProHeart 6) were recently tested in vitro for binding activity at 64 different biological receptors. This assay is commonly used in drug discovery and development to identify any ancillary pharmacologic activities of a molecule which may result in undesirable biological effects. A final concentration of 10 ng/mL moxidectin was tested, which is approximately two-fold the average C_{max} value in serum of dogs after an SC injection of ProHeart 6 at the clinical dosage of 0.17 mg/kg. The receptors tested included those for neurotransmitters and neurotransmitter-related receptors, ion channels, steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes. Moxidectin in either form did not significantly inhibit the binding of appropriate

radioligands to these receptors, indicating a lack of significant, competitive binding activity for moxidectin at the concentration evaluated.. These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels greater than those required for efficacy.

3.3.2 Single- and Repeat-Dose Toxicology Studies

Single-dose toxicology studies of moxidectin were conducted to assess effects after a single administration of large doses in the event of accidental overdose and to assist in selection of dose levels for subsequent repeat-dose toxicology studies. In single-dose toxicity studies of mice and rats given moxidectin orally, the median lethal dosage (LD₅₀) values were 118 mg/kg and 42 to 78 mg/kg in male and female mice, respectively, and 122 and 97 mg/kg in male and female rats, respectively. After a single SC dose, LD₅₀ values were 285 and 247 mg/kg in male and female mice, respectively, and > 640 mg/kg in rats. Common clinical signs in these studies were decreased activity, tremors, and prostration. These studies demonstrate a large margin of safety for ProHeart 6 since the lethal SC dose in rats is more than 3700-fold the approved ProHeart 6 dose of 0.17 mg/kg.

Repeat-dose oral (diet) toxicity was evaluated to assess long-term consequences of repeated, daily oral exposure to moxidectin. The objective of these studies was to expose animals to high levels of moxidectin to identify potential toxic effects, and to include lower doses to assess a possible dose-response relationship and a dose without significant adverse effects (NOAEL).

The following studies were conducted: 4-week studies in mice, rats, and dogs; 13-week studies in rats and dogs; and a 1-year study in dogs. Evaluations consisted of mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry (except mice), organ weights, and macroscopic and microscopic examinations of organs and tissues. Ophthalmic examinations and urinalysis were also included in the dog studies.

In repeat-dose diet toxicity studies in rats and dogs of durations up to 2 years in mice and rats, and 1-year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects to any organ system. There were no proliferative lesions identified in any tissue which may signal the development of neoplasia, and no increase in tumors in 2-year studies in mice or rats. The toxicity of moxidectin manifested at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-receptor. Interim analysis at day 21 in an ongoing 28-day diet pharmacokinetic study of moxidectin in dogs at a concentration of 45 ppm in feed (approximately 1 mg/kg, the NOAEL in the 1-year dog toxicity study) revealed a serum concentration of 278.5 ng/mL 24 hours after the preceding dose in feed (ie, trough level). This value is approximately 234-fold the AUC_{0-∞} (217 ng•days/mL) observed for moxidectin after a single SC dose in dogs of ProHeart 6.

3.3.3 Carcinogenicity Studies

3.3.3.1 Mice

A 2-year carcinogenicity study was conducted in male and female mice at diet doses of 15, 30, and 60 ppm (lowered to 50 ppm due to high mortality at week 9). Mortality was increased in females at doses of 60/50 ppm during the last 13 weeks of the study. There were no compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

3.3.3.2 Rats

A 2-year carcinogenicity study was conducted in male and female rats at diet doses of 15, 60 and 120 ppm (lowered to 100 ppm due to high mortality in females at week 8). There were no compound-related findings for hematology values, organ weights or at macroscopic or microscopic examination; there was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

3.3.4 Reproductive and Developmental Toxicity Studies

Reproductive toxicity was evaluated in a rat multigeneration diet study and in developmental studies in rats and rabbits dosed daily by oral gavage. Based on the results from these studies, moxidectin was not found to be a selective reproductive toxin in rats, nor a teratogen in rats or rabbits.

3.3.5 Genotoxicity Studies

Moxidectin was tested for genotoxicity in 4 in vitro and 2 in vivo standard test systems. These assays assessed the ability of moxidectin to induce gene mutations, chromosome damage, or increased DNA repair which may be related to the carcinogenic potential of the test article. Moxidectin was uniformly negative in these assays, indicating that moxidectin is not a genotoxic compound.

3.4 Experience with Oral Moxidectin in Human Volunteers

A study in healthy, male volunteers was conducted to assess the pharmacokinetics and safety of moxidectin given orally as part of the development of this compound for onchocerciasis therapy in humans. Safety assessments indicated that moxidectin was safe and well tolerated, with a slightly higher incidence of transient, mild, and moderate CNS adverse events (dizziness and somnolence) as compared to placebo. Moxidectin was safe and well tolerated in humans after single oral doses of 3 mg to 36 mg, the highest dose evaluated.

3.5 Conclusions

Moxidectin is a potent antiparasitic therapeutic that acts to paralyze susceptible organisms through activity at GABA- and glutamate-gated chloride ion channels. Moxidectin has a long half-life, distributes predominantly to fat, shows little metabolism, and is excreted primarily in the feces. In single-dose toxicity studies, the lethal SC dose in rats was more than 3700-fold the efficacious dose of moxidectin given as ProHeart 6 to dogs. In repeat-dose diet toxicity studies of durations up to 2 years in mice and rats, and 1 year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects on any organ system. There were no proliferative lesions identified in any tissue which may signal the

development of neoplasia, and no increase in tumors in mice or rats. The toxicity of moxidectin manifested itself at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-A-receptor. Moxidectin was not genotoxic or carcinogenic and was without reproductive or developmental toxicity. The highest dosage evaluated in the 1-year dog study resulted in an estimated monthly exposure 234-fold the exposure observed after a single SC dose in dogs of ProHeart 6. Based on the toxicology studies of moxidectin where the dose, dosing duration, and resulting systemic exposure to moxidectin were significantly exaggerated, clinical SC administration of 0.17 mg/kg as ProHeart 6 to dogs is expected to be without significant adverse effects.

4.0 PROHEART 6 OVERVIEW

4.1 Clinical Trials with ProHeart 6 in Dogs

ProHeart 6 (moxidectin) is indicated for use in dogs ≥ 6 months of age for the prevention of heartworm disease caused by *Dirofilaria immitis* and for existing larval and adult hookworm infections (*Ancylostoma caninum* and *Uncinaria stenocephala*). The safety and efficacy of ProHeart 6 was demonstrated during a development program that was established in close collaboration with the FDA that included agreement on study requirements, protocol review, in-life inspections of selected development studies and a thorough review of data obtained during the program. Moxidectin is well established as an anti-parasitic product for cattle, sheep, horses, and dogs and is generally recognized as safe for these uses in all animals. The efficacy profile of ProHeart 6 was demonstrated in a series of dose-determination and dose-confirmation studies conducted in accordance with Good Clinical Practice guidelines. The safety of the product was evaluated through a series of safety studies in the target population as well as unique canine populations that would receive the product. These included reproducing males and females, dogs that had existing heartworm infections, and Collie dogs that had a demonstrated sensitivity to ivermectin. Safety and efficacy studies were conducted not only in laboratory Beagles but also in a variety of breeds and cross-breeds. In the sections that follow, dosages of ProHeart 6 expressed as mg/kg refer to mg of moxidectin per kg of animal bodyweight.

4.1.1 Heartworm

4.1.1.1 Dose Determination

Two (2) studies were conducted to determine the dosage of a single injection of ProHeart 6 required to effectively prevent *Dirofilaria immitis* infections for 6 months. Both studies had a similar experimental design. Study animals determined to be negative for *D. immitis* by antigen and a modified Knott's test were included in the studies. One study (0899-C-US-1-96, Georgia) utilized Beagle dogs (12 males and 20 females) and a second study (0899-C-US-2-96, Pennsylvania) utilized mongrel dogs (16 males and 16 females).^{11,12} ProHeart 6 was administered as a single SC injection to dogs at a moxidectin dosage of 0.06, 0.17, or 0.50 mg/kg. Control animals received saline. At approximately 180 days (6 months) after treatment, all dogs were inoculated by intravenous (IV) injection with 50 *D. immitis* L₃ infective larvae. Infections were allowed to develop for 150 days, at which time each animal was euthanized, necropsied, and the heart and lungs removed for the recovery and quantification of heartworms. Immediately after treatment with ProHeart 6 and at various times throughout the studies, dogs were observed for adverse reaction to treatment. Additionally, injection sites were evaluated after treatment and throughout the study as well as histologically at necropsy.

In the Georgia study, an average of 25 worms were recovered in the saline treated controls. No worms were recovered from any of the dogs dosed with ProHeart 6, indicating that all dosages tested were 100% effective in preventing heartworm disease for 6 months.

In the Pennsylvania study, an average of 36 worms were recovered from the saline treated controls. No worms were recovered from any dog that received ProHeart 6 at 0.17 and 0.50 mg/kg. However, 14 adult *D. immitis* worms were found in 1 dog in the low-dose group (0.06 mg/kg). The results of this study indicated that a ProHeart 6 dosage of 0.17 mg/kg was appropriate to prevent canine heartworm disease for a period of 6 months.

During the dose determination studies, moxidectin concentrations were quantified in the serum of treated dogs. Following injection with ProHeart 6, peak moxidectin levels (approx. 5 ppb) were observed at 7 to 14 days post-treatment. At the end of the 6-month treatment period, residual moxidectin concentrations were negligible and generally below the limit of quantification of the assay methods. The drug did not accumulate with repeated doses. Serum

moxidectin levels evaluated after 4 treatments (6 months apart) confirmed that there was no accumulation of moxidectin in the serum of animals after successive doses (0899-C-US-9-98, Texas).¹³

4.1.1.2 Dose Confirmation

4.1.1.2.1 Adult Dogs

The efficacy of ProHeart 6 for the prevention of heartworm disease in dogs was confirmed in a series of studies conducted using the proposed commercial ProHeart 6 dosage of 0.17 mg/kg. Efficacy was evaluated at 6 months post-infection, 12 months post-infection and in dogs with existing heartworm infections to determine retroactive efficacy. The 6- and 12-month infection studies used similar experimental designs as the dose-determination studies. Animals were treated and challenged with L₃ infective larvae at either 6 or 12 months after treatment and necropsied for quantification of adult heartworms after the infections had matured. For activity against existing infections (retroactive efficacy), animals were challenged with L₃ infective larvae at various times prior to treatment with ProHeart 6 and necropsied after an appropriate period for the development of microfilariae to become adult heartworms.

ProHeart 6, administered to dogs at an SC dosage of 0.17 mg/kg, was 100% effective for prevention of heartworm disease for 6 or 12 months (0899-C-US-10-98, Texas).¹⁴ When administered to dogs at an SC dosage of 0.17 or 0.27 mg/kg (0899-C-US-20-99, Pennsylvania), ProHeart 6 was 100% effective against development of canine heartworm disease for 12 months after treatment.¹⁵

The retroactive efficacy of ProHeart 6 with existing heartworm infections was evaluated at 4 and 6 months after challenge with L₃ infective larvae (0899-C-US-11-98, Georgia, Table 4.1.1.2.1-1).¹⁶ At 0.17 mg/kg, ProHeart 6 was highly effective against 4-month-old *D. immitis* infections (85.9%). Efficacy was even higher (97.2%) against 4-month-old infections, when a second injection was given 6 months after the first injection; *D. immitis* was found in only 1 of 5 animals in this group. A single injection had low efficacy against 6-month-old infections (24.7%). Efficacy was not improved with 3 additional treatments 6 months apart. In a second retroactive study (0899-C-US-28-01, Georgia, Table 4.1.1.2.1-2), ProHeart 6 at 0.17 or 0.50 mg/kg was highly effective against 3-month-old infections (98.8 and 96.0% efficacy, respectively).¹⁷

Table 4.1.1.2.1-1. Retroactive Activity of ProHeart 6 at 0.17 mg/kg versus 4- and 6-Month Heartworm Infections

Treatment (Time Post-Infection in Months)		Geometric Mean Worm Counts (Percent Efficacy)		
Saline	Moxidectin	Male	Female	Total
4 and 6		14.07	17.31	31.66
	4	1.24* (91.2)	3.42* (80.3)	4.46* (85.9)
	6	12.09 (14.1)	11.61 (32.9)	23.85 (24.7)
4, 6, 10, 12, and 18		8.97	7.86	15.24
	4 and	0.32* (96.4)	0.25* (96.9)	0.43* (97.2)

*Statistically significantly different ($p < 0.05$) from control group based on analysis of geometric means.

Table 4.1.1.2.1-2. Retroactive Activity of ProHeart 6 versus 3-month Heartworm Infections

Treatment (mg/kg)	Geometric Mean Worm Counts (Percent Efficacy)		
	Male	Female	Total
Saline	16.0	22.0	38.3
0.17	0.3 (98.4)	0.3 (98.8)	0.4 (98.8)
0.50	0.6 (96.3)	1.1 (95.1)	1.5 (96.0)

Evaluation of efficacy was for male dogs only, where adequate infection was observed in control animals.

4.1.1.2.2 Puppies

When administered to 12-week-old small, medium and large breed puppies at 0.17 mg/kg (0899-C-US-30-02, Pennsylvania), ProHeart 6 reduced heartworm infection >99.8% compared with control puppies.¹⁸ Treatment completely prevented heartworm infection in small and

medium breed puppies. One of six large breed puppies was infected with a single worm following challenge with 50 L₃ *D. immitis* infective larvae.

4.1.2 Hookworms

Efficacy was determined to be 100% for both larval and adult stages of *A. caninum* in three dose confirmation studies (0899-C-US-12-98, North Carolina; 0899-C-US-15-99, Georgia; 0899-C-US-16-99, Michigan).^{19,20,21} Efficacy against both larval and adult *U. stenocephala* infections was 100% in study 0899-C-US-16-99.

Three (3) additional experimental infection studies were conducted to demonstrate the effectiveness of ProHeart 6 versus larval and adult stages of the hookworm *U. stenocephala*. Studies 0899-C-US-17-99 (Michigan), 0899-C-US-18-99 (New Jersey), and 0899-C-US-19-99 (Georgia) provided additional data that confirmed the efficacy of the product as >99.0%.^{22,23,24}

Two studies were conducted to evaluate the persistent activity of ProHeart 12 against subsequent hookworm infections in dogs following treatment. In this program, animals were challenged with larvae of *U. stenocephala* and *A. caninum*. ProHeart 12 prevented infections of these 2 species of hookworm for a period of 4 months in a study in Georgia. In a study conducted in Michigan, ProHeart 12 prevented infection by *U. stenocephala* for a period of 8 months and *A. caninum* for 5 months.

4.1.3 Safety

4.1.3.1 Healthy Dogs

The clinical and possible pathological effects were evaluated when ProHeart 6 was administered to healthy dogs at either 1, 3 or 5 times the recommended dosage of 0.17 mg/kg in Study 0899-C-US-4-98 (Wisconsin).²⁵ Physical examinations were conducted prior to treatment and throughout the study. Blood and urine samples were collected for hematology, clinical chemistry, coagulation, and urinalysis. Dogs were also evaluated for clinical signs, food consumption, and body weight. At the end of the study, dogs were necropsied and evaluated for overt changes. Tissues from the control (saline treated) and 5-times dosage groups were examined microscopically. Dogs treated with ProHeart 6 did not demonstrate any signs or findings associated with the possible systemic toxicity of the drug. A single SC injection of

Proheart 6 equivalent to either 1, 3, or 5 times the commercial dosage caused swelling/slight edema at the site of injections starting within 8 hours of injection and lasting for up to 3 weeks. One dog, that received the 5-times dosage of ProHeart 6, displayed excessive salivation after treatment on Day 78. The only overt lesion observed was a 2.0 cm red focus at the SC injection site in 1 male at the 5-times dosage.

The safety of multiple injections of ProHeart 6 was studied in dogs given injections at 6 monthly intervals (0899-C-US-9-98, Texas) through 2 years.¹³ No adverse reactions to treatment were observed following 5 injections. The injection sites were palpated externally, then the skin and underlying muscle tissue excised and examined. There were no gross findings at the injection sites. Microscopically, the injected areas generally had granulomatous panniculitis with microvacuolation (spheres) that was interpreted to be a reaction to the injected microspheres. Three (3) of the experimental dogs were maintained and received a total of 14 ProHeart 6 injections. At necropsy, there were no adverse reactions attributed to test article during this time, including no gross findings in the injection sites at necropsy.

The safety of ProHeart 6 was demonstrated in reproducing females (0899-C-US-3-98, Michigan) and males (0899-C-CN-1-98, Canada) at 3 times the recommended commercial dosage (0.5 mg/kg).^{26,27} No adverse effects were observed in reproductive parameters of treated breeding females or the seminal quality of treated males.

When administered to healthy 10-week-old puppies at 3 or 5 times the recommended dosage rate of 0.17 mg/kg (0899-C-US-37-02, Michigan), ProHeart 6 caused no physical or neurological changes, and no changes in clinical chemistry or urinalysis parameters.²⁸

4.1.3.2 Ivermectin-Sensitive Collie Dogs

Some genetic lines of Collie dogs are sensitive to the administration of ivermectin. A safety study (0899-C-US-13-98, Illinois) was conducted to determine the safety of a single dose of ProHeart 6 at 1, 3 and 5 times the proposed commercial SC dosage of 0.17 mg/kg.²⁹ Collie dogs shown to react to a 120 µg/kg bodyweight dosage of ivermectin (depression, ataxia, mydriasis, and excessive salivation) were enrolled in the study. Following treatment, dogs were observed intensively for the first 24 hours and twice daily through 21 days. There were no health conditions suggestive of toxicity in any of the dogs treated with ProHeart 6.

4.1.3.3 Heartworm-Positive Dogs

The safety of ProHeart 6 in heartworm-positive dogs was evaluated in 2 studies. The first study (0899-C-US-14-98, Alabama) tested a 3 times the proposed SC dosage in dogs with patent heartworm infections as measured by circulating microfilarial counts and heartworm antigen.³⁰ Clinical observations, physical exams, and microfilarial counts were used to evaluate the effects of treatment. The results demonstrated that a dosage of 0.51 mg/kg did not cause adverse reactions in dogs with patent heartworm infections. There were no post-treatment adverse health effects. Reduction in microfilariae compared with controls began as early as Day 7 post-treatment and peaked at 99.6% on Day 21 post-treatment. There was no significant ($p < 0.05$) adulticidal effect observed with ProHeart 6.

As part of the ProHeart 12 development program, the safety of this product for dogs was evaluated in dogs that had been surgically implanted with 20 adult heartworms via the jugular vein (0899-C-US-39-02, Georgia).³¹ On Day 61 following implantation, dogs were treated with ProHeart 12 at 1.5 mg/kg (approximately 9 times the ProHeart 6 and 3 times the ProHeart 12 proposed commercial dosages). Animals were observed twice daily for signs of toxicity with physical and clinical examination. There were no treatment-related effects in any of the dogs. Microfilariae counts were reduced to almost 0 at 3 weeks after treatment, with no effect on the adult population demonstrating no adulticidal activity in heartworm-positive dogs.

4.1.4 Field Studies

The safety and efficacy of ProHeart 6 at 0.17 mg/kg was evaluated under field conditions in dogs dosed twice at 6-month intervals (0899-C-US-5-98, California; 0899-C-US-6-98, Texas; 0899-C-US-7-98, Wisconsin; 0899-C-US-8-98, Connecticut).^{32,33,34,35} A total of 374 client-owned dogs representing 84 breeds (280 ProHeart 6 treated, 94 ProHeart oral tablet controls) completed the study. Dogs were ≥ 6 months of age and were of a variety of breeds, weights, physical condition, and were of both sexes (either intact or altered). Prior to enrollment, animals were tested for both heartworm antigen and microfilariae to ensure that dogs were negative for existing heartworm. None of the 374 dogs that completed this study tested positive for heartworms at either 3, 6, or 12 months after the initiation of ProHeart 6 treatment. The following potential adverse drug reactions were observed (number of cases): vomiting (3), diarrhea (2), weight loss (2), listlessness (1), seizures (1), injection site pruritus (3), and elevated

body temperature (1). Injection site evaluation revealed no abnormalities. This level of potential reactions for the 374 dogs that completed the study was extremely low and demonstrated the safety of the product under field conditions. Twelve (12) ProHeart 6 animals were euthanized or died during the 18-month study. It was determined following thorough review of each case that these deaths could not be attributed to treatment with ProHeart 6.

4.1.5 Exaggerated Moxidectin Overdose in Dogs

FDAH markets an oral formulation of moxidectin for use in horses to control internal parasites. This product is supplied as a syringe with a plunger calibrated by weight so that the correct dose can be given to horses varying in weight up to 1150 pounds.

While uncommon, dogs have been exposed to this product. Sometimes this exposure is intentional; owners believe it is cost effective and safe to administer the product to dogs. Occasionally dogs find discarded syringes and chew on them or they consume gel mixed with treats intended to entice a reluctant horse.

From 1997 to 2004, FDAH received approximately 250 reports. These cases were characterized by a wide range of neurological manifestations. Most (90%) of these dogs recovered to normal; the remaining 10% died. Thus, very high doses of moxidectin may lead to neurological manifestations of toxicity that are often reversible with no evidence of any long-term or non-neurological toxic effects

4.1.6 International Studies

ProHeart products have been registered in a number of international markets including Australia, Canada, the European Union (France, Greece, Italy, Portugal, Spain), Korea, and Japan. Length of activity claims and active ingredient concentration vary depending on the market. US data formed the basis of each registration with supporting local data, where required. These studies included dose-confirmation and field-efficacy testing.

Three (3) studies (0899-C-IT-01-99, 0899-C-IT-02-99, 0899-C-IT-03-99) were conducted in Italy to evaluate ProHeart 6 (trademark Guardian SR in Europe) at a dosage of 0.17 mg/kg for the prevention of heartworm disease caused by *Dirofilaria immitis* and *Dirofilaria repens*.^{36,37,38} Two hundred and fifty-one (251) client-owned dogs of various breeds (41) completed this series

of field-efficacy and safety studies. ProHeart 6 given at 6 month intervals was 100% effective in protecting animals from heartworm infection in this heartworm endemic area (verified by untreated animals enrolled in the same area). No adverse reactions to treatment were reported.

In Australia, 3 studies (0899-C-AU-01-97 dose confirmation, 0899-C-AU-02-00 puppy safety, and 0899-C-AU-02-98 clinical field study) were conducted in support of a 12-month protection product administered at a dosage of 0.50 mg/kg.^{39,40,41} ProHeart SR 12 was 100% effective in preventing heartworm disease in the laboratory dose-confirmation study. When administered at 3 times the recommended dose (9 times the ProHeart 6 dosage) in puppies 10 to 12 weeks of age, no clinically apparent adverse effects or adverse injection site reactions were observed. Breeds of dogs included Maltese cross, Lhasa Apso cross, Fox Terrier, Staffordshire Bull Terrier, Poodle, Border Collie, Labrador Retriever, German Shepherd and Rottweiler and represented small, medium, and large breeds. Two hundred and ten (210) animals representing 75 breeds completed the field clinical study. The study demonstrated the effectiveness of ProHeart SR 12 at 0.50 mg/kg (3 times the ProHeart 6 dosage) in protecting dogs from heartworm infection for 12 months. No adverse reactions or drug interactions were observed in treated dogs.

4.1.7 ProHeart 12

ProHeart 12, a moxidectin based product similar to ProHeart 6 is currently in development in the US. This product, administered at an SC dosage of 0.50 mg/kg will protect dogs from heartworm disease for a period of 12 months and is identical to the commercial product in Australia. A safety and field clinical program has been conducted. These studies demonstrate the same safety profile as ProHeart 6 in reproducing males and females, heartworm-positive dogs, ivermectin-sensitive Collies, and a variety of canine breeds during the field evaluation program.

4.1.8 Conclusion

The efficacy and safety of Proheart 6 has been thoroughly evaluated during the initial development program and in subsequent studies designed to expand label claims for the product. These programs were designed in close cooperation with the FDA and are comprehensive in scope. ProHeart 6 has been shown to be efficacious in the protection of dogs from heartworm disease. It is safe when administered to healthy dogs and to unique canine populations, such as heartworm-infected or ivermectin-sensitive dogs.

4.2 Postmarketing Surveillance of Adverse Events

FDAH designed a postmarketing surveillance system to detect a signal of potential drug effects and subsequently to estimate the incidence and causality of a potential drug effect. The data used for postmarketing surveillance generally consisted of adverse event reports (AERs).

To determine if AERs have clinical relevance, incidence is estimated and comparisons are made with a group representative of the general population that has not been treated with the drug. FDAH calculates reporting rates using the number of reports divided by an estimate of the doses sold to veterinarians for the same period. In contrast, regulatory authorities generally do not utilize estimates of the frequency of drug administration. Additionally veterinary epidemiologists lack an understanding of the rate of occurrence of even commonly observed medical problems. Thus, it is difficult in assessing AERs to determine whether a drug is directly related to the observed events. Even after determining that an adverse event may be likely related to drug administration, the clinical importance of the reaction is unknown without an understanding of its incidence. Frequent serious reactions may warrant withdrawal of a drug from the market, while rare reactions may require appropriate warnings to prescribers and clients.

Further confounding the interpretation of AERs is the potential for bias. There is a considerable opportunity for extraneous events to stimulate over-reporting of adverse observations in animals as possible drug associated adverse events. For ProHeart 6 in particular, there are additional biases that may have impacted reporting of adverse observations. Because ProHeart 6 is a new innovative product, veterinarians lack a frame of experience from which to judge whether or not adverse observations are likely to be associated with the drug. The long duration of action makes it appear plausible that adverse observations might be associated with drug administration that occurred several months earlier. Further, since ProHeart 6 is administered parenterally by veterinarians and the monthly oral medicines are administered by pet owners (often as a treat), there is a potential for greater apparent concern with ProHeart 6. Also, veterinarians received Dear Doctor letters discussing ProHeart 6 safety issues that may have stimulated AERs. Lastly, there were several widely-disseminated news reports and website postings critical of ProHeart 6 that may have stimulated AERs.

Thus, while postmarketing surveillance of AERs is a valuable tool in monitoring drug safety, the use of this system for regulatory decisions is complicated by the absence of a control group, the lack of an estimate of use, the lack of knowledge of the background rate of systemic diseases in the canine population, and the impact of reporting bias to stimulate over-reporting.^{42,43,44}

4.2.1 Overview

In the subsequent sections, FDAH further evaluates AERs (1) relative to product usage, (2) relative to likelihood that they were associated temporally with ProHeart 6 administration, and (3) relative to independent expert assessment of the possible causality of the event as result of drug administration. On September 3, 2004, FDAH announced the voluntary recall of ProHeart 6 from the US market until resolution of FDA safety concerns. The primary concerns cited by FDA were the large number of AERs that were attributed to ProHeart 6 and that the numbers of these AERs were increasing in the months leading up to the recall. Additionally, the FDA expressed concerns regarding symptoms associated with several different body systems. These included neurologic, hematologic, hepatic, and cardiac systems, as well as a concern regarding neoplasia in association with ProHeart 6 administration.

FDA's website cites the submission of "more than 5500 AERs in compliance with federal regulations (21 CFR 514.80) that require sponsors to submit serious and unexpected AERs within 15 working days of first receiving the information." FDAH respectfully disagrees that all of these reports are medically serious or unexpected, or attributable to ProHeart 6. AERs defined as serious and unexpected are submitted to FDA within 15 working days. Those reports defined as not serious or not unexpected are normally submitted yearly in the annual Drug Experience Report. However, because of FDA's continuing concerns, FDAH began submitting all reports in a 15-day window in the third quarter of 2003, including those that were not serious and unexpected. Additionally, all events reported to FDAH were relayed to FDA in an unfiltered manner, regardless of causality assessment. Many AERs contain an assessment by the reporting veterinarians that their suspicion of product involvement in the event is low. This is particularly true for reports that were not deemed allergic events. FDAH has also assessed many of these events as having a low causal relationship. Thus, FDAH considers most of the AERs to be unrelated to ProHeart treatment.

Approximately 18 million doses of ProHeart 6 have been sold with more than 12 million doses administered. The calculated reporting rate is 2.5 reports per 10,000 doses, based on doses sold to veterinary clinics through August of 2004. This is the equivalent of one report (without regard to causality) per 4000 doses sold. It is recognized in a voluntary reporting system that not all potential adverse events associated with product use are reported. However, the trends over time need to be considered and indicate that the rate of AERs for ProHeart 6 was low and declined over time.

Another critical element is the background rate of disease in the canine population at large. The concerns regarding specific body systems are addressed in detail in section 4.2.2.2. Several independent experts were consulted and their conclusions, which are included for consideration, strongly support the safety of ProHeart 6 and indicate that most of the AERs were not causally-related to ProHeart 6 treatment.

One should consider the system used by FDA to assign causality to each AER. The six point causality assessment system considers previous experience with the drug, whether alternative etiologic candidates exist, timing of the event, overdose, and dechallenge and rechallenge. The system was primarily established for immediate release products. ProHeart 6 is a 6-month sustained-release product. Sustained-release products have not previously been evaluated using this system. Dechallenge (drug removal from the patient's body) is not possible for at least 6 months and FDA has acknowledged that the "challenge" and "dechallenge" components of their scoring system are not applicable in this instance. The modified scoring procedures to account for this fact may have created unintended bias among their reviewers.

4.2.2 Review of Adverse Event Reports

Upon receipt of an AER, the reporting party is asked a series of questions by FDAH professionals, including patient description and identification, previous history, date of product administration, its dose, body location of administration, time to observation of the adverse event, concurrent treatments employed, diagnostic testing, and event outcome. Regardless of causality assessment by FDAH, every AER involving an FDA regulated product received by FDAH is submitted to the FDA.

To assist in the analysis of AERs, FDAH developed an AER categorization system. Each AER is assigned into one or more of the following categories:

1. Injection site reports
2. Allergic reports (signs consistent with an allergic response in the species involved, occurring less than 48 hours after product administration)
3. Non-allergy systemic reports

To calculate reporting rates for evaluation of the incidence of events, the number of reports received is divided by the number of doses sold to veterinary clinics in the same period. The total number of vials of product sold is converted to an estimate of doses using an average number of doses per vial. Based on interviews with a large number of veterinarians, FDAH determined that the average number of doses per vial was 21. This dosage is equivalent to an 18 kg dog which is consistent with the average weight of the population at large.

There is a significant seasonality to the pattern of use of all heartworm preventative products. Figure 4.2.2-1 illustrates this seasonal pattern for doses of heartworm preventatives dispensed by veterinarians in the course of a typical year. This pattern is important to understand, when analyzing report numbers and reporting rates, as discussed below.

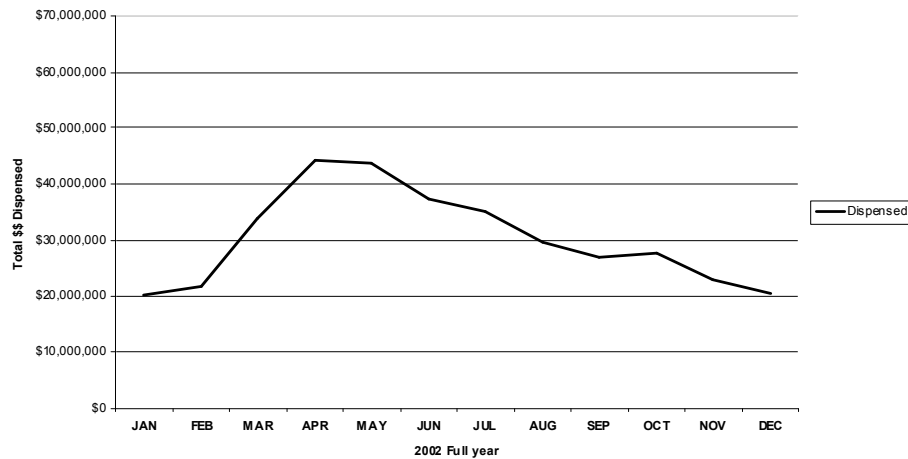
Figure 4.2.2-1. Seasonality of Dispensing Heartworm Medication 2002 (All Products)

Figure 4.2.2-1 demonstrates the strong seasonal use patterns of heartworm preventative products in the US. The risk (and heightened awareness) of heartworm infection increases as mosquito populations either reappear after a typical northern winter, or crescendo after the more mild winters in southern areas of the US. Therefore, there is a large peak in use of all heartworm preventatives in April and May of the year.

Figure 4.2.2-2 demonstrates the sales patterns of ProHeart 6. Sales are increasing over the period. Sales peaks also occur in each year in essentially the same periods of time as the use patterns of heartworm products demonstrated in Figure 4.2.2.2-1.

Figure 4.2.2-2. Doses Sold by Quarter

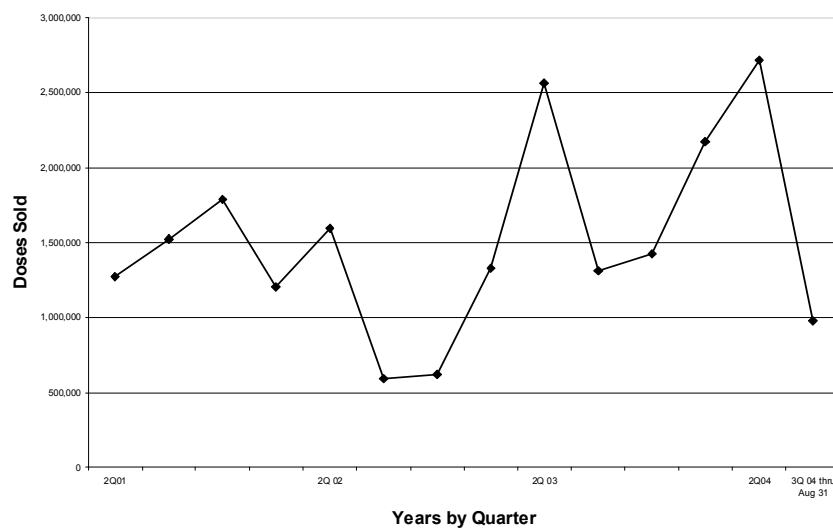


Figure 4.2.2-3 demonstrates the number of AERs received by FDAH associated with ProHeart 6. The number of AERs from launch through August of 2004 is generally decreasing. The peaks in the number of AERs in the second quarter of each marketing year correspond to the peaks in seasonal use and sales previously described. These peaks in AER numbers decrease in each marketing year despite large increases in sales of ProHeart6 shown in Figure 4.2.2-2. This seasonality in use, in conjunction with the increasing sales trends marketing dynamics of ProHeart 6, results in patterns of AER numbers that are difficult to interpret without proper perspective on the number of doses administered. Therefore reporting rates are calculated using report numbers found in Figure 4.2.2.-3 divided by sales data found in Figure 4.2.2.-3 to create Figure 4.2.2-4.

Figure 4.2.2-3. Number of Adverse Event Reports by Quarter

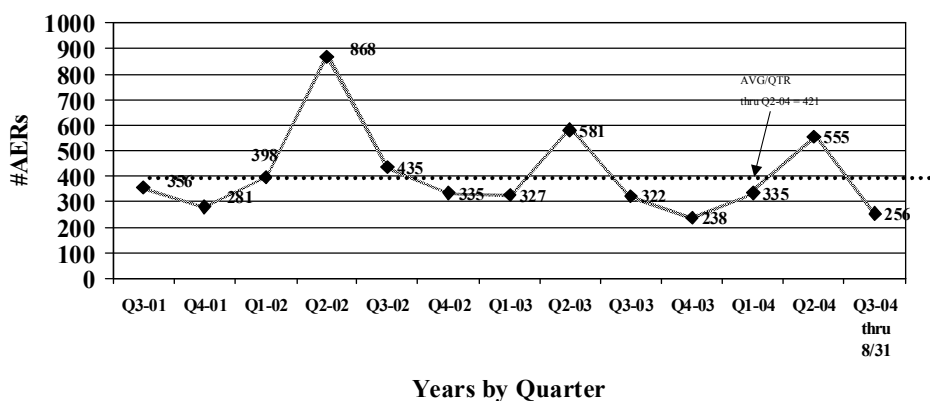
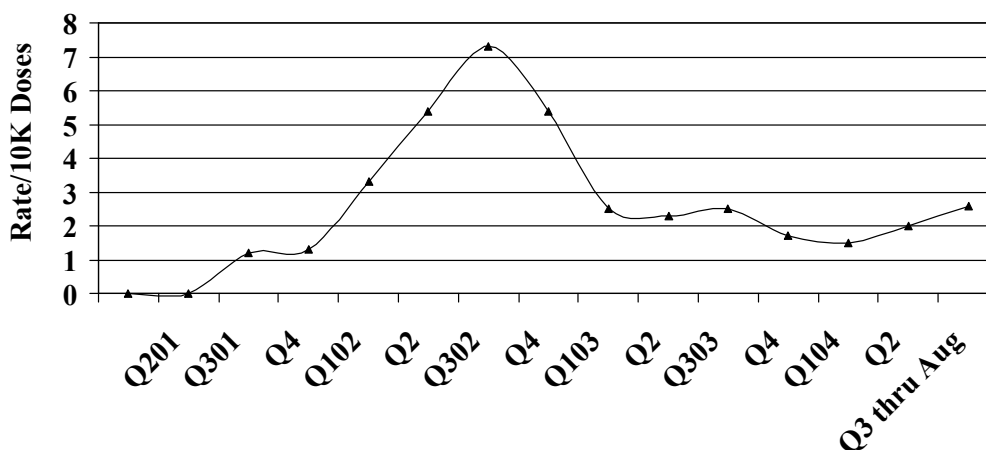


Figure 4.2.2-4. Reporting Rate by Quarter



The reporting rate shown in Figure 4.2.2-4 puts these trends into perspective. Marketing year two produced higher reporting rates, after which a more steady reporting rate was observed. Higher AERs were recorded in the 2nd quarter of 2002 (refer to Figure 4.2.2-3), but tapered off considerably following the August 2002 implementation of the manufacturing change of zero tolerance for residual solvents in the moxidectin used to manufacture ProHeart 6 (see Section 4.3). In the 2nd quarter of 2002, reporting rates peak not only due to an increased number of reports but also due to the return of large amounts of product in 2002, as a result of outdated product sold in 2001.

Evaluation by marketing year, which eliminates reporting rate fluctuations due to seasonality of use, reveals that the average reporting rate for AERs is less than 4 reports per 10,000 doses sold per year. By this same method of analysis, reports that include the death of the patient (regardless of causality) are fewer than 0.5 reports per 10,000 doses sold per year. Additionally, there is no peak in the number of death reports during the peaks in AERs seen in the 2nd quarter of each year. Further, the adverse event case fatality rate associated with ProHeart 6 reports is lower than many FDAH pharmaceuticals and similar to case fatality rates for the FDAH canine vaccine product lines including Duramune Max 5/4L. Thus the incidence of death does not appear to be causally related to ProHeart 6 usage.

Most AERs occurred within 10 days of product administration. Overall, 72% of the AERs occurred within 48 hours of administration, (17%) were reported from 2 days to 10 days post-administration, and 10% occurred at 11 days or later. This information suggests that a significant percentage of reports occur in a short time frame, consistent with a possible allergic etiology from administration of ProHeart 6 alone or in combination with vaccines or other medication.

When the numbers of AERs were evaluated with consideration of the seasonality of use and the increases in the numbers of doses sold over time, the rate of reporting associated with ProHeart 6 was low and was decreasing with time. In addition, the seriousness of reports as estimated by case fatality rates was not increasing and was consistent with commonly used pharmaceutical and biological products. Thus, FDAH concludes that AERs were rare and the product should remain available as an alternative for prevention of canine heartworm disease.

4.2.2.1 Analysis by Report Category

4.2.2.1.1 Injection Site Reports

The reporting rate for injection site reports through 31 August 2004 was 0.2 reports per 10,000 doses sold. The majority of the events were self-limiting and consisted of swelling, pain and/or pruritus at the site of administration.

The occurrence of injection site reports after the use of ProHeart 6 has remained consistently low and the types of events reported were similar to other injectable products in the FDAH database. For comparison, 2 of the most widely used vaccines in the FDAH line have reporting rates of 0.1 reports per 10,000 doses sold (Duramune Max 5/4L, a distemper/parvo/leptospirosis combination vaccine) and 0.5 reports per 10,000 doses sold (Rabvac 3, a rabies vaccine).

4.2.2.1.2 Allergy Event Reports

The allergy report category has trended down over time. The reporting rate through 31 August 2004 was 1.26 reports per 10,000 doses sold. The occurrence of allergy events was most prevalent in the most popular breeds, supporting the conclusion that there are no specific breed sensitivities. Thirty seven percent (37%) of the reports include concurrent vaccine

administration, which likely contributed to the reporting rate. For the vaccines previously cited, Duramune Max 5/4L has an allergy reporting rate of 0.4 reports per 10,000 doses sold and Rabvac 3 has an allergy reporting rate of 0.5 reports per 10,000 doses sold.

The occurrence of allergy events are described in the product label. The observations include facial swelling, angioedema, and urticaria, alone or in combination with gastrointestinal (GI) signs such as vomiting or diarrhea, anaphylaxis, or a low percentage of less common signs such as lethargy.

4.2.2.1.3 Non-Allergy Event Reports

Non-allergy events are those not considered to be an allergic response and not categorized as injection site. This non-allergy category includes systemic responses (regardless of the plausibility of product association) and may overlap with other categories. For example, an individual event report describing injection site swelling would be classified as an injection site report; however if fever and myalgia also occur, it would also be categorized as a non-allergy event. Similarly, there is an overlap in the symptoms designated as allergy and non-allergy. Acute GI symptoms occurring within 48 hours of product administration may be categorized as an allergic event, whereas the same symptoms occurring at 96 hours after product administration would typically be categorized as a non-allergy systemic event. Forty five percent (45%) of reports categorized as non-allergy occurred within 48 hours of product administration. In many cases, some of the clinical signs reported are consistent with allergy, while other signs vary enough to result in the event being placed in the non-allergy category. Therefore, FDAH concludes that a significant number of events placed in the non-allergy category are actually allergy mediated.

As observed in the allergy group, no specific breeds appear to be over-represented in the analysis when the population at large is considered. The overall reporting rate for the non-allergy category through 31 August 2004 was 1.19 reports per 10,000 doses. Concurrent vaccine use was reported in 42% of the non allergy reports. Duramune Max 5 /4L has 0.3 reports per 10,000 doses recorded in the non-allergy group and Rabvac 3 has 0.35 reports per 10,000 doses.

The signs reported in the non-allergy group cover a wide range, with a large number of the signs being reported in relatively few cases. The more commonly reported events include vomiting

and/or diarrhea, lethargy, seizures and ataxia. With the exception of ataxia, all of the above clinical signs are included in the product label.

4.2.2.2 Causality Analysis of Medical Events by Selected Body Systems

Events involving specific body systems were further analyzed to establish causality. These included events associated with neurologic reports, hematologic reports, hepatic reports, cardiac reports, and reports with a diagnosis of neoplasia.

Each ProHeart 6 case was individually reviewed to assess the likelihood that the observation was the result of administration of ProHeart 6. Medical association assessments were based on the approved International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) pharmacovigilance draft guidelines. These draft guidelines were developed with regulators from Europe, Japan, and the US to provide guidance on global pharmacovigilance harmonization. All events were assigned to the medical association “possible” category as a starting point. When the causality was considered “unlikely,” sufficient information existed to establish that a reported event was not likely associated with product use because there were other more plausible explanations for the reported event. For the analysis by body system that are presented in the sections that follow only the medical association “possible” group was reviewed.

This medical association “possible” group was further reviewed to distinguish between events that could potentially be associated with a specific body system compared with those events for which it is probable that the specific body system was involved. Therefore, for each body system to be analyzed, 2 case definitions were developed: “potential” and “probable.” The “potential” case definition is intended to include all clinical signs potentially reflective of an adverse effect on that body system. The “probable” case definition is more refined to include only those clinical signs that have a reasonable probability of being related to that body system, and the “probable” excludes all events classified as allergic. If any individual report included more than 1 of the body systems evaluated, it was included in multiple evaluations. For example, if the report involved a dog with anemia and elevated hepatic enzymes, it was reviewed under both the hematologic and hepatic body systems.

4.2.2.2.1 Neurologic

The analysis of neurologic events is shown in Table 4.2.2.2.1-1. The rate of reporting is low at 0.12 reports per 10,000 doses. The difference between the number of potential and probable neurologic events is relatively large because events classified as allergic and events with non-specific neurologic signs are included in the number of potential events but not the number of probable events. Non-specific neurologic signs are clinical signs (eg, muscle tremors) that are seen without other clinical signs and, therefore, are not likely to include a primary neurologic disorder.

For neurologic events, seizure and ataxia are the primary clinical signs while other individual clinical signs each account for less than 10% of the total in the neurologic group. As is true with each of the systems, causality assessments are confounded by concurrent vaccine use in 47% of the AERs. Additionally, 54% of the reported events occurred within 48 hours or less, suggesting that many may be allergic events.

Table 4.2.2.2.1-1. Neurologic Adverse Events – Number of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	98	23	0.05
2002	342	85	0.21
2003	235	69	0.10
2004-Aug	211	68	0.12
Total	886	245	0.12

The “probable” neurologic reports were reviewed by Dr. Alexander deLahunta D.V.M., PhD., diplomate of the American College of Veterinary Internal Medicine, specialty neurology and honorary member of the American College of Veterinary Pathologists (Appendix 6.2). FDAH randomly selected about 75% of the neurologic AERs for his review. Dr. deLahunta noted that seizures were the most common clinical sign reported in the cases, which is consistent with the general observations in the practice of clinical neurology. He also commented that the most common cause of seizures in dogs is idiopathic epilepsy. Dr. deLahunta concludes his assessment with the following statement: “The extensive toxicologic studies performed by

FDAH clearly support the safety of ProHeart 6 at the dose injected in these dogs. There is no rational scientific reason to believe that this product played any role in the post-injection clinical signs reported in these case summaries.”

4.2.2.2.2 Hematologic Events

The analysis of hematologic events is shown in Table 4.2.2.2.2-1. The rate of reporting is low at 0.09 reports per 10,000 doses. As is true with each of the systems, causality assessments are confounded by concurrent vaccination in 49% of the AERs.

Table 4.2.2.2.2-1. Hematologic Adverse Events – Number of Reports

Year	Potential	Probable	Rate (Probable) per 10K
			Doses Sold
2001	75	13	0.03
2002	212	63	0.16
2003	172	48	0.07
2004-Aug	139	60	0.10
Total	598	184	0.09

FDAH consulted with Dr. Alan Rebar, a diplomate of the American College of Veterinary Pathologists with a specialty in clinical pathology, to review all potential hematologic events (Appendix 6.3). Dr. Rebar was provided with clinical case summaries and all available clinical laboratory data for all the clinical cases identified by FDAH criteria as probable hematologic or hepatic adverse events to ProHeart 6. (The review of the hepatic events follows in Section 4.2.2.2.3.)

In contrast to FDAH’s assessment (Table 4.2.2.2.2-1), Dr. Rebar determined that 151 of the AERs he reviewed should be categorized as probable hematologic AERs. Particular emphasis was placed on potential toxic-induced hematologic events: immune mediated hemolysis (IMHA), immune mediated thrombocytopenia (ITP), Heinz body hemolysis, and bone marrow hypoplasia/aplasia (IMMD). Of these, only IMHA, ITP and/or IMMD were identified among the 151 hematologic reports.

Dr. Rebar also evaluated the 151 probable hematologic events to determine which may have been immune mediated. Using a conservative case definition he determined that 79 could be immune mediated. In many of the 79 cases, however, not enough data were provided to establish a definitive diagnosis of IMHA, ITP or IMMD. For example, in many cases, blood films were not evaluated for the presence of spherocytes, direct antiglobulin tests (DAT, Coombs' tests) were not run, and blood films were not scanned to confirm an instrument reported thrombocytopenia.

Of the 79 cases determined to be potentially immune mediated, 76 cases were determined to be IMHA/ITP. Of these, 53 cases occurred after the first injection of ProHeart 6, and 26 occurred after 2 or more injections. Of the 53 cases occurring following a single ProHeart 6 injection, only 23 (those occurring 8 to 30 days post-injection) were considered possibly related to ProHeart 6. Fourteen (14) occurred too soon following ProHeart 6 injection (0 to 7 days) to have allowed sufficient antibody to form against ProHeart 6 to precipitate an immune-mediated hematologic event. Thirteen (13) occurred after 30 days or more, too long an interval to suggest a likely role for ProHeart 6 injection.

Of the remaining 23 cases, it is not possible to rule out a role for ProHeart 6, although IMHA and ITP are relatively common disorders in all breeds of dogs.

Of the 26 cases occurring following multiple injections of ProHeart 6, twenty two (22) (those occurring between 0 and 30 days post ProHeart 6 injection) were considered possibly related to ProHeart 6. The 10 cases occurring within 7 days post-injection are relatively unlikely to be related to ProHeart 6 injection but are included because of potential anamnestic immune response to multiple injections.

Three (3) cases of apparent IMMD were identified. The cause of the IMMD in each case could not be determined from the diagnostic data available. Two (2) cases occurred after the first dose of ProHeart 6; the first occurred at 7 days post administration and the second occurred at more than 30 days post administration. The third case occurred more than 30 days after the dog had received its fourth dose of ProHeart 6. The timing of all 3 events indicates that they were unlikely to be related to ProHeart 6 administration.

In summary, 45 cases of hematologic AERs may have been induced by ProHeart 6. However, since more than 18 million doses of ProHeart 6 have been sold it is possible that these findings represent the normal baseline incidence in canines.

4.2.2.2.3 Hepatic Body System

The analysis of hepatic events is shown in Table 4.2.2.2.3-1. The rate of reporting is low at 0.07 reports per 10,000 doses sold. As is true with each body system, causality assessments are confounded by concurrent vaccine use in 38% of the AERs.

Table 4.2.2.2.3-1. Hepatic Adverse Events – Numbers of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	36	12	0.03
2002	125	48	0.12
2003	109	49	0.07
2004-Aug	118	47	0.08
Total	388	156	0.07

One hundred (100) probable hepatic AERs were reviewed by Dr. Rebar. This number of 100 probable hepatic reports is different from the total probable hepatic reports in Table 4.2.2.2.3.-1 because Dr. Rebar removed 56 reports that he determined were not probable hepatic events. Forty-three (43) cases of possible primary liver disease were identified among the 100 AERs evaluated. Fifty-seven (57) cases were probably not primary hepatic events, and the mild non-specific elevations in hepatic enzyme(s) were thought to be due to anorexia and/or stress.

Of the remaining 43 cases, 42 occurred between 0 and 3 days post- injection; again, however, a causal relationship with ProHeart 6 cannot be ruled out. However, since more than 18 million doses of ProHeart 6 have been sold it is possible that these findings represent the normal baseline in the canine population.

Pathology reports from all the probable hepatic AERs that contain any pathology reports (15 cases) were reviewed by Dr. Keith Harris D.V.M., Assistant Vice President Pathology and Bioresources, Wyeth Research and diplomate of the American College Veterinary Pathologists. There was no pattern of liver pathology indicative of a common toxicological agent in all or a subset of the 15 cases (other than corticosteroids in two cases). Only one case out of the 15 exhibited histomorphologic changes consistent with a direct acting hepatotoxin that could be temporally related to ProHeart 6 administration. Pathology reports from 15 cases with liver disease were reviewed. There was no obvious pattern of liver pathology that would indicate toxicity common to all or a subset of the 15 cases (other than corticosteroids in two cases). Only one case out of the 15 exhibited histomorphologic changes consistent with a direct acting hepatotoxin that could be temporally related to ProHeart 6 administration. The acute hepatocellular necrosis described in this particular case is a non-specific finding and could have been caused by a number of different toxicants.

4.2.2.2.4 Cardiac Events

The analysis of cardiac events is seen in Table 4.2.2.2.4-1. The reporting rate is low at 0.02 reports per 10,000 doses.

Table 4.2.2.2.4-1. Cardiac Adverse Events – Numbers of Reports

Year	Potential	Probable	Rate (Probable) per 10K Doses Sold
2001	100	7	0.02
2002	254	15	0.04
2003	186	10	0.02
2004-Aug	153	15	0.02
Total	693	47	0.02

Concurrent vaccination confounds the assessment of the cardiac events. Forty-nine percent (49%) of the cases classified as cardiac events included concurrent vaccination. Sixty percent (60%) of the reports occurred within 48 hours of ProHeart 6 administration. The timing of these

reports is not indicative of a direct cardiac effect. Many events appear to overlap as non-typical allergic events, as observed for the other body systems, so that an indirect effect associated with an allergic event cannot be ruled out.

Dr. Keith Harris DVM, Assistant Vice President Pathology and Bioresources Wyeth Research, and diplomate of the American College of Veterinary Pathologists, reviewed the histopathological slides from 2 cases of cardiac necrosis thought to be associated with ProHeart 6 administration. Histopathologic evaluation of tissue specimens from the 2 dogs identified in an FDA presentation revealed cardiac pathology secondary to uremia in a Boxer dog and chronic heart disease that clearly predated ProHeart 6 administration in a Labrador Retriever. The two IDEXX pathologists who had originally indicated that these cases might be associated with ProHeart 6 subsequently concurred with this interpretation.

Based on these data, including timing of the events and histopathological assessments, FDAH concludes that there is no causal relationship between ProHeart 6 and these cardiac events.

4.2.2.2.5 Neoplasia Events

The analysis of neoplasia cases is shown in Table 4.2.2.2.5-1. The rate of reporting is low at 0.06 reports per 10,000 doses.

Table 4.2.2.2.5-1. Neoplasia Adverse Events – Numbers of Reports

Year	Potential	Rate per 10K Doses Sold
2001	7	0.01
2002	38	0.09
2003	41	0.06
2004-Aug	36	0.06
Total	130	0.06

Dr Philip Bergman, D.V.M, MS, PhD, diplomate American College of Veterinary Internal Medicine, Oncology (Appendix 6.4) reviewed all 130 cases involving a diagnosis of neoplasia, regardless of medical association. A summary of Dr. Bergman's comments follows.

The vast majority of ProHeart 6-related cancers occurred within 21 days or less of ProHeart 6 administration. Veterinary oncologists agree that at least 6 to 8 weeks are required to develop a tumor after exposure to a carcinogen. Therefore, cases that were diagnosed with cancer within a 3 to 4 week period after ProHeart 6 administration likely had a tumor present before ProHeart 6 administration. There was not a relationship between additional doses of ProHeart 6 administered and increasing reports of neoplasia. This lack of a dose-response relationship with repeated ProHeart 6 administration further supports the conclusion that ProHeart 6 is not responsible for canine tumor induction. This is further supported by the moxidectin nonclinical toxicology studies showing no evidence of carcinogenicity (see Section 3.3.3 and Appendix 6.1).

Dr. Bergman's review of the 130 cases revealed that 100 cases were clearly not associated with ProHeart 6 administration. Twenty eight (28) cases did not allow the immediate exclusion of an association to ProHeart 6 administration. However the association was deemed unlikely due to 1 or more of the following factors: 1) a time period from product administration to observation of the neoplasia was too short to be considered a causal relationship; 2) most of the reports revealed no association between the site of administration and the location of the neoplasia; 3) there was a broad cross section of neoplasia types, rather than a predilection for a specific tumor type, as would be expected in a product-specific effect; and 4), the types were representative of those seen in the general dog population. There were 2 cases in which a relationship to ProHeart 6 administration could not be ruled out.

4.2.3 Conclusions

Based on the in-depth analysis described in this summary section, it is the conclusion of FDAH that ProHeart 6 is a safe and effective product for the prevention of canine heartworm disease. The overall reporting rate for AERs was low and generally trended down over time to the time of the recall. At that time, the frequency and severity of AERs was not increasing. Analysis of specific body and organ systems support the conclusion that the AER clinical finding were generally not causally related to ProHeart 6 administration and appeared to occur at a rate consistent with naturally occurring disease in the canine population.

4.3 Manufacturing Change

ProHeart 6 was launched in the US in June 2001. Shortly after launch, FDAH received a number of reports of allergic-type reactions after administration. The reactions reported ranged from mild and self-limiting (eg, urticaria, itching at injection site, an episode of vomiting or diarrhea) to severe anaphylactoid reactions.

A working group of FDAH and Wyeth immunology experts was convened to investigate the possible causes, and outside experts were retained to assist. There were 2 aspects of the investigations: (1) field reports and their follow-up, and (2) product analysis for any abnormalities, contaminants, and/or reactive components.

A “cluster effect” was observed where some practices reported several adverse events, while others in close proximity with usage patterns of ProHeart 6 did not report reactions. This was observed in both the US and Australia. Visits were made to practices to evaluate product storage, handling, and administration, and veterinarians and dog owners were interviewed to try to identify any predisposing factors. No age or breed predispositions were found, nor any interactions with concurrent treatment with other veterinary therapeutics or biologicals.

Extensive investigations into reactor dogs (dogs which showed allergic reactions) found no evidence that the allergies were IgE (immunoglobulin E) or IgG (immunoglobulin G) mediated (L. Gershwin, Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis, and R. Schultz, Professor and Chair, School of Veterinary Medicine, Department of Pathological Sciences, University of Wisconsin, Madison [see Appendix 6.5]). The reactions appeared to be idiosyncratic and mediated either by histamine or complement.^{45,46,47} Attempts to induce reactions in dogs using passive cutaneous allergy testing after sensitization with serum from reactor dogs were unsuccessful.^{48,49}

Extensive testing of all raw materials and formulated products used in manufacture of ProHeart 6 showed that all were within quality specifications. Tests for 16 trace metals did not reveal any contamination. Quality Assurance audits were conducted at the manufacturing sites of glyceryl tristearate (Germany) and hydroxypropyl methylcellulose (US) to evaluate the potential for cross contamination during or after manufacturing. No potential problems were found. Cleanout

validation was repeated at the formulation plant to confirm that no carryover from other manufacturing processes could occur.^{50,51,52}

Both in the US and Australia, differences were found in reaction rates between batches, so investigations focused on trying to identify any batch differences. Thin layer chromatography (TLC) analyses detected no unknown components either in moxidectin technical material or in finished product. However, evaluation of minor component profiles between batches revealed a trend to lower reactions for lots with no detectable residual solvents. Coincident with this investigation, FDAH was optimizing the manufacturing process and initiated a manufacturing change to produce moxidectin with no detectable solvents.

Although additional studies were done to better understand the cause of the allergic-type reactions, no conclusive findings were generated. Nevertheless, there has been a decline in the adverse event reporting rate from all markets since the manufacturing change was implemented.

4.4 Safety Profile in Dogs

In August of 2004, FDAH requested a review of the safety of ProHeart 6 use in general veterinary practice and a comparison of its safety profile with that of commonly used oral monthly heartworm drugs by Dr. Larry Glickman VMD, DrPh, FACE, Professor of Epidemiology and Public Health and Head, Section of Clinical Epidemiology, School of Veterinary Medicine, Purdue University (Appendix 6.6). This section summarizes the experience with ProHeart 6 by Banfield the Pet Hospital™ veterinarians nationwide who had administered 735,654 doses of ProHeart 6 to dogs from January 1, 2002 through August 31, 2004.

4.4.1 Methods

The source of data for this analysis was the medical records of Banfield the Pet Hospital™. Banfield was founded in 1955 in Oregon to deliver primary health care to companion animals, and by 2005 will operate a national network of 440 full-service veterinary hospitals in 42 states. Banfield practices employ more than 900 full and part-time veterinarians, have over 1.4 million active patients, and conduct approximately 50,000 patient visits per week. The Banfield database is paperless and contains over 8 million patient records in electronic format. A quality assurance team consisting of veterinarians and veterinary technicians regularly monitors the safety profile of all medications, vaccines, and procedures used by Banfield veterinarians and tracks the incidence of diseases that are preventable by these vaccines or drugs.

All encounters (office visits) were characterized as being associated with ProHeart 6, 2 oral monthly heartworm preventative drugs (Heartworm Preventative 1 or Heartworm Preventative 2), vaccine, or none of these exposures. Adverse events (AEs) of interest included liver disease, neurological disease, ocular disease, immune-mediated disease, allergic reaction, death, cancer (mast cell, lymphosarcoma, and histiocytoma), cardiovascular disease, anaphylaxis, or inflammatory bowel disease. The specific diseases or laboratory findings comprising each of these AEs based on Banfield computer codes are shown in Table 4.4.1-1. Each encounter was then evaluated for potential AEs over the following 30 days. Of these encounters, 275,189 that occurred from August 1 to August 31, 2004, were excluded from analysis because they lacked a full 30-day followup interval. This followup period was

terminated early if a dog had another exposure to ProHeart 6, either of the 2 monthly heartworm preventatives, a vaccine, or died. Except in the case of death, a new followup period was initiated after this new exposure. The incidence of AERs, expressed as either the number of AEs per 10,000 encounters or the number of AE per 10,000 days at risk following an exposure, were calculated for the following exposure groups: no exposure, vaccine alone, ProHeart 6 with or without vaccine, and Heartworm Preventative 1 or Heartworm Preventative 2 with or without vaccine. Formal testing to identify statistically significant differences in the AE rates between exposure groups was generally not done for the univariate analyses due to the very large sample size within each exposure group. That is, the power to detect statistically significant differences was so high for common events that even very small differences in event rates were likely to be statistically different at $p < 0.001$. However, the same was not necessarily true for less common events. For this reason, the focus was placed on the clinical relevance of differences in the AE rates and the 95% confidence intervals of the odds ratios in multivariate analysis.

Table 4.4.1-1. Adverse Events

Disease Category	Adverse Event	Identification Criteria
Liver Disease	liver any dx	dx = hepatopathy, hepatitis, hepatic enceph, hepatic acute, hepatic dis, hepatic conserv, hepatic extensv
	liver alp	lab = alp $\geq$ 393
	liver alt	lab = alt $\geq$ 236
	liver gam	lab = gamma gt $\geq$ 24
	liver bil	lab = tot bilirubin $>$ 1.0
	liver lab	any liver adverse lab code
	liver any dx + any lab	any liver adverse dx + any liver adverse lab code
	liver any	any liver adverse dx or any liver adverse lab code
Neurological Disease	neuro	dx = enceph mening, epilepsy, behavioral uk, shock-cardio, seizures-acq lab = paresis, paralysis, ataxia
Ocular Disease	ocular	dx = optic neuritis, retinal-degen-s, anisocoria
		lab = vis acuity, vis deficit-lft, visual deficit-rgt
Immune Mediated Disease	Thrombocytopenia	dx = thrombocytopenia, thrombo im
	immun_med1	dx = (immune med dis or AHA) and lab = abnormal reticulocyte count
	immun_med2	dx = (immune med dis or AHA) and not lab = abnormal reticulocyte count
	immune any	any immune mediated disease adverse event
Allergic Reaction	allergic reaction	dx = allergic reaction, drug reaction, drug induc dis, allergic rct acut, vaccine reaction, urticaria, drug eruption
Death	death	dx = dead on arrival, sudden death death date within 30 days based on reported death in demographics records
Anaphylaxis	anaphylaxis	dx = anaphylaxis
Cardiac	cardiac murmur	dx = murmur
	cardiac arrhythmia	dx = cardiac arrest, atrial fibrillation, atrial premature contractions, atrial tachycardia, bundle branch block, heart block 1 st deg, heart block 2 nd deg, heart block 3 rd deg, cardiac arrhythmia, ventricular premature contractions, ventricular tachycardia
	cardiomyopathy	dx = cardiomyopathy, canine dilated, cardiomyopathy; canine hypertrophic, cardiomyopathy; boxer, cardiomyopathy; canine familial, cardiomyopathy; dilated, cardiomyopathy; hypertrophic
	cardiac any	any cardiac adverse dx
	mast cell tumor	dx = mast cell tumor
Cancer	lymphosarcoma	dx = lymphosarcoma
	histiocytoma	dx = histiocytoma
	cancer any	any cancer adverse dx
Inflammatory Bowel Disease	ibd	dx = inflammatory bowel disease

For the purposes of this study, it was assumed that oral monthly heartworm preventatives had been administered by owners on the same day of the encounter in which they had been dispensed. In contrast, ProHeart 6 and vaccines were assumed to have been administered during the same office encounter indicated in the medical record. Also, a search for potential AEs was limited to the 30 days immediately following an encounter of interest. The potential consequences of these assumptions would be to underestimate the incidence of AEs associated with oral monthly heartworm drugs, compared with those associated with ProHeart 6 or vaccines, because it was not certain if, or when, the monthly heartworm preventative dispensed for a dog was actually given to the dog by its owner. That is, some of the oral heartworm preventatives dispensed by Banfield veterinarians were probably never given to the dogs, yet AEs were calculated as if these drugs had been administered.

4.4.2 Results

From January 1, 2002 to August 31, 2004, there were 6,800,061 dog visits or encounters at 403 Banfield hospitals. The following number of encounters was associated with the administration of: ProHeart 6 (735,654), Heartworm Preventative 1 (411,082), Heartworm Preventative 2 (18,405), or vaccine (2,230,202), (Table 4.4.2-1). In addition, there were 5,634,016 encounters during which no heartworm preventative was administered or dispensed. Heartworm preventatives were often administered or dispensed at the same time as a vaccine. The proportion of encounters associated with vaccination was 62.9% for Proheart 6, 59.9% for Heartworm Preventative 1, and 65.1% for Heartworm Preventative 2. In contrast, vaccines were only administered during 26.4% of the encounters for which no heartworm preventative was given. That is, these dogs may have presented with signs of disease for which diagnostic tests were performed and other drugs administered. The number of doses of ProHeart 6 administered monthly by Banfield veterinarians increased over time since January 2002 and a higher number of doses was administered each year during the peak time of mosquito activity, namely from March through September (Figure 4.4.2-1).

Table 4.4.2-1. Rate per 10,000 of Any Adverse Event by Treatment Category Total Number of Encounters = 6,800,061

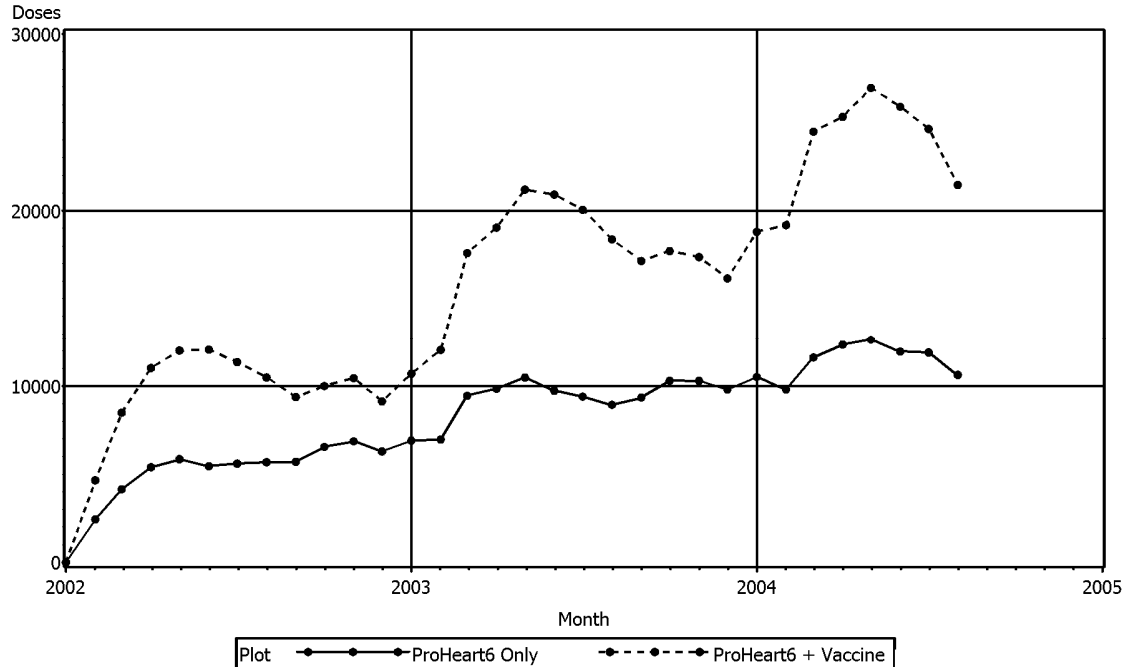
Vaccine	ProHeart6			HW Prev 1			HW Prev 2			No HW Treatment		
	N	N _A	Rate	N	N _A	Rate	N	N _A	Rate	N	N _A	Rate
Yes	483,064	6,292	130.3	246,131	2,804	113.9	11,975	120	100.2	1,489,032	17,406	116.9
No	252,590	2,253	89.2	164,951	1,469	89.1	6,430	45	70.0	4,144,984	120,529	290.8
Total	735,654	8,545	116.1	411,082	4,273	103.9	18,405	165	89.4	5,634,016	137,935	244.8

N = Total Number of Encounters

N_A = Total Number of Adverse Events

Rate = Number Adverse Events Per 10,000 Encounters

Figure 4.4.2-1. Doses Dispensed by Month; ProHeart 6 Only or With Vaccine



4.4.2.1 Univariate Analyses

ProHeart 6 was associated with a higher rate of liver-related AE compared with either of the 2 monthly heartworm preventatives, regardless of whether a vaccine was administered or not, while Heartworm Preventative 1 was associated with the highest death rate (Table 4.4.2.1-1). In general, vaccine administration was associated with an increased rate of liver disease for dogs receiving ProHeart 6, but not for dogs on monthly heartworm preventative. The rates of all other diseases or conditions except for cancer were similar among all of the heartworm preventatives, whether given orally or parenterally.

Table 4.4.2.1-1. Adverse Event Rate per 10,000 by Treatment Group

Treatment Category					Potentially Associated Adverse Event Type									
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine	N	Liver Disease		Neurological Disease		Ocular Disease		Immune Mediated Disease		Allergic Reaction	
					N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	25,531	61.6	3,157	7.6	134	0.3	2,948	7.1	6,832	16.5
			Y	1,489,032	5,207	35.0	522	3.5	27	0.2	265	1.8	6,598	44.3
		Y		6,430	14	21.8	4	6.2	0	0.0	1	1.6	12	18.7
		Y	Y	11,975	24	20.0	2	1.7	0	0.0	2	1.7	62	51.8
	Y			164,951	523	31.7	68	4.1	1	0.1	40	2.4	236	14.3
	Y		Y	246,131	671	27.3	94	3.8	2	0.1	22	0.9	1,336	54.3
Y				252,590	880	34.8	123	4.9	4	0.2	59	2.3	465	18.4
Y			Y	483,064	2,011	41.6	178	3.7	7	0.1	98	2.0	2,581	53.4
Any				6,800,061	34,866	51.3	4,149	6.1	175	0.3	3,435	5.1	18,123	26.7

Treatment Category					Potentially Associated Adverse Event Type									
ProHeart6	HW Prev 1	HW Prev 2	Any Vaccine	N	Death		Cancer		Cardio Disease		Anaphylaxis		IBS	
					N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	74,470	179.7	3,724	9.0	8,089	19.5	139	0.3	767	1.9
			Y	1,489,032	2,690	18.1	562	3.8	1,804	12.1	108	0.7	62	0.4
		Y		6,430	11	17.1	0	0.0	4	6.2	0	0.0	1	1.6
		Y	Y	11,975	17	14.2	2	1.7	10	8.4	2	1.7	0	0.0
	Y			164,951	363	22.0	67	4.1	219	13.3	4	0.2	17	1.0
	Y		Y	246,131	354	14.4	75	3.0	261	10.6	18	0.7	17	0.7
Y				252,590	392	15.5	155	6.1	250	9.9	13	0.5	19	0.8
Y			Y	483,064	709	14.7	205	4.2	635	13.1	34	0.7	26	0.5
Any				6,800,061	79,006	116.2	4,790	7.0	11,274	16.6	318	0.5	909	1.3

The rate of potential liver-related AEs was examined further on the basis of a clinical diagnosis only, an increase in the serum concentration of a liver-associated enzyme or bilirubin, or any combination of a clinical diagnosis plus an abnormal laboratory finding (Table 4.4.2.1-2).

ProHeart 6 when administered either with or without a vaccine, was associated with a higher rate of any liver-related clinical diagnosis, enzyme ALT, bilirubin, or a combination of a clinical diagnosis plus any abnormal laboratory test result (Table 4.4.2.1-3). However, in an analysis based on the rate of potential AEs per 10,000 days at risk, the rate of liver disease was comparable between ProHeart 6 and the 2 monthly heartworm preventatives, while the rate was highest for dogs that received no heartworm drug. It should be noted that the mean days at risk per encounter for ProHeart 6 was 29.2 compared with 27.2 for Heartworm Preventative 1. This could lead to a slight underestimation of the AE rate associated with Heartworm Preventative 1 compared with ProHeart 6. The liver-related AEs appeared to occur with similar frequency during days 0 to 2, 3 to 14, and 15 to 30, following the exposures of interest.

Table 4.4.2.1-2. Liver Adverse Events Definitions Based on Lab Measure or Lab Abnormal Flag

Measure	Criterion	Times Normal	Lab Measure N	Lab Abnormal Flag N
ALP	>= 393	3X	22,913	37,869
ALT	>= 236	2X	12,201	32,406
Tot Bilirubin	>= 1.0	3X	24,823	27,049
Gamma GT	>= 24	2X	485	14,092
Total			60,422	111,416

Table 4.4.2.1-3. Potential Liver-related Adverse Events per 10,000 by Treatment Group

Treatment Category				N	Potentially Associated Adverse Event Type															
PH6	HW Prev 1	HW Prev 2	Any Vaccine		Any DX		ALT		ALP		GAM		BIL		Any LAB		DX + LAB		DX or LAB	
					N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
				4,144,984	3,776	9.1	6,616	16.0	12,422	30.0	391	0.9	8,754	21.1	23,536	56.8	1,452	3.5	25,531	61.6
			Y	1,489,032	460	3.1	1,006	6.8	1,703	11.4	20	0.1	2,688	18.1	4,997	33.6	218	1.5	5,207	35.0
		Y		6,430	0	0.0	4	6.2	3	4.7	0	0.0	9	14.0	14	21.8	0	0.0	14	21.8
		Y	Y	11,975	0	0.0	8	6.7	8	6.7	0	0.0	13	10.9	24	20.0	0	0.0	24	20.0
	Y			164,951	52	3.2	118	7.2	201	12.2	8	0.5	237	14.4	498	30.2	20	1.2	523	31.7
	Y		Y	246,131	45	1.8	94	3.8	173	7.0	3	0.1	416	16.9	645	26.2	15	0.6	671	27.3
Y				252,590	100	4.0	215	8.5	326	12.9	7	0.3	400	15.8	836	33.1	43	1.7	880	34.8
Y			Y	483,064	206	4.3	389	8.1	696	14.4	8	0.2	984	20.4	1912	39.6	95	2.0	2,011	41.6
Any				6,800,061	4,641	6.8	8,450	12.4	15,536	22.8	437	0.6	13,502	19.9	32,467	47.7	1,845	2.7	34,886	51.3

Vaccine administration was associated with a markedly increased rate of allergic reactions for dogs on ProHeart 6 as well as for dogs on monthly heartworm preventative (Table 4.4.2.1-1). The rate of allergic reactions per 10,000 days at risk was similarly increased for vaccinated dogs compared with dogs receiving any one of the heartworm preventative drugs or those receiving no heartworm drug. Unlike liver-related AEs, allergic reactions occurred more commonly during days 0 to 2 following an encounter of interest.

There was no apparent association of immune-mediated or cardiovascular events with any of the heartworm preventatives or with vaccines, and the rate of these AEs was relatively low (Table 4.4.2.1-1).

The rate of mast-cell tumor, lymphosarcoma, or histiocytoma was generally < 3 AEs per 10,000 encounters (Table 4.4.2.1-4). ProHeart 6, whether administered alone or with a vaccine, was associated with a slight (~ 2 per 10,000 encounters), but higher rate of mast-cell tumors compared with administration of vaccines alone or any of the monthly heartworm preventatives. The rate of mast cell tumors per 10,000 days at risk was similarly elevated in dogs receiving ProHeart 6 compared with those receiving a vaccine or any one of the monthly heartworm preventative drugs. However, compared with dogs that had received 5 doses of ProHeart 6, there was no statistically significant difference in the age-adjusted risk of developing mast cell tumor for dogs that had received 1, 2, 3, or 4 doses of ProHeart 6 from Banfield veterinarians. That is, all of the odds ratios included 1.0. There was also no apparent dose-response relationship

between ProHeart 6 dose number and mast cell tumor risk. However, it is not known if any dogs had previously received ProHeart 6 from a non-Banfield veterinarian.

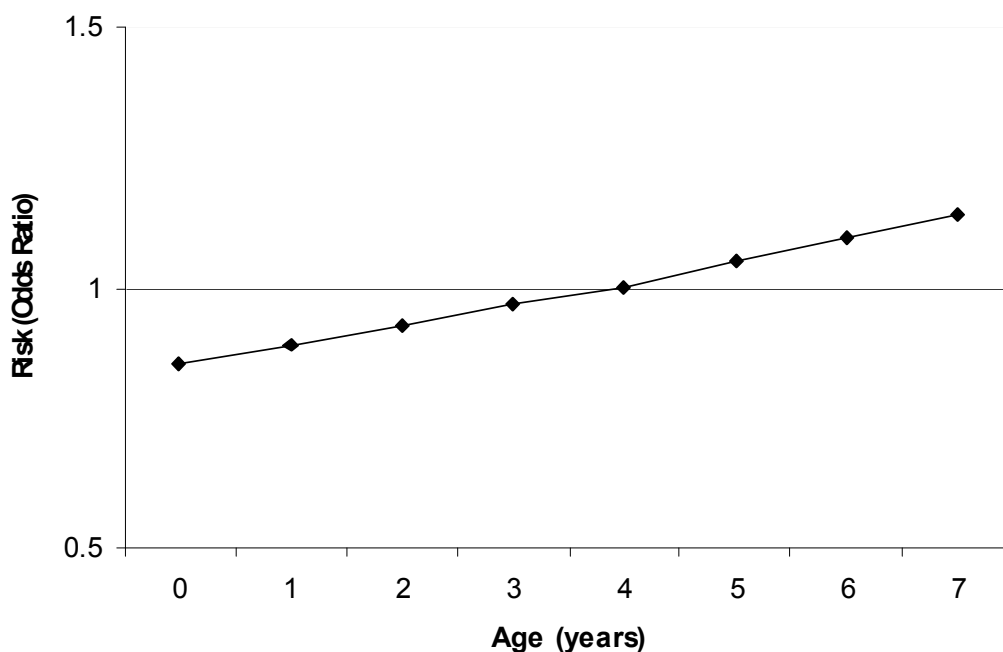
Table 4.4.2.1-4. Potential Cancer-related Adverse Events per 10,000 by Treatment Group

Treatment Category				N	Mast Cell Tumor		Lymphosarcoma		Histiocytoma	
PH6	HW Prev 1	HW Prev 2	Any Vaccine		N	Rate	N	Rate	N	Rate
				4,144,984	1,285	3.1	1,021	2.5	1,434	3.5
			Y	1,489,032	172	1.2	36	0.2	359	2.4
		Y		6,430	0	0.0	0	0.0	0	0.0
		Y	Y	11,975	0	0.0	0	0.0	2	1.7
	Y			164,951	10	0.6	12	0.7	45	2.7
	Y		Y	246,131	13	0.5	0	0.0	62	2.5
Y				252,590	54	2.1	13	0.5	89	3.5
Y			Y	483,064	90	1.9	14	0.3	101	2.1
Any				6,800,061	1,624	2.4	1,096	1.6	2,092	3.1

4.4.2.2 Multivariate Analyses

To control for potential confounding effects and to identify interactions between the variables, multivariate logistic regression models were constructed that included the following variables: heartworm preventative, vaccine, age, weight, non-steroidal anti-inflammatory (NSAID), steroid, and ProHeart 6 dose number. In the liver disease model, steroid use was associated with a 25% increased risk while ProHeart 6 was associated with a 15% reduction in risk. Each additional dose of ProHeart 6 was associated with an 8% reduction in liver disease risk. There was evidence of a strong interaction (effect modification) between age and ProHeart 6. Upon further examination of the relationship between ProHeart 6 dose number and age, the risk of liver disease increased with age, regardless of the exposure group. Using the best-fit equation generated from the logistic regression model, the relationship between the risk of liver disease associated with ProHeart 6 use was graphed as a function of age (Figure 4.4.2.2-1). ProHeart 6 administration was associated with a decreased risk of liver disease in dogs < 4 years of age, whereas there was an increased risk in dogs > 4 years of age.

Figure 4.4.2.2-1. Risk of Liver Disease by Age for ProHeart 6



Risk (1yr old) = $0.854 \times 1.043 = 0.89$; Risk(7yr old) = $0.853 \times 1.043^{**7} = 1.14$

Risk (age yrs) = $OR(\text{Proheart6}) * OR(\text{Proheart6*age interaction})^{**age}$

In the allergic reaction multivariate logistic regression model, ProHeart 6, Heartworm Preventative 1, vaccines, NSAIDs, and glucocorticoids, were all associated with an increased risk of allergic reactions; vaccine had the greatest affect. However, each additional dose of ProHeart 6 did not further increase the risk of allergic events.

Multivariate models for the risk of cancer indicated that ProHeart 6 was associated with a modest increase in the risk of mast cell tumor. It is not clear why NSAIDs were associated with a 423% increase in the risk of mast-cell tumor. Glucocorticoids were associated with a 182% increased risk of lymphosarcoma, probably because glucocorticoids are used as a treatment for this cancer. None of the heartworm preventatives were associated with the risk of histiocytoma. In the multivariate model for the risk of death, only Heartworm Preventative 1 was associated with an increased risk (23%), whereas ProHeart 6 was associated with a 71% reduction in risk of

death. There was no positive relationship between the number of ProHeart 6 doses administered and risk of death (odds ratio = 0.910).

4.4.2.3 Temporal Trends in Event Rates

The rate of cancer, deaths, liver disease, and allergic reactions, were evaluated by quarter of the year for ProHeart 6 and Heartworm Preventative 1, both with and without vaccines, to determine if AEs associated with ProHeart 6 increased during the 3rd quarter of 2004, as suggested by the FDA. No evidence was found to suggest that AE rates associated with either ProHeart 6 or Heartworm Preventative 1, when used without a vaccine, increased in the 3rd quarter of 2004. In contrast, there was an increase in the 3rd quarter of 2004 in the rate of allergic events associated with either ProHeart 6 or Heartworm Preventative 1 when administered with a vaccine.

Therefore, the increased rate of allergic events may be explained by 1 or more vaccines new to the market in mid-2004 that were used by Banfield veterinarians and that caused an increased rate of allergic reactions when administered with either ProHeart 6 or Heartworm Preventative 1 compared with administration of either of these heartworm preventatives without a vaccine.

4.4.3 Discussion

The results of these analyses involving almost 7 million dog encounters at Banfield clinics in the US did not reveal any clinically significant increase attributed to ProHeart 6 use in the risk of liver-related AEs, neurological disease, ocular disease, immune-mediated disease, cardiovascular disease, anaphylaxis, inflammatory bowel disease, or death, when compared with 2 commonly used monthly oral heartworm preventatives. While ProHeart 6 was associated with an increased rate of some liver-related AEs in the univariate analyses, this increased rate was not found in either the days at risk or in the multivariate analysis. In contrast, ProHeart 6, monthly heartworm preventatives, and vaccines were all associated with a clinically significant increased risk of allergic reactions in both univariate and multivariate analyses, especially during the first few days post-exposure.

The only potential AE studied that was independently associated with an increased risk following ProHeart 6 use in dogs was mast cell tumor. However, the absolute magnitude of the risk of mast-cell tumor associated with ProHeart 6 alone (2.1 events per 10,000 doses administered) or ProHeart 6 plus vaccine (1.9 events per 10,000 doses administered) was small. In addition, there was no statistically significant dose response relationship between the risk of

mast cell tumor and the cumulative number of doses of ProHeart 6 that a dog had received. Compared with the rate of mast cell tumor in dogs that had received a vaccine alone (1.2 events per 10,000 doses administered), the rate of mast cell tumor in dogs that had received ProHeart 6 plus a vaccine (1.9 events per 10,000 doses administered) does not appear to be clinically significant. There is no known mechanism that would explain how ProHeart 6 or any other heartworm preventative induces or promotes mast cell tumor in dogs, especially within 30 days of its administration.

Evidence was presented to show that the number of AEs associated with ProHeart 6 use increased in the 3rd quarter of 2004 compared with previous quarters. However, this increase primarily involved allergic reactions, was also observed in dogs that had received monthly oral heartworm preventatives, and was restricted to dogs that simultaneously received a vaccine. These findings suggest that any observed increase in adverse events associated with heartworm preventatives in the 3rd quarter of 2004, were likely due to one or more vaccines that were given with heartworm preventative drugs. Since nearly two-thirds of the heartworm preventative drugs studied were administered simultaneously or in close proximity with a vaccine, and since vaccines are generally associated with a higher rate of allergic reactions than are heartworm preventative drugs, AE reports involving administration of ProHeart 6 or other heartworm preventative drugs must be interpreted cautiously and take into account a dog's vaccine history.

4.4.4 Conclusions

In summary, the safety profile of ProHeart 6 appears similar to that of 2 commonly used monthly oral heartworm preventatives. The results of this study provide no support for the withdrawal of ProHeart 6 from the veterinary market. Lack of compliance is recognized as a common reason for lack of efficacy for both human and veterinary drugs. Since the likelihood of exposure of dogs to *Dirofilaria immitis* infected mosquitoes is common during many months of the year, drugs are needed that prevent heartworm infection for an extended period of time, thus obviating the need for owners to remember to retreat their dog. The results of this study indicate the risks associated with ProHeart 6 use are few and similar to that for monthly oral heartworm preventatives that only offer protection from heartworm infection for a period of 30 days.

4.5 Field Efficacy

4.5.1 Overview

While the clinical efficacy of ProHeart 6 has been established in controlled laboratory and field studies, evaluation of efficacy under conditions of commercial use after launch can be complicated by many confounding factors. These include heartworm testing protocols, the age at which dogs commence a ProHeart 6 program, and timing of change from other prophylaxis to ProHeart 6.

Products for heartworm prophylaxis have been available in veterinary medicine for decades, initially as daily oral treatments; later, a range of monthly oral and topical treatments were introduced with ivermectin, selamectin, or milbemycin oxime as the active ingredient.^{2,3,5} Some breeds of dogs exhibit toxic signs at doses of ivermectin and/or milbemycin oxime that are well tolerated in most other breeds, and a genetic basis for this sensitivity has been identified.^{10,53,54,55,56,57,58,59} Moxidectin can be used safely in these breeds based on FDAH clinical studies.

4.5.2 Compliance

A high level of efficacy is found with these therapeutic options in controlled studies. However, under field conditions, an increasing incidence of heartworm infections in dogs in the US in the 1990s was reported with approximately 240,000 dogs testing heartworm positive in 2001. Surveys of dog owners have shown that compliance (ie, reliable administration of monthly treatments by owners) is problematical. Despite reminder systems such as calendar stickers, a survey in the US in 2000 found that >80% of participants had failed on multiple occasions to give their dogs the monthly preventative on the indicated day, and about one-third of participants completely missed the monthly dosage. Approximately one-fifth of the participants had missed giving their dogs the monthly oral heartworm preventative and then stopped altogether.⁶⁰ Another survey conducted in 2001 found that only 55% of dog-owning households in the US were using heartworm prevention, which was down from a high of 66% in 1998, despite heartworm having been diagnosed in all states.⁶¹ Similarly, Yabsley et al. reported an increased prevalence of heartworm in shelter dogs in South Carolina in 1999-2000 (12.7%) versus 1991-1992 (8.7%).⁶² Compliance with dosing schedules is a limiting factor in the control of heartworm infections in the dog population.

Several years ago, Cummings et al. demonstrated that clinic compliance failure is generally higher than predicted by individual hospitals before their records are examined.⁶³ A veterinary practice survey conducted by Fort Dodge veterinary technicians at Michigan State in 2004 showed a similar picture.⁶⁴ Compliance was better with ProHeart 6 than with the other heartworm preventatives studied. Average compliance was 58% for ProHeart 6 (11 clinics), 45% for Heartgard Plus (the most widely used preventative)(16 clinics), 50% for Sentinel (6 clinics), and 37% for Interceptor (3 clinics).

Moxidectin is a poor substrate for P glycoprotein compared with other macrocyclic lactones.^{59,65,66} It can be used safely in ivermectin sensitive Collies. It is effective in the face of ivermectin resistance in nematodes. Additionally, recent work has demonstrated that with use of moxidectin, unlike some other compounds, animals are not more susceptible to infection with filariid parasites after product withdrawal.⁶⁷ This provides an additional safety factor, if owners are late in returning for treatment. Moxidectin has retroactive activity against *D. immitis* larval stages for 3 months, again providing a safety factor, if owners are late in returning for treatment.

4.5.3 Field Efficacy from 2001 to 2004

Field experience with ProHeart 6 in the US is limited to the time period from June 2001 to August 2004. There is a time-lag between infection and the first possible heartworm diagnosis of minimally 5 to 6 months. Therefore, the field evaluation of ProHeart 6 efficacy essentially spans the years 2002 to mid 2004. Proving “lack of efficacy” of any heartworm preventative product in client-owned dogs is inherently difficult, unless the dog is started on a prevention program at 6- to 8-weeks of age, remains on the product year-round for life and clinic records indicate the owner acquired the recommended number of doses. With orally or topically administered products, one is seldom confident the owner properly administered all of the doses. Owner compliance is greatly improved with ProHeart 6, but switching products tends to complicate the picture. To prove with reasonable confidence that a new product is completely effective, the dog must be tested prior to switching products and within 4 months later. If the dog is heartworm positive during this 4-month period, the original product failed. If the dog is positive during the next few months, it is virtually impossible to determine whether the dog was infected before or after switching products. Voluntary reports of product inefficacy to FDA are summarized in Table 4.5.3-1.

Table 4.5.3-1. Voluntary Reports of Product Inefficacy Against Larval Heartworm

Active	2001	2002	2003	2003 Market Share
IVM	16	108	13	6%
IVM+PYR	21	195	137	37%
MILB	0	0	748	21%
MILB+LUF	0	0	347	8%
SEL	16	1162	888	4%
ProHeart 6	0*	70	196	24%

* indicates year of launch

IVM = ivermectin; PYR = pyrantel; MILB = milbemycin oxime; LUF = lufenuron; SEL = selamectin

The 2003 market share information is indicative of the numbers of dogs treated and provides context when interpreting the significance of the number of reports. When ProHeart 6 is compared with the market leaders the adjusted efficacy rates for 2003 (when market share information is available) are equivalent or lower than ivermectin plus pyrantel, or milbemycin.

The overall reporting rate for ProHeart 6 is low at 1 report per 41,000 doses through marketing year 2003. Further, only 10% have a history that justifies classification as a potential efficacy concern. The majority are thought to be associated with a misunderstanding of the heartworm life cycle in relation to testing procedures and limitations. When potential dosing errors, administration errors, and mixing and storage errors are considered, the low reporting rate of failures in efficacy appears to be within acceptable parameters.

FDAH guarantees the efficacy of ProHeart 6 as a preventative for heartworm disease. This program encourages veterinarians to contact the company about potential concerns related to efficacy. When received, these reports are submitted to the FDA unfiltered. Based on unfiltered reports and doses sold, regardless of whether FDA or FDAH reports are considered, ProHeart 6 delivers a high level of efficacy under field use conditions.

4.5.4 Tuskegee University Experience with ProHeart 6

Tuskegee University is located in Macon County, in eastern Alabama. It is a teaching hospital and unlike some universities which are predominantly referral centers, Tuskegee operates largely as a community practice. Most pets in the area receive their primary care at this hospital, so it is reflective of the population of dogs receiving preventative care, rather than specialist or tertiary care levels.

4.5.4.1 Retrospective Study: Tuskegee University School of Veterinary Medicine

The effectiveness of heartworm preventatives in this endemic area was studied during the period of 2000-2004 (unpublished data).⁶⁸ In 2001, 97.7% of the dogs on a heartworm preventative received an oral product, while 1.0% received ProHeart 6. By 2004, 82.9% received an oral product and 17.1% received ProHeart 6. During this time, the percentage of heartworm-positive dogs dropped from 14.0% (of 898) to 5.8% (of 833), and the percentage of dogs treated with Immiticide dropped from 5.2 to 3.0. More importantly, at no time was any dog receiving ProHeart 6 diagnosed as heartworm-positive, while dogs on the oral products accounted for 15.8%, 29.4%, and 50.0% of the dogs that received a first, second, or third Immiticide treatment, respectively. This study also reviewed owner compliance in a limited number of dogs that received Immiticide treatment. Of the 100 dogs studied, 61.5% of the dogs receiving ProHeart 6 were up-to-date on purchasing their heartworm product, while only 17.2% of those on oral products were compliant. Furthermore, it is known that 100% of the dogs on ProHeart 6 received their full treatment, whereas the number of oral doses administered is not known.

While this study represents a limited number of dogs, it supports the position that ProHeart 6 is highly effective in preventing heartworm infection, and along with increased owner compliance, has led to a decrease in the number of dogs requiring Immiticide treatment.

These results indicate that ProHeart 6 introduction into the canine heartworm preventative market is helping to achieve the desired goals. By overcoming the problems with owner compliance with monthly dosing, ProHeart 6 not only protects the individual dog to which it is administered, but also provides the veterinary professional with an important medicine to reduce the prevalence of heartworm in the canine population.

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6.0 APPENDICES

APPENDIX 6.1

MOXIDECTIN OVERVIEW

Pharmacology – Mechanism of Action

The mechanism of action of moxidectin is multifaceted and continues to be evaluated in laboratory studies. Moxidectin has been shown to have activity at the γ -aminobutyric acid (GABA)-A receptor-chloride channel complex resulting in an influx of chloride ions and hyperpolarization of cell membranes¹. This hyperpolarization causes the nerve fibers to be less excitatory and results in paralysis and death of the parasitic organism. The specificity of moxidectin for the parasite versus the mammalian host results from 1) this compound having low affinity for mammalian GABA-gated chloride channels², and 2) the observation that GABA-containing neurons and receptors are found in mammals in the central nervous system, whereas in arthropods and nematodes these are found in the neuromuscular junctions of the peripheral nervous system and thus are more accessible to a blood-borne therapeutic. Another proposed mechanism of action for moxidectin is through activity at glutamate-gated chloride ion channels also resulting in paralysis and death of the organisms^{3,4}.

In dogs, the approved, oral monthly dosage of moxidectin for prevention of heartworm is 3 $\mu\text{g/kg}$; the approved subcutaneous (sc) dosage of moxidectin as ProHeart 6 is 0.17 mg/kg administered every 6 months.

Pharmacokinetics and Drug Metabolism

A series of studies was conducted in various animal species to characterize the absorption, distribution, metabolism, and excretion of moxidectin after oral administration. In rats, moxidectin was absorbed at a moderate rate, with a mean time to peak concentration (t_{max}) of 4.8 hours⁵. The bioavailability of moxidectin was moderate at 19% and the apparent terminal half-life ($t_{1/2}$) was long (22.9 to 44.6 hours). After intravenous (IV) administration in rats, the clearance of moxidectin was low and the steady-state volume of distribution (V_{dss}) was high, indicating that the compound is widely distributed to tissues. In beagle dogs after an oral dose of 90 $\mu\text{g/kg}$ moxidectin in tablet form, the peak concentration (C_{max}) was 29.8 ng/mL with a t_{max} of

8 hours and a serum half-life of 8.1 days⁶. A single sc injection of the approved dosage of 0.17 mg/kg moxidectin as ProHeart 6 to beagle dogs resulted in a serum $C_{\max}$ of 5.1 ng/mL, a $t_{\max}$ of 7 to 10 days, an $AUC_{0-\infty}$ of 217 ng•day/mL, and a half-life of approximately 35 days⁶. Moxidectin did not accumulate in the serum of dogs after injection with ProHeart 6 once every 6 months for a total of 6 injections⁶. A recent study of the administration of moxidectin once in the diet to female dogs at 45 ppm (corresponding to approximately 1 mg/kg as used in the 1-year toxicology study) resulted in a $C_{\max}$, $AUC_{0-\infty}$, and half-life values of 290 ng/mL, 678 ng•day/mL and 8.3 days, respectively. Administration in the diet at this same level for 21 days to dogs resulted in a plasma concentration of 278 ng/mL approximately 24 hours after the previous feeding (ie, trough level). The previous 2 ongoing diet pharmacokinetic studies in the dog, and an ongoing 28-day pharmacokinetic study in rats by the diet route were initiated because of FDA concerns regarding the safety of ProHeart 6, and to document the high degree of systemic exposure to moxidectin achieved in the toxicology studies conducted by the diet route.

After oral administration in rats, the major site of moxidectin distribution was fat⁵. The $t_{1/2}$ in fat was 11.5 days. Moxidectin represented the major component of total radioactivity in tissues and feces, and was primarily eliminated through feces (60% to 91% of the recovered dose over 7 days)⁵. Studies in other species such as cattle, sheep and horses have confirmed the distribution of moxidectin primarily to fat and the fecal route of excretion⁷. Six (6) metabolites were isolated from rat liver and fecal samples, none of which accounted for more than 10% of the radioactivity in tissue samples collected from animals 7 days after dosing⁵. Therefore, these metabolites are not of toxicologic concern because of the low levels observed. Similarly limited metabolism was noted in cattle, sheep and horses⁷ and in rat and human liver microsomes⁸ where the metabolites were characterized as hydroxylations at various positions.

In human liver microsomes, there was no significant inhibition of selected cytochrome P450 (CYP) enzyme activities (CYP2A6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4) at the highest substrate concentration used (100 μ M)⁹. Human CYP enzymes were used in this study since they are the best characterized. Based on plasma concentrations at efficacious doses and the high substrate concentrations, clinical metabolic drug-drug interactions for all the CYPs tested are unlikely to occur.

P-glycoproteins (P-gps) are transmembrane proteins which transport a wide variety of endogenous and exogenous molecules across cell membranes. Moxidectin, as do other macrocyclic lactones, acts as a substrate for P-gps¹⁰. This mechanism has been found to be of clinical importance in the development of nematode resistance to ivermectin and plays a significant role in breed sensitivity¹¹. A mutation in the P-gp gene of ivermectin-sensitive Collie dogs has been shown to be responsible for ivermectin-induced CNS toxicity¹². Moxidectin, however, was well-tolerated by these ivermectin-sensitive dogs. Moxidectin transport, therefore, is less dependent on P-gp and subsequent toxicity is less likely to be altered by factors which alter P-gp activity.

Toxicology

The toxicologic profile of moxidectin administered by the oral route has been well established. This profile is relevant to other routes of administration because of limited metabolism of moxidectin in the body and an understanding of its pharmacokinetics by different routes of administration. The toxicologic program for moxidectin was reviewed during the 45th meeting of the Joint Expert Committee on Food Additives¹³ and was subsequently published⁷. In addition, this toxicology program was deemed sufficient by regulatory authorities to proceed with Phase 1 trials of oral moxidectin in normal, human volunteers in preparation for efficacy studies in people in countries where onchocerciasis is endemic. The toxicology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations.

In Vitro Side-Effect Profiling

Moxidectin and moxidectin microspheres (as present in ProHeart 6) were recently tested in vitro for binding activity at 64 different biological receptors¹⁴, based on some of the safety concerns raised by the FDA. This assay is commonly used in drug discovery and development to identify any ancillary pharmacologic activities of a molecule which may result in undesirable biological effects. A final concentration of 10 ng/mL moxidectin was tested, which is approximately two-fold the average C_{max} value in serum of dogs after a subcutaneous injection of ProHeart 6 at the clinical dosage of 0.17 mg/kg. The receptors tested included those for neurotransmitters and neurotransmitter-related receptors, ion channels, steroids, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides and enzymes. Moxidectin in either form did not significantly inhibit the binding of appropriate radio-ligands to these receptors, indicating a lack of binding activity for moxidectin. These results are consistent with the absence of undesirable pharmacologic and toxic effects of moxidectin in animal studies at plasma levels many fold those required for efficacy.

Single-Dose Studies

Single-dose toxicology studies of moxidectin were conducted to assess effects after a single administration of large doses in the event of accidental overdose and to assist in selection of dose levels for subsequent repeat-dose toxicology studies. In single-dose toxicity studies of mice and rats given moxidectin orally, the median lethal dosage (LD₅₀) values were 118 mg/kg in male mice¹⁵, 42 to 78 mg/kg in female mice^{16,17}, and 122 and 97 mg/kg in male and female rats¹⁸, respectively. After a single sc dose, LD₅₀ values were 285 and 247 mg/kg in male and female mice¹⁹, respectively, and > 640 mg/kg in rats²⁰. Common clinical signs in these studies were decreased activity, tremors, and prostration. The decreased toxicity with sc dosing is likely the result of a lower C_{max} and daily exposure, albeit of longer duration, as compared to oral gavage dosing. These studies demonstrate a large margin of safety for ProHeart 6 in which the approved sc dose in the dog is 0.17 mg moxidectin/kg, less than 3700-fold the lethal sc dose in the rat. Field results from the accidental and sometimes intentional overexposure of dogs orally to moxidectin likewise demonstrate a large margin of safety. Oral overdoses occur when a product intended for use in horses is administered to dogs. In these cases, the dogs can receive up to a 63-fold higher dose orally (ie, 10.7 mg/kg) than the 0.17 mg moxidectin/kg when given sc as ProHeart 6, but in most cases the actual dose is not known. From 1997 to 2004, FDAH received approximately 250 such cases. In all cases the events were characterized by a wide range of neurological symptoms. In those cases where FDAH was informed, the dogs had typical hematology or serum panels. In 90% of these cases, the animals fully recovered whereas the remainder died. These cases demonstrate that neurological symptoms induced by high, oral doses of moxidectin in dogs are typically survivable without any nonneurologic toxic effects.

Repeat-Dose Studies

Repeat-dose oral (diet) toxicity was evaluated to assess more long-term consequences of repeated, daily oral exposure to moxidectin. The objective of these studies was to dose the animals high enough to identify potential toxic effects, and to include lower doses so as to assess a dose-response relationship and identify a dose without significant adverse effects (i.e., No-Observed-Adverse-Effect-Level; NOAEL).

The following studies were conducted: 4-week studies in mice, rats, and dogs; 13-week studies in rats and dogs, and a 1-year study in dogs. Moxidectin was administered in the diet providing for a continuous exposure for the duration of each study, which is a significant exaggeration of the exposure of dogs to one sc dose of 0.17 mg moxidectin/kg as ProHeart 6 every 6 months.

Evaluations consisted of mortality, clinical observations, body weight, food consumption, hematology, clinical chemistry (except mice), organ weights, and macroscopic and microscopic examinations of organs and tissues. Ophthalmic examinations and urinalysis were also included in the dog studies.

Mice

In the 4-week study in mice, doses in the diet were 33.7, 75, 100, 125, and 150 ppm²¹. Mortality occurred at ≥ 75 ppm. Microscopic examination did not reveal the cause of death in these animals. Clinical observations were tremors, hypersensitivity to touch, and urine-stained fur at ≥ 75 ppm. Body weights and body-weight gains were decreased at ≥ 100 ppm. There were no other compound-related effects. Based on mortality, the no-observed-adverse-effect-level (NOAEL) was 33.7 ppm (6.9 mg/kg/day).

Rats

In the 4-week study in rats, doses in the diet were 100, 200, 400, and 600 ppm²². Mortality occurred at ≥ 200 ppm and resulted from anorexia based on microscopic examination. Clinical observations included ataxia, tremors, salivation, piloerection, and diuresis at ≥ 200 ppm, as well as decreased body weight, body-weight gain, and food consumption. There were no other compound-related findings in rats that survived the study. Based on mortality, the NOAEL was 100 ppm (12.2 mg/kg/day).

In the 90-day study in rats at diet doses of 25, 50, 100 and 150 ppm, mortality occurred for 3 females at the highest dose, 150 ppm²³. Microscopic examination did not reveal the cause of death for these animals. Clinical observations included hypersensitivity to touch at 100 ppm, and lethargy, anorexia, aggressive behavior, loss of righting reflex, ataxia, tremors, and urine-stained coat at 150 ppm. Body weight and body-weight gain were decreased in males at 100 ppm or more and in females at 150 ppm. Food consumption was decreased in males and females at 150 ppm. Adrenal gland and kidney weights were increased in females at ≥ 100 ppm, but there were no compound-related macroscopic or microscopic findings in these or any other organs or tissues. The NOAEL was 50 ppm (3.9 mg/kg/day).

Dogs

In the repeat-dose toxicity studies in beagle dogs, ophthalmic examinations and urinalysis were also included for evaluation of potential toxic effects.

In the 4-week study, there was no mortality at doses in the diet of 20, 80 and 160 ppm²⁴. The dose of 160 ppm was toxic, based on debilitating clinical observations, and the dose was reduced to 50 ppm. Clinical observations included tremors, languid appearance, ataxia, emesis, and mydriasis at ≥ 80 ppm. Testes weights were decreased at ≥ 80 ppm. Microscopic findings were decreased spermatogenic activity at ≥ 80 ppm and decreased colloid in the thyroid gland in males at 80 ppm. These findings may have been related to variations in age of maturation (study dogs were 5 to 6 months old at study termination) and were not seen in the 1-year toxicity study in dogs. Based on the testicular findings, the NOAEL in this 4-week study was 20 ppm (0.8 mg/kg/day).

In the 90-day toxicity study in dogs at diet doses of 10, 30 and 60 ppm, there was no mortality and clinical observations included lacrimation at ≥ 10 ppm, languid appearance and tremors at 10 and 60 ppm, thin appearance at ≥ 30 ppm, and slight salivation and slight ataxia at 60 ppm²⁵. At 60 ppm, alanine aminotransferase (ALT) was increased in 1 male and 1 female, and serum alkaline phosphatase was increased in 3 males and 3 females compared with pretreatment and/or control values (increases were small in magnitude and not toxicologically significant). However, there were no compound-related macroscopic or microscopic changes in the liver or any other tissues or organs. Based on the absence of toxicologically significant findings at any tested concentration, the NOAEL in this 90-day study was 60 ppm (1.6 mg/kg/day).

In the 1-year toxicity study in dogs at diet doses of 10, 20 and 45 ppm, there was no mortality²⁶. Decreased ovarian weights were observed at 45 ppm; however, the absolute weights were within reference or historic control ranges and the decreases were not considered to be biologically important. There were no compound-related effects on clinical chemistry or hematology parameters, and no compound-related microscopic findings. Based on the absence of toxicologically significant findings at any tested concentration, the NOAEL in this study was 45 ppm (1.1 mg/kg/day).

Interim analysis at day 21 in an ongoing 28-day diet pharmacokinetic study of moxidectin in dogs at a concentration of 45 ppm in feed (approximately 1 mg/kg, the NOAEL in the 1-year dog toxicity study) revealed a serum concentration of 278.5 ng/mL 24 hours after the preceding dose in feed (ie, trough level). This concentration is not yet at steady state, but would correspond to a daily AUC of 278.5 ng•d/mL which would represent the minimal daily exposure to moxidectin

for most of the duration of the 1-year toxicology study in dogs, or an AUC of 50826 ng.day/mL over a 6-month period, the retreatment interval for ProHeart 6.. This value is approximately 234-fold the AUC_{0-∞} (217 ng•d/mL) observed for moxidectin after a single sc dose in dogs of ProHeart 6.

Carcinogenicity Studies

Mice

A 2-year carcinogenicity study was conducted in male and female mice at diet doses of 15, 30, and 60 ppm (lowered to 50 ppm due to high mortality at week 9)²⁷. Mortality was increased in females at doses of 60/50 ppm during the last 13 weeks of the study. There were no compound-related findings in hematology values, organ weights, or at macroscopic or microscopic examination. There was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

Rats

A 2-year carcinogenicity study was conducted in male and female rats at diet doses of 15, 60 and 120 ppm (lowered to 100 ppm due to high mortality in females at week 8)²⁸. There were no compound-related findings for hematology values, organ weights or at macroscopic or microscopic examination; there was no evidence of moxidectin-related target-organ toxicity or tumorigenicity.

Reproductive and Developmental Toxicity Studies

Reproductive toxicity was evaluated in developmental studies of rats²⁹ and rabbits³⁰ dosed orally by gavage and in pilot³¹ and definitive³² multigeneration diet studies. Maternal toxicity was evident at ≥ 10 mg/kg/day in the rat developmental study, 125 ppm (calculated dosage averaging between 10.9 and 12.0 mg/kg/day) in the rat pilot multigeneration study, and at ≥ 5 mg/kg/day in the rabbit developmental study; the toxicity consisted primarily of decreased body weight and/or food consumption. At maternally toxic dosages (≥ 10 mg/kg/day) in the rat developmental study only, there were statistically significant increases in the number of fetuses with malformations and/or variations, largely reflective of increases in cleft palate and reversible delays in ossification. There was decreased fetal and/or pup survival at 10 mg/kg/day in the rabbit developmental study and at doses of ≥ 10 ppm (calculated maternal dosage of ≥ 0.8 mg/kg/day) in the rat pilot 1-generation and 3-generation studies. The reproductive NOAELs were

5 mg/kg/day in both the rat and rabbit developmental studies and was 5 ppm (0.4 mg/kg/day) in the rat 3-generation study. Therefore, moxidectin was not considered teratogenic in these species. This conclusion is consistent with that of the FDA Center for Veterinary Medicine, which concluded that moxidectin is neither a selective developmental toxicant nor a teratogen in rats or rabbits.

Genotoxicity Studies

Moxidectin was tested for genotoxicity in 4 in vitro and 2 in vivo universally recognized test systems. These assays assessed the ability of moxidectin to cause gene mutations, chromosome damage, and increased DNA repair which may be related to the carcinogenic potential of the test article. Moxidectin was negative in the following assays for genotoxicity: bacterial reverse mutation assay in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP-2 uvrA-)³³; mammalian cell mouse lymphoma (L5178Y thymidine kinase) assay³⁴; chromosome aberration assay in Chinese hamster ovary cells³⁵; unscheduled DNA synthesis assay in primary rat hepatocytes³⁶; in vivo micronucleus assay in mouse bone marrow cells³⁷; and the in vivo chromosome aberration assay in rat bone marrow cells³⁸. The in vivo studies were conducted using the oral route of administration. The results from these studies indicate that moxidectin is not a genotoxic compound.

Experience with Oral Moxidectin in Human Volunteers

A study in healthy, male volunteers was conducted to assess the pharmacokinetics and safety of moxidectin given orally as part of the development of this compound for treatment of onchocerciasis in humans³⁹. A total of 37 subjects in this study were treated with single doses of 3 mg to 36 mg (approximately 50 µg/kg to 600 µg/kg). The $t_{1/2}$ ranged from 19.9 to 37.4 days, the C_{max} at 36 mg was 296 ng/mL, and the distribution of moxidectin was extensive, as indicated by a large apparent volume of distribution. The C_{max} observed for humans dosed orally with 36 mg moxidectin was 59-fold the C_{max} observed in dogs dosed sc with the clinical dosage of 0.17 mg/kg moxidectin as ProHeart 6, and exposure (based on AUC) was approximately 6-fold the exposure in dogs administered ProHeart 6.

There was no significant relationship between the overall number of adverse events and the dose of moxidectin administered. Safety assessments indicated that moxidectin was safe and well tolerated, with a slightly higher incidence of transient, mild, and moderate central nervous system adverse events (dizziness and somnolence) as compared to placebo. There were no clinically significant changes in vital signs, clinical chemistries, physical examinations or

electrocardiograms. The conclusion was that moxidectin was safe and well tolerated in humans after single, oral doses of 3 mg to 36 mg.

Conclusions

Moxidectin is a potent antiparasitic therapeutic that acts to paralyze susceptible organisms through activity at GABA- and glutamate-gated chloride ion channels. Moxidectin has a long half-life, a high volume of distribution (predominantly distributing to fat), shows little metabolism, and is excreted primarily in the feces. These characteristics of moxidectin appear constant across the mammalian species studied, including humans. In single-dose toxicity studies, the lethal sc dose in rats was more than 3700-fold the efficacious dose of moxidectin given as ProHeart 6 to dogs. In repeat-dose diet toxicity studies in mice, rats, and dogs of durations up to 2-years in mice and rats, and 1-year in dogs, no target organs of toxicity were identified. There were no significant adverse histologic or biochemical effects on any organ system including the cardiovascular, gastrointestinal, hepatobiliary, genitourinary and central nervous systems. There were no proliferative lesions identified in any tissue which may signal the development of neoplasia, and no increase in tumors in mice or rats. The toxicity of moxidectin manifested itself at high doses in clinical signs such as lethargy, ataxia, tremors and mortality (rodents only) with concomitant decreases in food consumption and body weight. Such clinical signs of hypoexcitation are expected and are consistent with an exaggerated pharmacologic effect of moxidectin mediated via the GABA-receptor. Moxidectin was not genotoxic or carcinogenic, and was without reproductive or developmental toxicity. The NOAEL in the rat 2-year study was 12.2 mg/kg/day; the NOAEL in the dog 1-year study was 1.1 mg/kg/day.

Based on ongoing pharmacokinetic studies in the dog, a single dose of moxidectin in the diet at approximately 1 mg/kg (NOAEL in the 1-year dog study), when extrapolated to infinity, results in an overall exposure over 3-fold that of a single SC dose of ProHeart 6. Repeated dosing at this level resulted in an estimated daily exposure at least 1.3-fold the total exposure observed after a single SC dose in dogs of ProHeart 6 ($AUC_{1\text{day}}$ of 278.5 versus $AUC_{0-\infty}$ of 217 ng•days/mL, respectively). The total exposure over the duration of the 1-year study, therefore, would be approximately 365 times the daily AUC, or more than 450-fold a single SC dose of ProHeart 6. Moxidectin was also found safe in a human clinical trial after a single oral dose of

36 mg, which resulted in a C_{max} and AUC approximately 59- and 6-fold, respectively, that was observed in dogs dosed SC with the clinical dosage of 0.17 mg/kg as ProHeart 6.

Based on the toxicology studies of moxidectin where the dose, dosing duration, and resulting systemic exposure to moxidectin were significantly exaggerated without inducing significant adverse effects, the single, clinical sc administration of 0.17 mg moxidectin/kg as ProHeart 6 to dogs would be predicted to be without significant adverse effects.

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APPENDIX 6.2

BIOGRAPHICAL SKETCH

Name: Alexander de Lahunta	Title: James Law Professor of Anatomy	Birthdate: 3 December 1932
Education:		
Cornell University	DVM	1958
Cornell University	PhD	1963
		Veterinary Medicine
		Veterinary Anatomy

Professional Experience:

Veterinary Practice 1958-1960: Concord N.H. Faculty member in Department of Anatomy, New York State College of Veterinary Medicine, Cornell University 1960 to date; Chairman - Department of Clinical Sciences 1977-1986; Chairman - Department of Anatomy 1986 to 1991; Consultant in clinical neurology to Teaching Hospital 1963 to date; Diplomate - Neurology Specialty - American College of Veterinary Internal Medicine.
James Law Professor of Anatomy, 1992.

Awards:

National Teaching Award - Basic Sciences: Student AVMA 1991
Norden Teaching Award - 1973, 1984, 1992, 2001
ACVIM Dr. Robert W. Kirk Distinguished Service Award, 2000
Honorary Member - American College of Veterinary Pathologists, 2002

Research:

Correlation of clinical neurological signs with specific anatomic locations of lesions in nervous system.
Establishment of reliable data to differentiate between the various diseases that affect the nervous system in the different species of domestic animal.
Recognize and publish new diseases of the nervous system.
Recognize diseases of the nervous system of domestic animals that are models for similar diseases in man.

Textbook Publications:

Evans, H.E. & de Lahunta, A. - Miller's Guide to the Dissection of the Dog, 5th edition. 2000, W.B. Saunders Co., Phil.

de Lahunta, A. - Veterinary Neuroanatomy and Clinical Neurology, 2nd. edition. 1983, W.B. Saunders Co., Phil.

Noden, D. and A. de Lahunta - The Embryology of Domestic Animals, Developmental Mechanisms and Malformations 1985, Williams & Wilkins, Baltimore.

de Lahunta, A. and R.E. Habel - Applied Veterinary Anatomy 1985, W.B. Saunders, Phil.

Summers, B.A., J.F. Cummings and A. de Lahunta - Veterinary Neuropathology 1995, Mosby, St. Louis

260 Publications in refereed journals.

January 3, 2005

Teaching Responsibilities:

Block I: Lectures, Tutor, Gross dissection labs, Radiology labs. (Sept – Nov)

Vet Med 521: Neuroanatomy and Clinical Neurology
Entirely my responsibility, first 8 weeks of spring semester.

Block V: Applied Anatomy taught throughout most of Block V throughout the latter half of the spring semester and all of the fall semester.
Neuropathology – 12 hours, last 3 weeks of fall semester.

Vet Med 606: Advanced Neurology taught twice, in both of the last two quarters of the spring semester.

Neuropathology Seminar: One hour per week all year. Primarily for pathology residents.

Clinical Neurology Rounds: 12 hours per week all year.

Consultant to the Teaching Hospital for neurology patients:
Examine patients daily, all year long. This is done early each morning and often attended by interested students.

I regularly receive nervous tissue from practitioners and pathologists for study or consultations and videotapes from practitioners and owners for study and diagnosis. My lab is set up for blocking these nervous tissues and photographing the lesions. Tissue sections are cut and stained by the histology lab in the pathology section.

I study these sections and report results to the contributor. This is a valuable source of material for the teaching program both at the DVM and resident level and has led to the discovery of many new disorders.

APPENDIX 6.3

REBAR, ALAN H., DVM, PhD, DACVP

1/05

EDUCATION

DVM, 1973, Purdue University

Ph.D. (Clinical Pathology), 1975, Purdue University

Internship/Residency (Pathology), 1976, Purdue University

Diplomate – American College of Veterinary Pathologists (Clinical Pathology), 1978

EMPLOYMENT

July 1996 – Present	Dean, School of Veterinary Medicine, Purdue University
July 1989 – June 1996	Associate Dean for Research, School of Veterinary Medicine, Purdue University
July 1995 – June 1996	Head, Veterinary Pathobiology, School of Veterinary Medicine, Purdue University
July 1993 – June 1995	Interim Department Head, Veterinary Pathobiology, School of Veterinary Medicine, Purdue University,
July 1987 – June 1995	Acting Director of Continuing Education, School of Veterinary Medicine, Purdue University
July 1987 – July 1989	Director of Research Programs Development, School of Veterinary Medicine, Purdue University
1986 – Present	Director, Veterinary Cytology Resource Center, Purdue University,
July 1983 – Present	Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
July 1979 – July 1987	Co-Director of Clinical Pathology Laboratory, School of Veterinary Medicine, Purdue University
July 1979 – June 1983	Associate Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
Sept. 1977 – July 1979	Clinical Pathologist, Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico
Jan. 1976 – Aug. 1977	Director of Clinical Pathology Laboratory, School of Veterinary Medicine, Purdue University

- Jan. 1976 – Aug. 1977 Assistant Professor of Clinical Pathology, School of Veterinary Medicine, Purdue University
- Sept. 1974 – Dec. 1975 NIH Postdoctoral Fellow. (Ultrastructural studies on cobalt and isoproterenol induced cardiomyopathy in swine.) School of Veterinary Medicine, Purdue University,
- Sept. 1972 – Aug. 1974 Graduate Instructor, Veterinary Pathology, School of Veterinary Medicine, Purdue University
- May 1973 – Sept. 1973 Staff Veterinarian, Colonial Oaks Animal Hospital, Gainesville, Florida

HONORS

- Indiana Veterinarian of the Year Award. Presented by the Indiana Veterinary Medical Association, 2002.
- The Waltham Award given in recognition of outstanding activities or contributions by a veterinarian that have resulted in the improvement of the well-being companion animals in the international veterinary community. Presented by the American Animal Hospital Association, 2001.
- The Gaines Cycle Fido Award for outstanding contributions to small animal medicine and surgery. Presented by the American Animal Hospital Association, 1994.
- Distinguished Alumnus Award, School of Veterinary Medicine, Purdue University, 1990.

REPRESENTATIVE PUBLICATIONS (more than 115 overall)

1. Herbert, R.A., Stegelmeier, B.S., Gillett, **Rebar, A.H.**, Carlton, W.W., Singh, G., and Hahn, F.F.: *Plutonium-induced proliferative lesions and pulmonary epithelial neoplasms in the rat: immunohistochemical and ultrastructural evidence for their origin from type II pneumocytes*. Vet Pathol 31(3):366-374, 1994.
2. Stegelmeier, B.L., Gillett, N.A., Hahn, F.F., **Rebar, A.H.**, and Kelly, G.: *Expression of transforming growth factor alpha and epidermal growth factor receptor in rat lung neoplasms induced by plutonium-239*. Radiat-Res, Nov, 140(2):191-8, 1994.
3. Lipscomb, T.P., Harris, R.K., **Rebar, A.H.**, Ballachey, B.E., and Haebler, R.J.: *Pathology of Sea Otters*. In: Marine Mammals and the Exxon Valdez. Academic Press, San Diego, CA. 1994.
4. Reagan, W.J. and **Rebar, A.H.**, *Platelet Dysfunction*. In: Textbook of Veterinary Internal Medicine. W.B. Saunders Company, Philadelphia, PA. 1994.
5. Skowronek, L.A., LaFranco, L., Stone-Marschat, M.A., Burrage, T.G., **Rebar, A.H.**, and Laegreid, W.W.. *Clinical Pathology and Hemostatic Abnormalities in Experimental African Horsesickness*. Vet Pathol 32:112-121, 1995.

6. **Rebar, A.H.**, Lipscomb, T.P., Harris, R.K., and Ballachey, B.E. *Clinical and Clinical Laboratory Correlates in Sea Otters Dying Acutely in Rehabilitation Centers Following the Exxon Valdez Oil Spill*. Vet Pathol 32(4):346-350, 1995.
7. **Rebar, A.H.**, Metzger, F.: The Veterinary CE Advisor--*Clinical pathology for small-animal practitioners: Interpreting the hemogram*. Veterinary Medicine 90(6) (Suppl.):1-12, 1995.
8. Snipes, M.B., Barnett, Harkema, J.R., Hotchkiss, J.A., **Rebar, A.H.**, Reddick, L.J.: *Specific Biological Effects of an Anti-Rat PMN Antiserum Intraperitoneally Injected into F344/N Rats*. Vet Clin Pathol 24(1), 11-17. 1995.
9. **Rebar, A. H.**, Thrall, M. A.: *Blood Film Evaluation: Cytology of Circulating Blood Cells*. Vet Tech 16(9), 578-586, 607, 1995.
10. **Rebar, A.H.**, Metzger, F.: The Veterinary CE Advisor--*Clinical Pathology for Small-animal Practitioners: Profiling the Urinary System*. Vet Med 90(11) (Suppl.):1-16; 1995.
11. Christian, J.A., **Rebar, A.H.**, Boon, G.D., Low, P.S. *Methodological considerations for the use of canine *in vivo* aged biotinylated erythrocytes to study RBC senescence*. Experimental Hematology 24(1):82-8, 1996 Jan.
12. **Rebar, A.H.**, Metzger, , F.: The Veterinary CE Advisor--*Clinical Pathology for Small-animal Practitioners: Laboratory Evaluation of the Liver*. Vet Med 91(9) (Suppl.):1-12;1996
13. **Rebar, A.H.**, Section Editor, *Hematology and Immunology*. In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
14. **Rebar, A.H.**, *Metabolic Anemias (Anemias with Spiculated Red Cells)*. In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
15. Christian, J.A., **Rebar, A.H.**, *Anemia, Regenerative*. In: The 5 Minute Veterinary Consult, Tilley, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
16. **Rebar, A.H.**, *Anemia, Nuclear Maturation Defect (Anemia, Megaloblastic)*. In: The 5 Minute Veterinary Consult, Tilly, L., and Smith, F., ed., Williams and Wilkins, Media, PA. 1997.
17. **Rebar, A.H.**, *Hemogram Interpretation for Dogs and Cats*, Ralston Purina Company, St. Louis, MO, The Gloyd Group, Inc., 1998.
18. **Rebar, A.H.**, Boon, G.D., and Christian, J.A., *Biochemical Profiling in the Dog and Cat. A Case Oriented Approach*. Ralston Purina Company, St. Louis, MO, The Gloyd Group, Inc. 1999.
19. **Rebar, A.H.**, MacWilliams, P.S., Feldman, B.F., Metzger, F.L., Pollock, R.V.H., Roche, J., *A Guide to Hematology in Dogs and Cats*. Teton NewMedia, Jackson, WY. 2002.
20. Giger, U., **Rebar, A.H.**, Feldman, B.F., *Using White Blood Cell Information More Effectively: A Logical Approach* as part of Hematology Symposium. A Supplement to Compendium on Continuing Education for the Practicing Veterinarian, Vol. 25, No. 9(A), September 2003.
21. Thrall, M.A., Baker, D.C., Campbell, T.W., DeNicola, D., Fettman, M.J., Lassen, E.D., **Rebar, A.H.**, Weiser, G., *Hematology and Clinical Chemistry*, Lippincott Williams & Wilkins, Baltimore, MD, 2004.
22. Thrall, M.A., Baker, D.C., Campbell, T.W., DeNicola, D., Fettman, M.J., Lassen, E.D., **Rebar, A.H.**, Weiser, G., *Clinical Case Presentations for Veterinary Hematology and Clinical Chemistry*, Lippincott Williams & Wilkins, Baltimore, MD, 2005.

APPENDIX 6.4

GRANT NUMBER: _____

BIOGRAPHICAL SKETCH

Provide the following information for all **new** key personnel.
Copy this page for each person.

NAME		POSITION TITLE	
Philip J. Bergman, DVM, MS, PhD, DACVIM		Head, Donaldson-Atwood Cancer Clinic	
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Arizona - Tucson, AZ	DVM, BS	Undergrad	Microbiology
Colorado State University - Fort Collins, CO		1986-1990	Veterinary Medicine
Kansas State University - Manhattan, KS		1990-1991	Small Animal Intern
Colorado State University - Fort Collins, CO	MS	1991-1994	Oncology Residency
M.D. Anderson Cancer Center - Houston, TX	PhD	1994-1999	Cancer Biology

Professional Positions:

1990-1991	Rotating Small Animal Intern, Kansas State University, Manhattan, KS
1990-1994	Comparative Oncology Residency, Colorado State University, Fort Collins, CO
1994-1999	Cancer Biology Fellow, M.D. Anderson Cancer Center, Houston, TX
1994-1997	Staff Oncologist, Gulf Coast Veterinary Specialists, Houston, TX
1996-1999	American Cancer Society Physician Research Training Fellow, M.D. Anderson Cancer Center, Houston
1998-2000	Chair, ACVIM Forum, Oncology Subspecialty
1999-Present	Head, Donaldson-Atwood Cancer Clinic, The Animal Medical Center, New York, NY
2000-2002	President-Elect, Veterinary Cancer Society
2001-Present	Director, Flaherty Comparative Oncology Laboratory
2002-Present	Adjunct Associate Faculty Member, Memorial Sloan-Kettering Cancer Center & Sloan-Kettering Cancer Institute
2002-2004	President, Veterinary Cancer Society

Honors and Awards:

1989	R. Barry Prynne Memorial Scholarship. <i>For excellence in neurology.</i>
1990	AAHA Senior Student Award. <i>For excellence in small animal medicine and surgery.</i>
1993	William K. Riddell Memorial Scholarship. <i>For imminent success & broad impact in the biomedical research field.</i>
1999	R.E. "Bob" Smith Fellow, Department of Cell Biology, M.D. Anderson Cancer Center.
	AACR Symposium, Molecular Biology in Clinical Oncology. Invited Participant (Aspen, CO).
1997 & 1998	UT-Houston Graduate School of Biomedical Sciences Travel Award
1996 – 1999	American Cancer Society Physician Research Training Fellowship (PRTA #40)
	AACR Clinical Trials Symposium. Invited participant (Vail, CO)
2001	Jean Holzworth Keynote Address, Angell Memorial Animal Hospital
2001	Japanese Veterinary Cancer Society Keynote Address
2002	Adjunct Associate Faculty, Memorial Sloan-Kettering Cancer Center & Sloan-Kettering Cancer Institute
2003	World Small Animal Veterinary Association Hill's Award for Excellence in Veterinary Healthcare

Bibliography:

1. **Bergman PJ**, Withrow SJ, Straw RC, et al. Canine Infiltrative Lipoma: 16 Cases (1981-1992). *J Amer Vet Med Assoc* 1994;205:322-324.
2. **Bergman PJ**, Bruyette DS, Coyne BE, et al. Paraneoplastic Clinical Peripheral Neuropathy Associated with Canine Insulinoma. *Prog Vet Neuro* 1994;5:57-62.
3. Ogilvie GK, Moore AS, Chen C, Ciekot PA, Atwater SW, **Bergman PJ**, Walters LM. Toxicoses associated with the administration of mitoxantrone to dogs with malignant tumors: A dose escalation study. *J Amer Vet Med Assoc* 1994;205:570-573.
4. Ogilvie GK, Atwater SW, Ciekot PA, **Bergman PJ**, et al. Incidence of anaphylaxis associated with the intramuscular administration of L-asparaginase to 81 dogs with cancer: 1989-1991. *J Am Anim Hosp Assoc* 1994;30:62-65.
5. **Bergman PJ**, Ogilvie GK. Drug Resistance and Cancer Therapy. *Compend Contin Educ* 1995;17:549-558.
6. Macy DW, **Bergman PJ**. Vaccine-induced sarcomas in cats. *Feline Practice* 1995;23:24-27.
7. Gupta KP, Ward NE, Gravitt KR, **Bergman PJ**, O'Brian CA. Partial Reversal of Multidrug Resistance in Human Breast Cancer Cells by an N-myristoylated Protein Kinase C-8 Pseudosubstrate Peptide. *J Biol Chem* 1996;271:2102-2111.
8. **Bergman PJ**, MacEwen EG, Kurzman IL, et al. Amputation and Carboplatin for Treatment of Dogs with Osteosarcoma (48 Cases). *J Vet Intern Med* 1996;10:76-81.
9. **Bergman PJ**, Ogilvie GK, Powers BE. Monoclonal Antibody C219 Immunohistochemistry in canine Lymphoma: Predictive Ability and Sequential Analysis. *J Vet Intern Med* 1996;10:354-359.
10. **Bergman PJ**, Gravitt KR, Ward NE, Gupta KP, O'Brian CA. An N-myristoylated Protein Kinase C-8 Pseudosubstrate Peptide that Partially reverses Multidrug Resistance in Human Breast Cancer Cells is not a P-glycoprotein Substrate. *Cancer Chemotherapy Pharmacology* 1997;40:453-456.
11. McCaw DL, Miller MA, **Bergman PJ**, Withrow SJ, Moore AS, Knapp DW, Fowler D, Johnson JC. Vincristine therapy for mast cell tumors in dogs. *J Vet Intern Med* 1997;11:375-378.
12. **Bergman PJ**, Gravitt KR, Ward NE, Beltran P, Gupta KP, O'Brian CA. Potent induction of human colon cancer cell uptake of chemotherapeutic drugs by N-myristoylated protein kinase C-alpha (PKC-alpha) pseudosubstrate peptides through a P-glycoprotein-independent mechanism. *Inv New Drugs* 1997;15:311-318.
13. **Bergman PJ**. Etiology of feline vaccine-associated sarcomas: history and update. Vaccine-Associated Feline Sarcoma Symposium. *J Amer Vet Med Assoc* 1998;213:1424-1425.
14. **Bergman PJ**. Advances in the Treatment of Feline Vaccine-Associated Sarcomas. *Adv Small Anim Med Surg* 2000.
15. O'Brian CA, Stewart JR, Ward NE, **Bergman PJ**. Regulatory mechanisms governing protein kinase C signaling. *Electr J Pathol Histol* 2000;6:1-10.
16. Rocha TA, Mauldin GN, Patnaik AK, **Bergman PJ**. Prognostic Factors in Dogs with Urinary Bladder Carcinoma. *J Vet Intern Med* 2000;14:486-490.
17. Kovak JR, Ludwig LL, Noone KE, **Bergman PJ**, et al. The use of thoracoscopy to diagnose pleural effusion of ambiguous etiology. *J Am Vet Med Assoc* 2002;221(7):990-994.
18. Charney SC, **Bergman PJ**, Hohenhaus AE, McKnight JA. Risk factors for sterile hemorrhagic cystitis in dogs with lymphoma receiving cyclophosphamide with or without concurrent administration of furosemide: 216 cases (1990-1996). *J Am Vet Med Assoc* 2003;222(10):1388-1393.
19. **Bergman PJ**, McKnight J, Novosad A, Charney S, Farrelly J, Craft D, Sadelain M, Wulderk M, Jeffers Y, Hohenhaus AE, Segal N, Gregor P, Engelhorn M, Riviere I, Houghton AN, Wolchok JD. Long term survival of dogs with advanced malignant melanoma following DNA vaccination with xenogeneic human tyrosinase: A phase I trial. *Clin Cancer Res* 2003;9:1284-1290.
20. **Bergman PJ**. Clinical techniques in small animal molecular oncology. *Clin Tech Small Anim Pract* 2003;18:88-91.
21. Simpson AM, Ludwig LL, Newman SJ, **Bergman PJ**, Hottinger HA, Patnaik AK. Canine cutaneous mast cell tumors: A prospective study of surgical margins. *J Am Vet Med Assoc* 2004;224(2):236-240.
22. Farrelly J, Denman DL, Hohenhaus AE, Patnaik AK, **Bergman PJ**. Hypofractionated radiation therapy of oral melanoma in five cats. *Vet Radiol Ultras* 2004;45(1):91-94.
23. Newman SJ, **Bergman PJ**, Williams B, Scase T, Craft D. Characterization of Spindle Cell Component of Ferret (*Mustela putorius furo*) Adrenal Cortical Neoplasms – Correlation to Clinical Parameters and Prognosis. *Comp & Vet Oncol* 2004;2(3):113-124.

24. Patnaik AK, Newman SJ, Scase T, Erlandson RA, Antonescu C, **Bergman PJ**. Canine hepatic neuroendocrine carcinoma: An immunohistochemical study of 10 cases. *Vet Pathol* 2005, in press.
25. Jakubiak MJ, Zenger E, Siedlecki CT, Matteucci ML, Bruskiewicz KA, Rohn DA, **Bergman PJ**. Laryngeal, laryngotracheal and tracheal masses in cats: 27 cases (1998-2003). *J Am Anim Hosp Assoc* 2005, in press.
26. Winston J, Craft DM, Scase TJ, **Bergman PJ**. Immunohistochemical detection of Her-2/neu expression in spontaneous feline mammary tumors. *Vet Comp Oncol* 2005, in press.
27. McAbee KP, Ludwig L, Newman S, **Bergman PJ**. Cutaneous Hemangiosarcoma in 18 cats. *J Am Anim Hosp Assoc* 2005, in press.
28. Allenspach K, Grone A, Doherr MG, **Bergman PJ**, Gaschen F. P-glycoprotein expression in lamina propria lymphocytes of duodenal biopsies in dogs with inflammatory bowel disease. *J Vet Intern Med* 2005, submitted.
29. Charney SC, **Bergman PJ**, McKnight JA, Farrelly J, Novosad CA, Leibman NF, Camps-Palau MA. Evaluation of intracavitary mitoxantrone and carboplatin for treatment of carcinomatosis, sarcomatosis, and mesothelioma, with or without malignant effusions: A retrospective analysis of 12 cases (1997-2002). *Vet Comp Oncol* 2004, in press.
30. Novosad CA, **Bergman PJ**, O'Brien M, Charney SC, et al (VCOG). Retrospective evaluation of adjuvant chemotherapy for the treatment of feline mammary gland adenocarcinoma. *JAVMA* 2004, submitted.

APPENDIX 6.5

Dr. Ronald D. Schultz
Professor and Chair
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison

EDUCATION: North Penn High School, Lansdale, Pennsylvania, 1962
The Pennsylvania State University
BS (1966), MS (1967), PhD (1970)
Major - Microbiology/Immunology
Minors - Biochemistry and Veterinary Pathology

MILITARY SERVICE: Captain, Medical Service Corps, U.S. Army Reserve, 1966-1975

POSITIONS HELD:

1982 - present Professor (Tenured) and Chair, Department of Pathobiological Sciences, School of Veterinary Medicine. Professor (Joint Appointment), Department of Medical Microbiology and Immunology, School of Medicine. Professor (Affiliate Appointment), Department of Animal Health and Biomedical Sciences, College of Agriculture and Life Sciences. Professor, Environmental Toxicology Center, University of Wisconsin, Madison, Wisconsin.

1978 - 1982 Professor of Immunology (Tenured) and member of Graduate Faculty, Department of Microbiology and Animal Health Research Unit, School of Veterinary Medicine, Auburn University, Auburn, Alabama.

1977 - 1978 Associate Professor of Immunology (Tenured), James A. Baker Institute for Animal Health Research (Veterinary Virus Research Institute), Cornell University, Ithaca, New York.

1973 - 1978 Assistant Professor of Immunology and member of Graduate Faculty, James A. Baker Institute for Animal Health, Cornell University.

1972 - 1978 Associate Director, Human Health Services Clinical Laboratory, Department of Health Services, Cornell University, Ithaca, NY.

1971 - 1973 Research Associate, Department of Microbiology, New York State College of Veterinary Medicine, Cornell University, Ithaca, New York.

HONORS & MEMBERSHIPS:

First President American Association of Veterinary Immunologists
Honorary Diplomate of American College of Veterinary Microbiologists
Distinguished Veterinary Immunologist Award, American Association of Veterinary Immunologists, 1988
Walter F. Renk Distinguished Professor Award, Faculty, School of Veterinary Medicine, University of Wisconsin-Madison, 1989.
President of Conference of Research Workers in Animal Diseases, 1994.
Served on all School of Veterinary Medicine Committees and Numerous Campus Committees
Served on Review Committees for USDA, FDA, NIH and private foundations
Editorial Board Member for various journals

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RESEARCH INTERESTS

- Developmental aspects of immunology
- Immunopathology associated with viral diseases
- Immunomodulators
- Clinical immunology and virology
- Vaccinology
- Zoonotic diseases and foreign animal diseases

Trained approximately 50 graduate students and postdoctoral fellows

Published approximately 200 articles in peer reviewed journals, edited several books and hold a number of patents

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APPENDIX 6.6

LAWRENCE T. GLICKMAN

Biographical Sketch

Dr. Glickman is on the faculty of the Purdue University School of Veterinary Medicine. In addition to a degree in veterinary medicine, he has a doctoral degree in public health and a master's degree in physiology. He is board certified by the American College of Epidemiology. He served as Chairman of a committee of the National Academy of Sciences that authored a monograph titled *Animals as Sentinels of Environmental Health Hazards*. He has published over 275 journal articles, book chapters, and monographs, related to human and animal health. He studies relationships between humans, animals, and the environment. Dr. Glickman has received grants and contracts from federal agencies including the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the U.S. Department of Education, and the U.S. Department of Agriculture, and from private foundations, breed clubs, and industry. He has been recognized for contributions to human and animal health with honors including the Award of Recognition in Veterinary Public Health and Preventive Medicine in 1988 from the Teachers of Veterinary Preventive Medicine and Public Health, the Pfizer Award for Research Excellence in 1997, an award from the University of Pittsburgh Graduate School of Public Health in 1999 as one of the 50 top contributors to public health over the past 50 years, an Alumni Award of Merit in 2002 from the University of Pennsylvania School of Veterinary Medicine for advancing animal health, and the 2003 AKC Award for Excellence in Canine Research. He has trained more than 20 PhD students in epidemiology and chairs the Section of Clinical Epidemiology at Purdue University. Dr. Glickman directed the largest prospective companion animal health study to date, involving nearly 2000 pet dogs that were followed for five years to identify the causes of gastric torsion. His current research utilizes computerized veterinary medical records to detect biological, chemical, and physical hazards, resulting from acts of terrorism and to measure the incidence of adverse health effects associated with veterinary vaccines and pharmaceuticals. Dr. Glickman recently published the results of two studies showing that lawn herbicides are a probable cause of bladder cancer in dogs and chemicals in food can linings may be responsible for the current epidemic of hyperthyroidism in cats. He developed a simple method called the *Vaccinometer* to help veterinarians weigh the risks versus benefits of vaccines for individual patients. He is a strong advocate for the evidence-based approach to veterinary medical practice and preventive medicine.

Current Position	Professor of Epidemiology & Public Health Head, Section of Clinical Epidemiology
Office Address	Department of Veterinary Pathobiology School of Veterinary Medicine Purdue University West Lafayette, IN 47907 -1243
Education	
B.A.	1964- Biology, State University New York at Binghamton
M.A.	1966- Physiology, State University New York at Binghamton
V.M.D.	1972- University Pennsylvania, School Veterinary Medicine,
M.P.H.	1975- Epidemiology and Infectious Diseases, University Pittsburgh, Graduate School of Public Health
Dr.PH.	1977- Epidemiology and Public Health, University Pittsburgh, Graduate School of Public Health
Postgraduate Training	
1975-1976	N.I.H. Postdoctoral Fellow in Cardiovascular Disease Epidemiology, Graduate School Public Health, University Pittsburgh
1976-1977	Research Assistant, Department of Epidemiology, Graduate School Public Health, University Pittsburgh
Military Service	
1960-1966	United States Army National Guard, (Honorable Discharge)

Academic Appointments

1977-1980	Assistant Professor of Epidemiology and Preventive Medicine, Department of Preventive Medicine, and Head, Division of Epidemiology, Diagnostic Laboratory, New York State College of Veterinary Medicine, Cornell University
1980-1987	Associate Professor of Epidemiology and Chief, Section of Epidemiology and Public Health, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania (Tenure granted July 1, 1983)
1980-1985	Faculty in Graduate Group of Epidemiology, University of Pennsylvania
1981-1988	Faculty in Graduate Group of Comparative Medical Sciences, University of Pennsylvania
1982-1988	Faculty in Graduate Group of Parasitology, University of Pennsylvania
1985-1988	Adjunct Professor of Epidemiology, Section of General Medicine, Hospital of the University of Pennsylvania
1987-1988	Professor of Epidemiology and Head, Section of Epidemiology and Public Health, Department of Clinical Studies, School of Veterinary Medicine University of Pennsylvania
1988-1993	Head, Department of Veterinary Pathobiology, Purdue University, School of Veterinary Medicine
1988-1993	Head, Graduate Program in Veterinary Pathobiology with subspecialties in pathology, epidemiology and public health, microbiology, parasitology, and immunology, Purdue University Graduate School.
1988-present	Professor of Epidemiology and Public Health and Head of Section of Clinical Epidemiology, Department of Veterinary Pathobiology, Purdue University, School of Veterinary Medicine
1991-present	Adjunct Professor of Epidemiology, Indiana University School of Medicine, Indianapolis, IN
1991-present	Founding Member, Purdue University Interdisciplinary Graduate Program in Nutrition

Hospital and Administrative Appointments

1966-1967	Research Scientist, Research and Drug Development, Endo Laboratories, Garden City, New York
1972-1974	Practicing Veterinarian, Trooper Veterinary Hospital, Norristown, PA
1976-1977	Assistant Director, Laboratory Animal Care Facility, School of Medicine, University of Pittsburgh (Major responsibility for dogs, cats, and non-human primates)

Specialty Board Certification

1982	Fellow of the American College of Epidemiology

Awards, Honors, and Membership in Honorary Societies

- 1972- Borden Award for highest academic average in veterinary school
- 1972- J.B. Lippincott Prize for academic achievement in veterinary school
- 1972- Leonard Pearson Prize for Advancement of Veterinary Science and Research in Practice, Education and in Civilization
- 1972- 1930 Class Prize-for highest average in surgery
- 1983- Ralston Purina Small Animal Research Award
- 1987- Veterinary Student Government Award for Excellence in Teaching, University of Pennsylvania
- 1988- Award of Recognition in Veterinary Public Health and Preventive Medicine, Teachers of Veterinary Preventive Medicine and Public Health
- 1989- Delta Omega Society, for outstanding attainment in public health
- 1989- Sigma Xi National Scientific Research Honor Society
- 1991- Merck AGVET Award for Creativity in Veterinary Education
- 1991- National Society of Phi Zeta, Honor Society of Veterinary Medicine
- 1997- Pfizer National Award for Research Excellence
- 1999- University of Pittsburgh Public Health Award, Top 50 contributors to public health in past 50 years
- 2002- Alumni Award of Merit, University of Pennsylvania School of Veterinary Medicine
- 2003- American Kennel Club-American Veterinary Medical Association, Excellence in Canine Research

Memberships in Professional and Scientific Societies

- American Academy Veterinary Disaster Medicine
- American Academy Veterinary Nutrition
- American College Epidemiology (Fellow status)
- American Public Health Association (Chairman, Membership Committee, Veterinary Public Health Section, 1982-1986)
- American Veterinary Medical Association
- Association of Teachers Veterinary Public Health and Preventive Medicine
- Association of Veterinary Medical Educators
- National Association State Public Health Veterinarians
- Society for Epidemiologic Research
- Society of Toxicological Pathologists (Associate Member)
- Teachers of Veterinary Preventive Medicine and Public Health (Executive Board, 1987-1988)

Peer Reviewed Publications

Approximately 300 publications in medical journals, textbooks, and monographs
A detailed list is available upon request

ProHeart 6 Safety Assessment by Fort Dodge Animal Health

January 31, 2005



Fort Dodge Animal Health

Rami Cobb, BVSc (Hons.) MACVSc
Vice President
Pharmaceutical Research & Development
Fort Dodge Animal Health



ProHeart 6 Introduction

- Active ingredient: moxidectin
 - Macrocyclic lactone
- Anthelmintic agent
 - Dogs, horses, cattle, sheep, swine
- Co-development with WHO for humans
 - Onchocerciasis (river blindness)

ProHeart 6 Introduction

- Innovative Product
 - A single dose provides 6 months protection from heartworm disease caused by *Dirofilaria immitis*
 - Treats existing hookworm infections
 - Overcomes compliance failures associated with monthly heartworm preventives

Moxidectin

Extensive Toxicology Database

- Receptor-mediated adverse pharmacologic/toxicologic effects not expected (new study)
- Toxicology studies of up to 2 years in mice and rats and 1 year in dogs showed no adverse histologic or biochemical effects on any organ system
 - Exposure (AUC) of dogs to moxidectin in toxicology studies were 454-fold higher than after 2 doses of ProHeart 6 given 6 months apart (new study)
- No increase in tumors in 2-year carcinogenicity studies

Pre-Approval ProHeart 6 Clinical Study Results

- Safety study results demonstrate
 - Wide margin of safety
 - Safe in breeding animals
 - Safe in unique canine populations
 - Ivermectin-sensitive
 - Heartworm positive
 - 100% efficacy at commercial dose
 - 100% efficacy in large number (84) of breeds
 - A total of 770 dogs were evaluated for US registration



Factors Limiting Heartworm Control in US Dogs

- Widespread availability of heartworm preventives has not changed the infection rates in last 10 years
- 240,000 dogs in US tested positive for heartworm nationwide in 2001
- One-fifth of surveyed dog owners stopped giving their dogs the monthly oral preventive altogether

ProHeart 6 Approval

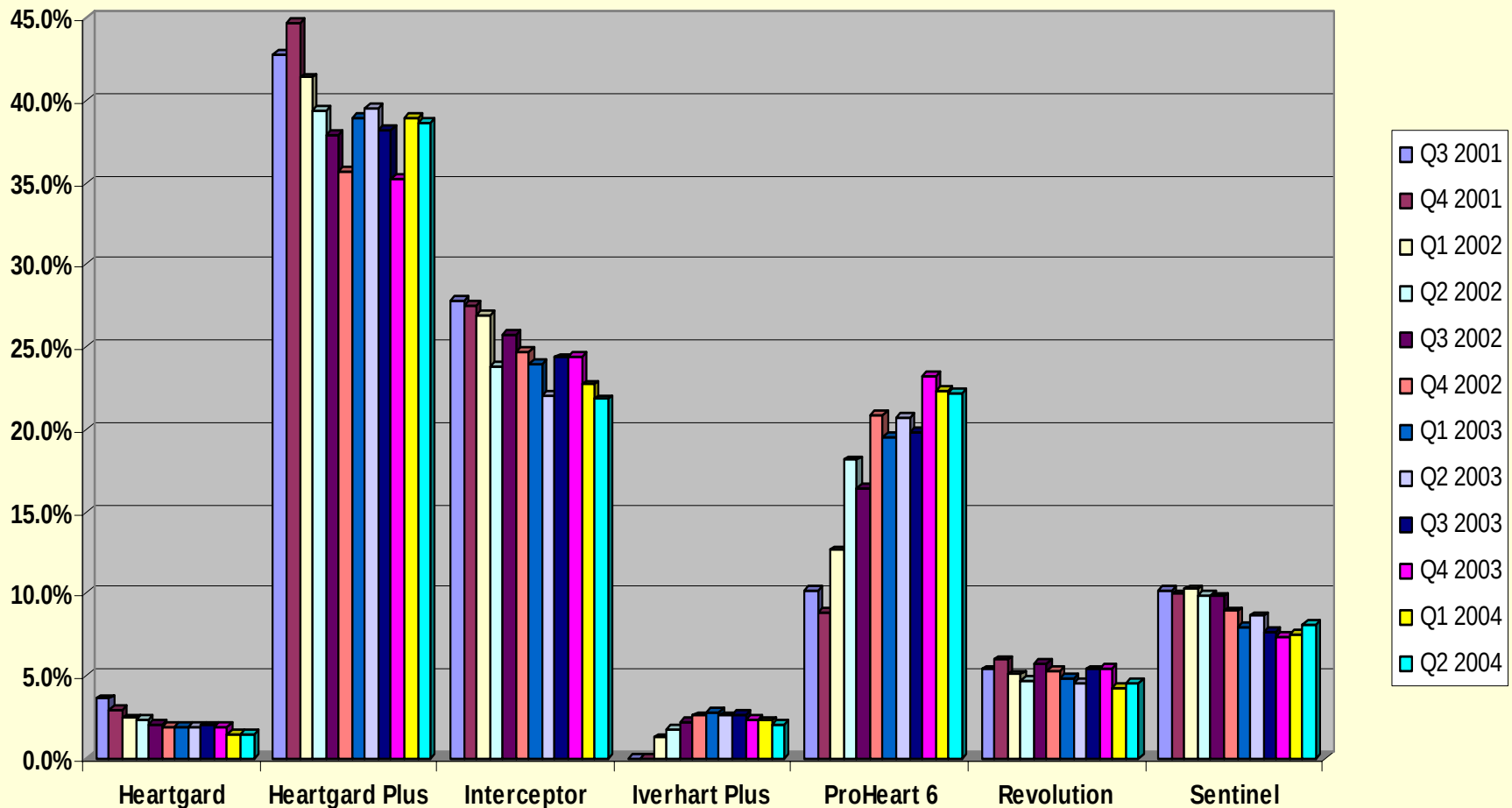
- Approved and marketed globally
 - US – June 2001
 - Canada, Japan, Italy, France, Spain, Portugal, Greece, Korea
- ProHeart SR 12
 - Australia – October 2000
 - 12 months heartworm protection
 - 3 times ProHeart 6 dose

ProHeart 6 Market Experience

- Rapid and broad acceptance by dog owners and veterinary professionals
 - 24% US market share
 - 47% Australian market share



Brand Share Change 2001 - 2004 Dispensed Units

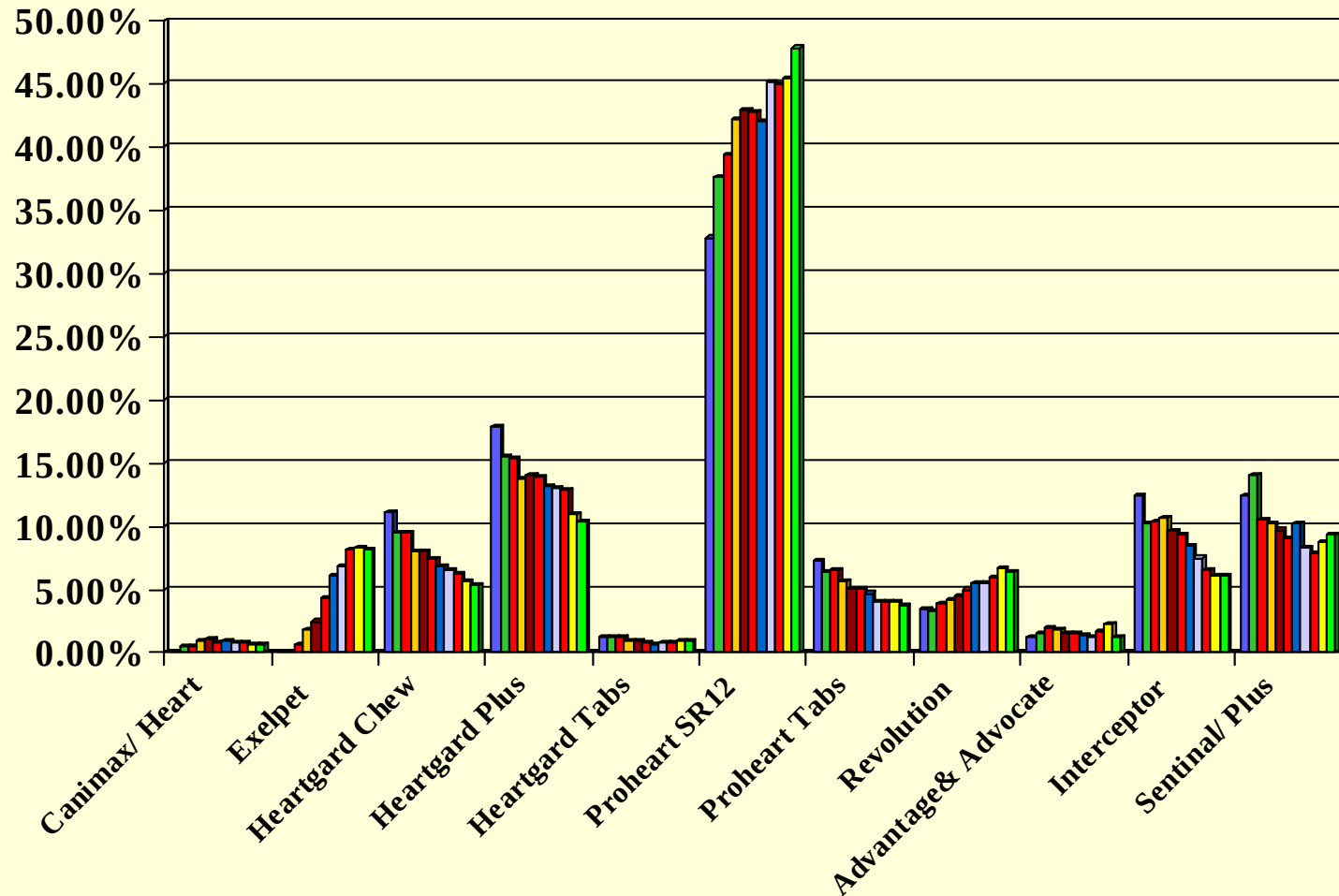


Source: June 2004 Doane Market Research: Heartworm Tracking Study



Fort Dodge Animal Health

ProHeart 12 - Australia



■ Mar-02
 ■ Jun-02
 ■ Sep-02
 ■ Dec-02
 ■ Mar-03
 ■ Jun-03
 ■ Sep-03
 ■ Dec-03
 ■ Mar-04
 ■ Jun-04
 ■ Sep-04



Fort Dodge Animal Health

US and Australian AER Reports

	<u>US</u>	<u>Australia</u>
Doses sold	18,000,000	2,000,000
AER rate (per 10,000 doses)	2.5	1.6
Allergy reporting rate (per 10,000 doses)	1.3	0.8
Death reporting rate (per 10,000 doses)	0.3	0.1

ProHeart 6 Introduction

- September 2004: FDAH voluntary recall of ProHeart 6 based on CVM concerns about adverse events
- Data reviewed by Canadian, Australian, European, and Japanese regulatory authorities
 - Confirmed authority to continue marketing



ProHeart 6

Epidemiological Evaluation

(presented by Dr. Larry Glickman, Purdue University)

- Large independent nation-wide database: Banfield The Pet Hospital™
 - Nearly 7 million “encounters” (office visits)
- ProHeart 6, two heartworm preventives, vaccines were evaluated
- Results demonstrate no clinically significant increase in adverse events following ProHeart 6 treatment
- ProHeart 6 safety profile similar to 2 monthly heartworm preventives



Fort Dodge Animal Health

Re-Evaluation of AERs by FDAH

(presented by Dr. David Hustead, FDAH)

- Post-marketing monitoring of AERs
 - Overall reporting rate is low
 - Reporting rate is declining
 - Most AERs appear to be allergic and self limiting
 - Assignment of causality confounded by concurrent vaccinations
 - Varied non-allergic AERs reflect diseases often seen in dogs

INTRODUCTION TO PROTOCOL AMENDMENT 3 / PROTOCOL HISTORY

A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind, Safety, Tolerability, Pharmacokinetic, and Efficacy Study of Orally Administered Moxidectin in Subjects with *Onchocerca volvulus* Infection

Onchocerciasis Chemotherapy Research Centre protocol number: 33

Wyeth Research protocol number: 3110A1-200-GH

Amendment 3

Date of Original Protocol: 18 November 2003

Date of Protocol Amendment 1: 21 April 2004

Date of Protocol Amendment 2: 14 July 2004

Date of Protocol Amendment 3: TBD 2005 (Draft)

Amendment 2 of this protocol was approved by all responsible personnel at WHO and Wyeth, as well as by the national and the WHO Ethics Committee and clearance to initiate the study under this amendment had been obtained from the Ghana regulatory authorities.

Amendment 3 is being proposed by Dr. Awadzi, the PI of the study, with the following changes relative to Amendment 2:

WHO substudy on the effect of moxidectin on intestinal parasites, the evaluation of the utility of ultrasonography in monitoring macrofilaricidal activity, and the determination of migration of microfilariae into body fluids, will not be conducted as part of this study. The rationale for this is the workload for site personnel given that none of these evaluations contributes to the primary or secondary objectives of this study.

The minimum weight in the inclusion criteria has been changed from 40 kg for both genders to 40 kg for women and 50 kg for men. The rationale for this is that adult males from the area in which the subjects will be recruited who weigh less than 50 kg may not qualify as the 'otherwise [i.e. other than infection with *Onchocerca volvulus*] healthy adults'.

Allowing inclusion of patients with moderate level of infection (10-20 mf/mg skin) who also have ocular involvement (< 10 mf in both eyes). The rationale is that

- this is a level of eye involvement frequently found among patients with moderate level of skin microfilaria
- eye involvement tends to be larger among patients with higher level of skin microfilaria
- including patients with low level eye involvement allows evaluation of the safety and efficacy of moxidectin in those patients, prior to proceeding to evaluation in patients with higher eye involvement. This parallels the tier system for skin microfilariae.

Performance of fundus colour photography and fluorescein angiogram in ALL patients up to 3 months post moxidectin administration, after that only in patients with lesions or visual defects. Previously fundus colour photography was planned for all patients only to day 14 and thereafter only in

patients with lesions, fluorescein angiography was planned to 3 months post treatment only in patients with a high (>20 mf/mg skin) level of skin microfilaria and thereafter only in patients with lesions. The change in the protocol is introduced in recognition of the fact that microfilariae do appear in the anterior chamber of the eyes in some subjects in whom none were found pretreatment. Thus the amended strategy ensures that no lesions attributable to ocular microfilariae are missed.

Paracetamol has been added to allowed medication during the screening period

A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind, Safety, Tolerability,
Pharmacokinetic, and Efficacy Study of Orally Administered Moxidectin in Subjects with
Onchocerca volvulus Infection

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Date of Protocol Amendment 3: TBD 2005 (Draft)

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**Moxidectin
Non IND**

**Protocol No. 3110A1-200-GH
OCRC Protocol No. 33**

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1. CONTACTS

1.1 Emergency Contacts

1.1.1 Wyeth

Contact 1 of the persons indicated below for serious adverse events and other emergencies:

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Emergency Telephone Number: If the persons named above cannot be reached, call +1 (610)-902-1200 and indicate that you have a product-related emergency.

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1.1.5 Trial Center in Ghana (all screening to be conducted at this location)

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1.2 Additional Contacts

Contact the following for all other inquiries and information about this study:

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2. MEDICAL MONITOR SIGNATURE

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

_____ Wyeth Medical Monitor's Signature	_____ Date of Signature (DDMmmYYYY)	_____ Time (24-hour clock, time zone)
Gilbert Rose, M.D		
_____ Wyeth Medical Monitor's Name (print)		
_____ WHO Clinical Coordinator's Signature	_____ Date of Signature (DDMmmYYYY)	_____ Time (24-hour clock, time zone)
Juntra Karbwang, M.D, PhD		
_____ WHO Clinical Coordinator's Name (print)		

Time Zone Abbreviations:

Atlantic Time Eastern Time – AT ET, Central European Time – CET, Central Time – CT, East Australia Time – EAT, Greenwich Mean Time – GMT, Japan Time – JT, Mountain Time – MT, Pacific Time – PT

3. INVESTIGATOR SIGNATURE

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsors to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsors, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Signature

Date of Signature (DDMmmYYYY)

Time (24-hour clock, time zone)

Kwablah Awadzi, MB FRCP DCMT

Investigator's Name (print)

4. INDEPENDENT ETHICS COMMITTEE (IEC)

The independent ethics committee (IEC) and its affiliation and address for *each site* implementing this protocol shall be identified below.

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Affiliation:	Ghana Health Service
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IEC:	WHO IEC (Research Ethics Review Committee (ERC)))
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5. DISCLOSURE STATEMENT

Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsors. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical trial for the sponsors. You may disclose the contents of this document only to study personnel under your supervision, IECs, or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical trial, disclosed to any other person or entity, and/or published without the prior written permission of the sponsors. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsors of any such disclosure.

Any information that may be added to this document also is confidential and proprietary to the sponsors and must be kept in confidence in the same manner as the contents of this document.

The Wyeth Research protocol number for this study is 3110A1-200-GH.

The Onchocerciasis Chemotherapy Research Centre protocol number is 33.

6. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
β-hCG	β-human Chorionic Gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CERT	Clinical Expert Review Team
CNS	Central nervous system
CRF	Case report form
CV	Curriculum vitae
DMPA	Depo-medroxyprogesterone acetate
EC	Ethics committee
ECG	Electrocardiogram
EMA	European Medicines Evaluations Agency
FDA	United States Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma aminobutyric acid
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GFDB	Ghana Food and Drugs Board
GHS	Ghana Health Services
GNCP	Ghana National Center for Pharmacovigilance
HPMC	Hypromellose (Hydroxypropyl Methylcellulose)
ICH	International Conferences on Harmonization
IV	Intravenous
IEC	Independent ethics committee
LDH	Lactate dehydrogenase
Mf	Microfilariae
NOEL	No observed effect level
NTEL	No toxic effect level
NCI	National Cancer Institute
OCPC	Onchocerciasis Control Programme
OCRC	Onchocerciasis Chemotherapy Research Center
OTC	Over the counter
PD	Pharmacodynamic
PRD	Product Research and Development Unit of TDR
PK	Pharmacokinetic
PI	Principal investigator
PRT	Project Review Team
SAE	Serious adverse event
SCRIHS	Secretariat Committee on Research Involving Human Subjects
t _{1/2}	Terminal elimination half-life

Abbreviation	Term
TEAE	Treatment Emergent Adverse Event
TIC	Tablets in capsules
TDR	UNICEF/United Nations Development Program/Worldbank/WHO Special Programme for Research and Training in Tropical Diseases
ULN	Upper limit of normal
URTI	Upper Respiratory Tract Infection
WBC	White blood cell or White Blood Cell Count
WHO	World Health Organization
WNL	Within normal limits

7. DEFINITION OF TERMS

Term	Definition
Regulation	Throughout this document the term <i>regulation</i> refers to all appropriate regulations, laws, and guidelines. This study will be conducted according to all appropriate regulations. The regulations may be international, national, or local and may include but not be limited to the Code of Federal Regulations (United States); the Good Clinical Practice: Consolidated Guideline (Canada); the International Conference on Harmonisation Guideline for Good Clinical Practice; the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); the Standard Operating Procedures for Clinical Investigators (UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (See Declaration of Helsinki section).
Regulatory Agency	Throughout this document the term <i>regulatory agency</i> refers to all appropriate health and regulatory agencies. These may be international, national, or local and may include but not be limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the European Agency for the Evaluation of Medicinal Products (EMA), the US Food and Drug Administration (FDA), and the Ghana Food and Drugs Board (GFDB).
Sponsors	Throughout this document the term <i>sponsors</i> refers to all appropriate research departments. These may include but not be limited to Wyeth Research Division of Wyeth Pharmaceuticals Inc. and Product Research and Development Unit (TDR), World Health Organization.
Study Start Date	Date screening of the first subject for this study in the hospital is initiated.
Subject	Any person who participates in a study, either as the recipient of a test article or as a control subject. A subject may be healthy or have a disease.
Test Article	Any drug, device, biological agent (including placebo) required by the protocol and supplied by the sponsors for use in the sponsor's clinical research and development studies.

8. SYNOPSIS

Study Title	A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind, Safety, Tolerability, Pharmacokinetic, and Efficacy Study of Orally Administered Moxidectin in Subjects with <i>Onchocerca volvulus</i> infection.
Clinical Phase	Phase 2
Study Rationale	Moxidectin, an anthelmintic, is currently licensed and marketed as an antiparasitic for use in cattle, sheep, swine, horses, and dogs. Preclinical experiments have shown that orally administered moxidectin may be useful treatment for onchocerciasis (river blindness) in humans. Moxidectin kills the microfilariae and may kill adult worms as well. Ivermectin, a related drug that is currently the standard treatment for river blindness, kills only the microfilariae. The first-in-man (FIM) study (protocol 3110A1-100-EU) investigating the effect of single doses of 3 mg to 36 mg of moxidectin in healthy subjects has been completed. In this study, 37 subjects were treated with single doses of 3 mg to 36 mg (approximately 50 µg/kg to 600 µg/kg). Subjects were randomized into placebo, 3 mg fasting, 9 mg fasting, 9 mg fed, 18 mg fasting, 36 mg fed and 36 mg fasting groups. Only 1 adverse event (AE) higher than grade 2 was reported in this study (enteritis due to food poisoning [grade 3] in the 36 mg fasting group) and was considered unrelated to study drug. The most common AEs were headache (35%) and infection (29%). Only half of the headaches reported and none of the infections reported were regarded as study drug related. The reported infections, including type of infection, time of occurrence after moxidectin administration, and dose group were: upper respiratory tract infection (URTI) on Day 19 and Day 63 (same subject), and a viral URTI on Day 14 in the 3 mg fasted group; toe infection on Day 52 in the 9 mg fasted group – URTI on Day 30 and Day 78 (different subjects) in the 9 mg fed group; tooth abscess on Day 47 in the 36 mg fasted group; head cold on Day 50 and Day 66 (different subjects) in the 36 mg fasted group; cold on Day 42 and cold-like symptoms on Day 59 (same subject) in the 36 mg fed group. No serious adverse events (SAEs) were reported. Four (4) subjects discontinued from the study (1 before receiving study drug and 3 after dose administration [one each in the 3 mg fasting, 9 mg fed, and 36 mg fasting groups]). The withdrawal from the study was unrelated to AEs. Overall, moxidectin appeared to be safe at the doses evaluated in this study. In a bioavailability study comparing the tablet and liquid forms of moxidectin

	(protocol 3110A1-101-EU) 58 healthy male subjects received a single dose of 10 mg of moxidectin either as the liquid formulation (29 subjects) used in the FIM study or as tablets (29 subjects) and were followed up for 180 days. During the course of this study, there were no SAEs and no subjects discontinued the study due to an AE. A total of 36 (62.1%) subjects had treatment emergent AEs (TEAEs) during the study, with the same number and percentage of subjects (18; 62.1%) reporting TEAEs in both the moxidectin liquid and tablet groups. During the first 7 days post treatment, 10 subjects (34.5%) receiving liquid moxidectin and 9 subjects (31.0%) receiving tablet reported AEs, including asthenia (10.3% in the tablet group), headache (13.8% and 6.9% in the liquid and tablet groups, respectively), infection (6.9% in the liquid group), diarrhea (6.9% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group). Between day 8 and 180 of follow up, 10 subjects (34.5%) receiving liquid and 12 subjects (41.4%) receiving tablet reported AEs. The most commonly reported events were flu syndrome (17.2% and 20.7% in liquid and tablet groups, respectively), headache (6.9% in the tablet group), and infection (6.9% in the tablet group). All of the TEAEs were mild to moderate in intensity, and none were considered to be related to treatment. No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory tests during the study. The data from the normal subject studies (protocol 3110A1-100-EU, 3110A1-101-EU) suggests that progression to a safety and tolerability study in subjects with different degrees of severity of infection with <i>Onchocerca volvulus</i> as described in this protocol is warranted. This will be the first study of moxidectin in subjects with <i>O. volvulus</i> infection and will examine the safety, tolerability, pharmacokinetics, and efficacy of oral moxidectin in subjects to determine safe and effective doses of moxidectin and provide proof of concept. The lowest dose of moxidectin to be used in this study (2 mg) is lower than the lowest dose used in the FIM study (3 mg). As noted above, the 3 mg dose was well tolerated in the FIM study.
Trial Design	This is a randomized, single-ascending dose, double blind, active drug-controlled, parallel design, inpatient/outpatient, study at a single center. See the flowchart(s) for the procedures to be performed at each visit.
Approximate Duration of Subject Participation	Each subject will participate for approximately 18 months including an initial 18-day inpatient period.
Approximate Duration of Study	The total duration of the study will be up to 36 months.

Study Objective(s)	Primary: To determine the safety and tolerability of orally administered moxidectin in subjects with <i>O. volvulus</i> infection, as measured by the incidence of clinical adverse events and clinically significant laboratory test results. Secondary: 1. To determine doses that effectively eliminate microfilariae and prevent their return to the skin as measured by the skin microfilarial loads at days 8, 30, 60, 90, 180 and at 12 and 18 months after treatment. 2. To determine the viability and fertility of adult worms at 18 months. 3. To assess the pharmacokinetics of moxidectin in male and female adult subjects.
Diagnosis and Main Criteria for Inclusion	Ivermectin-naïve men and women in good general health, with <i>O. volvulus</i> infection and: a) Written, signed (or thumb-printed), and dated informed consent b) Aged 18 to 60 years, inclusive c) Body weight ≥ 40 kg for women and ≥ 50kg for men d) Nonpregnant, nonbreastfeeding women. Women of child bearing potential must agree to use birth control during the first 150 days after treatment. e) Healthy, as determined by a physician on the basis of a physical examination, ECG, and a thorough review of the medical history and clinical laboratory results f) No previous exposure to moxidectin . g) Adequate hematologic, renal, and hepatic function, defined as: 1) White blood cell (WBC) count $\geq 2,800$ and $\leq 11,800$ cells/mL 2) Hemoglobin: ≥ 11.0 g/dL for men and ≥ 10.0 g/dL for women 3) Platelet count: $\geq 110,000$ mm³ 4) Serum creatinine: ≤ 1.25 x upper limit of normal (ULN) 5) Total bilirubin: ≤ 1.25 x ULN 6) AST/SGOT: ≤ 1.25 x ULN 7) AP: ≤ 1.25 x ULN 8) Prothrombin time WNL 9) Urinalysis WNL h) Skin microfilarial density within the required range for the cohort
Main Criteria for Exclusion	a) Participation in any studies other than purely observational ones, within 4 weeks before test article administration. b) Any vaccination within 4 weeks before test article administration

	c) Acute infection requiring therapy within the last 10 days before test article administration d) Administration of any medication (with the exception of medication required to treat any reactions during the screening fluorescein angiography or paracetamol) or herbal preparation within 10 days prior to test article administration or any condition currently requiring regular medication e) Clinically significant ECG abnormalities or history of cardiac abnormality f) Subjects with orthostatic hypotension at the screening evaluation g) History of drug or alcohol abuse or regular use of ≥ 3 cigarettes per day h) Use of alcohol or other drugs of abuse within 72 hours before test article administration i) Any condition, in the investigator's opinion, that places the subject at undue risk j) Subjects who have donated blood within 8 weeks before study entry k) Subjects with ocular onchocerciasis in cohorts intended to enroll subjects with mild infection. Ocular onchocerciasis is defined by the presence of live or dead microfilariae, onchocercal punctate opacities, onchocercal lesions of the posterior segment or lesions that mimic those seen in onchocerciasis. l) Subjects with hyperreactive onchodermatitis m) No antifilarial therapy within the previous 5 years n) Coincidental infection with Loa Loa o) Female subjects of childbearing potential with a contraindication to DMPA if not on Norplant p) Any other condition which the investigator feels would exclude the subject from the study
Approximate Number of Subjects	A total of 192 subjects will be enrolled in 9 consecutive cohorts: 2 mg: 16 subjects with > 0 and < 10 microfilariae/mg of skin 2 mg: 16 subjects with 10-20 microfilariae/mg of skin 2 mg: 32 subjects with > 20 microfilariae/mg of skin with or without ocular involvement (to be enrolled in 2 consecutive groups of 16 subjects) 4 mg: 16 subjects with > 0 and < 10 microfilariae/mg of skin 4 mg: 16 subjects with 10-20 microfilariae/mg of skin 4 mg: 32 subjects with > 20 microfilariae/mg of skin with or without

	ocular involvement (to be enrolled in 2 consecutive groups of 16 subjects)
	8 mg: 16 subjects with > 0 and < 10 microfilariae/mg of skin 8 mg: 16 subjects with 10-20 microfilariae/mg of skin 8 mg: 32 subjects with > 20 microfilariae/mg of skin with or without ocular involvement (to be enrolled in 2 consecutive groups of 16 subjects)
Approximate Number of Study Centers	1
Concomitant Treatment	Depo-medroxyprogesterone acetate (DMPA), 150 mg, will be given twice to all women of childbearing potential. The first dose will be given on study day 11 and the second dose will be at month 2 (± 1 week). Women who have contraceptive protection by the Norplant system will be excluded from the DMPA injections. All medication given after admission to the hospital will be documented in the CRF. Treatment with ivermectin, albendazole, or other anthelmintic agents will be prohibited for the duration of the study.
Test Article(s) and Administration	Moxidectin, ivermectin and placebo capsules are identical in appearance. Moxidectin tablets in capsules (TIC) will be supplied as 2 mg tablets encapsulated in hydroxypropyl methylcellulose (HPMC) capsules. The capsules are filled with a mixture of inert ingredients including lactose, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. One (1) moxidectin TIC is required for a 2 mg dose; 2 TICs are required for a 4 mg dose; 4 TICs are required for an 8 mg dose. Ivermectin TIC will be supplied as 3 mg tablets encapsulated in HPMC capsules filled with the same inert ingredients as the moxidectin capsules. Ivermectin will be dosed according to the weight-based dosing schedule approved for the treatment of onchocerciasis in the ivermectin package insert ranging from 6-12 mg. Placebo will be supplied as HPMC capsules filled with the same inert ingredients as the moxidectin and ivermectin capsules. Each subject will receive a single dose of 4 capsules, including moxidectin, moxidectin plus placebo, ivermectin or ivermectin plus placebo depending on body weight and treatment assignment.
Safety Evaluation	Vital signs, ECGs, physical examinations (including a neurologic examination), ocular examinations, AEs, serum chemistries, hematology studies, prothrombin times, and urinalyses.

Efficacy Evaluation	Efficacy evaluations (skin snips) will be performed at 8, 30, 60, 90, and 180 days and 12 and 18 months after dosing and the number of microfilariae/mg of skin determined. Evaluation of the viability and fertility of the adult worms will occur at 18 months. All located nodules will be excised at 18 months, processed for histopathology, and slides interpreted by one or more observers. All subjects who have skin microfilariae at the 18-month visit will be treated with the approved dosage of ivermectin.
Pharmacokinetics	Blood samples for determination of moxidectin plasma concentrations will be collected within 2 hours prior to dosing (0 hr), and at 1, 2, 4, 8, 24, and 72 hours after study drug administration and on study days 8, 13, 18, 30, 60, 90, and 180. Pharmacokinetic (PK) samples will be drawn from all subjects in all cohorts with the exception of the 2nd group of 16 subjects with >20 microfilariae/mg of skin in cohorts 3, 6, and 9. Samples from subjects will be analyzed by a validated bioanalytical method. A PK analysis will be performed using model independent methods to characterize the PK parameters of moxidectin, such as maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration vs. time curve (AUC) and the apparent terminal elimination half-life ($t_{1/2}$).
Pharmacodynamics	Analysis of a correlation between PK parameters, gender, severity of infection, efficacy, and efficacy-related AEs.
Statistical Analysis	This is a randomized, double blind, active-control, dose-escalation trial comparing 3 doses of moxidectin (2, 4, and 8 mg) with ivermectin, stratified by microfilariae density (mild, moderate, severe) and gender. Subjects will be treated as inpatients for the first 18 days and as outpatients for the remainder of the 18-month study. The primary analysis population for safety will be the intent-to-treat (ITT) population, which consists of all subjects who receive study medication. For efficacy, the primary analysis population will be the evaluable subject population, which is defined as all subjects who receive study medication and have baseline and 18 month microfilariae count data. An ITT sensitivity analysis will also be performed to evaluate the effect on the efficacy results of dropouts occurring before 18 months. The primary objective of the study is to evaluate the safety of escalating moxidectin regimens. Both the incidence of clinical AEs and clinically significant laboratory test results will be used to assess safety. The primary efficacy endpoint is the reduction from baseline in skin microfilariae at 18

	months. Microfilariae count will be defined as the geometric mean of skin microfilariae/mg taken at 4 sites (iliac crests and calves). In addition, important secondary endpoints are the reduction from baseline in skin microfilariae at 8, 30, 60, 90, and 180 days, and at 12 months, area under the curve (calculated by using the trapezoidal method through the 18 month visit), ocular examination (time of maximum reduction of microfilariae and number (%) of subjects with complete clearance) and nodulectomy (viability and fertility of macrofilariae) at 18 months.
Rationale for Number of Subjects	At each dose level, 16 mildly, 16 moderately and 32 severely infected subjects will be treated with moxidectin or ivermectin in a 3:1 ratio. The probability of detecting at least 1 AE of grade 2 or higher among 12 moxidectin-treated subjects will be 0.114 and 0.718 when the true rates are 1% and 10%, respectively. The probability of detecting at least 1 AE of grade 2 or higher among 24 moxidectin-treated subjects will be 0.214 and 0.92 when the true rates are 1% and 10%, respectively.

9. SUBJECT FLOWCHART

	Visit Number																									
Clinical Planned Events	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
	Study Day																									
Study Procedures	-4 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	1 mo ±1 wk	2 mo ±1 wk	3 mo ±1 wk	6 mo ±1 mo	12 mo ±1 mo	18 mo ±1 mo
Informed consent	X ^a																									
Demographics	X																									
Admission	X																									
Medical history	X																									
Medication history	X																									
Physical examination	X																				X	X	X	X	X	X
Height	X																									
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X		X ^b	X	X					X																
Ocular examination	X				X				X							X					X	X	X	X	X	X
Retinal Photographs and Fluorescein angiogram ^c	X				X				X							X					X	X	X	X	X	X
Interim physical examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Hematology	X		X	X		X				X					X					X	X	X	X	X	X	X
Serum chemistry	X		X	X		X				X					X					X	X	X	X	X	X	X
Pregnancy test		X																								
Urinalysis	X		X	X		X				X					X					X	X	X	X	X	X	X
Clinical Planned Events	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26

- Will be obtained prior to admission.
- ECG to be done approximately 4 hours after study drug administration. Can be repeated on days 4 through 7 if clinically indicated.
- For all subjects until month 3, then only in subjects with lesions or visual defects.

SUBJECT FLOWCHART (Continued)																										
	Visit Number																									
Clinical Planned Events	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
	Study Day																									
Study Procedures	-4 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	1 mo ±1 wk	2 mo ±1 wk	3 mo ±1 wk	6 mo ± 1 mo	12 mo ±1 mo	18 mo ±1 mo
Skin snips	X									X											X	X	X	X	X	X
Randomization		X																								
Drug packaging and dispensing		X																								
Double-blind drug administration			X ^d																							
Moxidectin Plasma Samples		X ^e	X ^f	X		X				X				X						X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DMPA ^g													X									X				
Discharge																				X						
Nodulectomy																										X ^h
Clinical Planned Events	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26

- d. Will be given after an overnight fast and 2 hours before breakfast.
e. Day -1 sample will be taken approximately 2 hours before drug administration.
f. Day 1 samples will be taken at 1, 2, 4, and 8 hours after drug administration.
g. Depo-medroxyprogesterone acetate (DMPA) on women of childbearing potential not protected by Norplant system.
h. All located nodules will be processed for histopathology and slides read by 1 or more blinded observers.

10. INTRODUCTION

Moxidectin is a macrocyclic lactone drug that is derived from the actinomycete *Streptomyces cyanogriseus* (eg, milbemycin). The compound was developed by Fort Dodge Animal Health as a veterinary product, and is registered worldwide for the prevention of canine heartworm (ProHeart®) and for the treatment of internal and external parasites in cattle, sheep, and horses (Cydectin®).

The World Health Organization (WHO) is interested in using moxidectin for the control of human onchocerciasis. Onchocerciasis, often referred to as river blindness, is a parasitic disease caused by the filarial worm *Onchocerca volvulus* and is transmitted between humans through the bite of black flies of the genus *Simulium*. Onchocerciasis is still endemic in 34 countries: 27 in WHO's African region, 6 in the region of the Americas, and 1 in the Eastern Mediterranean region. Each adult female worm, which can live for an average of 11 years but up to 18 years in the human body, produces millions of microfilariae that migrate throughout the body. The manifestations of onchocerciasis are caused by the microfilariae. Onchocerciasis primarily affects the skin, eyes, and lymph nodes. Severe itching and rash are the most frequent manifestations of the disease. Visual impairment, including blindness, is the most serious consequence. Both manifestations have serious social and economic consequences that justify the vigorous efforts being made to control the disease. The current estimate is that approximately 18 million people are infected, of whom 6.5 million suffer from severe itching or dermatitis, 270,000 are blind, and a further 500,000 are severely visually disabled.

The ultimate goal of the WHO's African Programme for Onchocerciasis Control is to eliminate onchocerciasis as a disease of public health and socioeconomic importance. Currently, the strategies to control the disease include killing the larvae of the black fly vector with insecticides and the treatment of populations at risk with the macrocyclic lactone drug ivermectin (Mectizan®). Ivermectin is a microfilaricide that must be administered at least once per year to control the disease by reducing the numbers of microfilariae in the skin and eyes. Because this treatment has to be given for the life span of adult worms and does not protect subjects from reinfection, it is widely recognized that an alternate treatment is needed, preferably a macrofilaricide that can effect a cure. In addition to its microfilaricidal properties, ivermectin has been shown to have some activity against other stages of *Onchocerca volvulus*: it has a partial in-vivo effect against third-stage, but not fourth-stage, larvae in experimentally infected

chimpanzees¹; after multiple dosage, it reduces insemination and impairs oogenesis in adult female worms²; and causes some decrease in adult worm numbers and viability.³

Moxidectin has some known mechanistic differences from ivermectin. It is considered significantly more potent than ivermectin and may also disrupt additional stages within the parasitic life cycle. Although structurally related to ivermectin, moxidectin is more lipophilic and is therefore expected to have a longer duration of action in humans than ivermectin after oral administration.

Pharmacology

The exact mechanism of action of moxidectin is still under investigation. Studies indicate that moxidectin binds to glutamate-gated chloride channels in the neurons and muscle cells of parasites.⁴ Binding to the ion channel results in hyperpolarization of the nerve and muscle fibers leading to paralysis and death of the parasitic organism. Specificity of moxidectin for the parasite versus the mammalian host results from this compound having a low affinity for the mammalian chloride channels. An additional action of moxidectin is its activity at the GABA-A (gamma aminobutyric acid-A) receptor complex.⁵ The multidrug transporter P-glycoprotein has been implicated in the mechanism of resistance to macrocyclic lactones.⁶ However, moxidectin has been shown to control parasites that are resistant to other macrocyclic lactones as well as benzimidazoles^{7,8} suggesting a different mechanism or susceptibility to resistance. A different binding activity has been demonstrated for a GABA-gated chloride ion channel between ivermectin and moxidectin.⁹

Various in vitro and in vivo studies in mice, jirds, dogs, and cattle have evaluated the activity of moxidectin against *Onchocerca* species and *Brugia pahangi*. In in vitro test systems, moxidectin, ivermectin, doramectin, and milbemycin oxime were evaluated against microfilariae from *Onchocerca volvulus* and *Onchocerca lienalis* in 7-day motility assays. Worm motility was significantly reduced by all 4 compounds at 2 hours, followed by a steady decline up to 120 hours. At the end of the study, the mean percentage reductions in worm motility for ivermectin, moxidectin, doramectin, and milbemycin oxime were 86%, 93%, 93%, and 74%, respectively.^{10,11}

Studies in CBA/Ca mice experimentally infected with *Onchocerca lienalis* and *Onchocerca volvulus* consistently showed that subcutaneous or oral moxidectin was more efficacious than ivermectin in clearing microfilariae.^{10,11}

Investigation of Guadali cattle in Cameroon addressed the effect of moxidectin and ivermectin on preventing infection of *Onchocerca ochengi* L3 to L4 stage larvae in naïve calves under very high natural challenge (infection) conditions. Ivermectin (150 µg/kg) or moxidectin (200 µg/kg) was subcutaneously administered monthly or at 3-month intervals. At the end of the study, 11 of 14 control animals had 110 nodules. Animals treated with ivermectin every month had no nodules, but 2 of 10 animals treated with ivermectin every 3 months had 2 nodules. In moxidectin-treated animals, no nodules were found in animals treated monthly or once every 3 months.¹²

The activity of moxidectin against *Brugia pahangi* was evaluated in a jird and a dog model. In the jird model, the effect of moxidectin, ivermectin, and doramectin on microfilariae was determined. Moxidectin induced a rapid reduction in microfilariae, with none detectable after day 224. Ivermectin and doramectin treatment resulted in a gradual reduction in microfilariae through day 336; however, most jirds still had few microfilariae remaining. The effect on macrofilariae (adult worms) was also assessed. Treatment of jirds with moxidectin resulted in >90% killing of adult worms, whereas ivermectin or doramectin did not have any effect on adult worm burden.¹³ In the dog model, moxidectin at doses of 250 µg/kg or 1000 µg/kg was given 1, 3, 6, or 12 times over a 12-month period. After the first dose of moxidectin, the microfilariae count for all treated dogs gradually declined from pretreatment levels during the first 2 weeks after treatment. By 3 months, the microfilariae counts were suppressed 90% or more from pretreatment levels. The microfilariae counts remained suppressed to the end of the study at 12 months, with 3 of the 78 moxidectin-treated dogs not clearing microfilariae.¹⁴ In the same study, the effect of moxidectin on the macrofilariae was evaluated. At 6 months after the first dose, dogs treated with moxidectin at 250 µg/kg for 3 or 6 doses had 77% and 92% fewer worms, respectively, than controls. At 12 months after the first dose, dogs given 1 or more doses of moxidectin at either 250 µg/kg or 1000 µg/kg had at least 92% fewer worms than controls, with only 6 of 48 treated dogs having live adult worms at necropsy. The worm recoveries from all of the moxidectin treatments were significantly less ($p < 0.05$) than the recoveries for the controls, but there was no significant difference ($p > 0.05$) among the worm recoveries for the different moxidectin treatments. In conclusion, moxidectin was a potent microfilaricidal agent. The suppression of microfilariae is independent of the dosage or the number of treatments and, in the dog model, the effect is sustained for at least 1 year. Furthermore, moxidectin was also effective against *B. pahangi* adults.¹⁴

Animal data indicate that moxidectin is highly lipophilic, residing primarily in fatty tissue. The compound has a long half-life, approximately 20 days in dogs, sheep, and horses. Based on initial PK

data for the 3 mg to 36 mg dose groups in the single-ascending-dose FIM study (protocol 3110A1-100-EU) conducted in volunteer subjects, mean half-life ($t_{1/2}$) in humans ranges from approximately 19.9 to 37.4 days.

Toxicology

Safety studies have been completed in mice, rats, dogs, sheep, cattle, horses, and humans. Repeated-dose toxicity was evaluated in oral (diet) studies in mice (4 weeks), rats (4 and 13 weeks), and dogs (4 and 13 weeks and 1 year), and in oral (diet) carcinogenicity studies in mice and rats (2 years). Results of the repeated-dose studies indicate that moxidectin was well tolerated with no toxicologic effects at calculated dosages of up to 6.9 mg/kg/day in mice for 4 weeks, 3.9 mg/kg/day in rats for 13 weeks, or 1.1 mg/kg/day in dogs for 1 year. At toxic dose levels, events such as decreased activity, prostration, tremors, chromodacryorrhea, decreased respiration, diarrhea, hypersensitivity to touch and sound, and epistaxis were observed. However, the no-toxicologic-effect levels (NTEs) in all animal models were high multiples of the anticipated human dosage on the basis of body weight. The anticipated maximum human dose is a single 8 mg dose per year (0.16 mg/kg for a 50 kg human). The lowest NTEL in single dose studies in the most sensitive species (mice) was 78 mg/kg, the NTEL in repeated dose studies were 6.9 mg/kg/day in mice for 4 weeks, 3.9 mg/kg/day in rats for 13 weeks, and 0.8 mg/kg/day and 1.1 mg/kg/day in dogs for 4 week and 1 year, respectively.

Reproductive Toxicology

Moxidectin was administered by oral gavage at dosages of 0, 2.5, 5, 10, and 12 mg/kg/day once daily to presumed pregnant rats from gestation day 6 through 15. Moxidectin was maternally toxic at dosages of ≥ 10 mg/kg/day as evidenced by decreased body weight, body-weight gain, and food consumption during the daily dosing period. Although not statistically significant, fetal body weights at ≥ 5 mg/kg/day tended to be decreased ($\leq 6\%$) in comparison with controls. At ≥ 10 mg/kg/day, there were statistically significant increases in the number of fetuses with malformations and/or variations (3.1%, 4.3%, 5.5%, 7.9% and 8.4% at 0, 2.5, 5, 10, and 12 mg/kg/day, respectively). The numbers of litters with malformations and/or variations also increased (26.1%, 41.7%, 40.0%, 54.2% and 54.2% at 0, 2.5, 5, 10, and 12 mg/kg/day, respectively). These increases largely reflected increases in cleft palate and/or reversible delays in ossification that were not considered related to reduced fetal weight. It is well

established in the scientific literature that maternal toxicity can result in fetal alterations including malformations and delays in ossification.

There were no moxidectin-related effects on any other maternal or embryo-fetal parameter examined. The maternal and developmental no-toxic-effect level (NTEL) was concluded to be 5 mg/kg/day, with increased incidences of cleft palate and delayed ossification in the presence of maternal toxicity at the higher dosages of 10 and 12 mg/kg/day.

Moxidectin was also administered by oral gavage at dosages of 0, 1, 5, or 10 mg/kg/day to groups of artificially inseminated rabbits from gestation day 7 through 19. Maternal toxicity was evident at dosages ≥ 5 mg/kg/day as evidenced by decreased body weight, body-weight gain, and food consumption during the dosing period. Reduced litter size (6.2 compared with 7.1 in controls), reflective of increased early resorptions (1.2 compared with 0.2 in controls) was observed at 10 mg/kg/day. There were no other moxidectin-related effects, including malformations or other fetal alterations, observed in this study. The maternal and developmental NTEs were concluded to be 1 and 5 mg/kg/day, respectively.

The highest dose of moxidectin to be studied in Phase 2 and possibly Phase 3 clinical trials is a single, oral dose of 8 mg, which is a dosage of 0.16 mg/kg or 5.4 mg/m² (based on body surface area) for a 50kg human. Moxidectin was well tolerated in healthy male subjects after oral administration (liquid formulation) of single doses as high as 36 mg (24.5 mg/m²). The developmental NTEL in both the rat and rabbit studies was 5 mg/kg/day administered in 10 and 13 consecutive, daily doses in rats and rabbits, respectively. The NTEL of 5 mg/kg is approximately 32 times the highest single dose (8 mg) to be administered to humans based on body weight, and approximately 3 times (rat) or 8 times (rabbit) based on body surface area. In the female rat, moxidectin has a half-life of 45 hours (data not available for the rabbit). Therefore, daily administration of moxidectin to pregnant rats, as was done in the teratogenicity study of moxidectin, would likely result in accumulation of the drug in the body, further increasing exposure of the fetus to the drug. Based on the dose per unit of body weight, or dose based on body surface area, the intake by a woman of a single 8 mg dose of moxidectin would be unlikely to pose a risk to the developing human fetus.

Developmental risk can also be assessed based on actual exposure of the body to moxidectin, assuming placental transfer is similar in rats and humans. In a Phase 1 clinical trial using the liquid formulation of

moxidectin, a single oral dose to healthy males of 18 mg of moxidectin resulted in an area under the concentration-time curve (AUC) value of 227 ng/day/mL, which is equivalent to 9.55 ng/hr/mL. In female rats, a single oral gavage dosage of 0.2 mg/kg of moxidectin resulted in an AUC value of 470 ng/hr/mL, which is approximately 50 times the human AUC after a single dose of 18 mg of moxidectin. Assuming linear PK in rats, the developmental NTEL of 5 mg/kg would correspond to an AUC value of approximately 11,750 ng/hr/mL, which is more than 1200 times the human AUC after a single dose of 18 mg of moxidectin. Assuming similar bioavailability of the liquid and tablet formulations of moxidectin in humans (as demonstrated in protocol 3110A1-101-EU), and based on the above exposure considerations, the oral administration of up to 8 mg of moxidectin is unlikely to pose a risk to the developing human fetus.

Prior Human Experience-Potential Risks and Benefits to Human Subjects

The results of nonclinical studies supported the development of moxidectin for the control of human onchocerciasis and the initiation of study 3110A1-100: a single-ascending dose, placebo-controlled, double-blind, safety, tolerability, and pharmacokinetic study of orally administered moxidectin in normal subjects. In this study, 38 healthy subjects were treated with single doses of 3 mg to 36 mg (approximately 50 µg/kg to 600 µg/kg). Subjects were randomized into placebo, 3 mg fasting, 9 mg fasting, 9 mg fed, 18 mg fasting, 36 mg fed and 36 mg fasting groups. Rapid absorption was seen in all dose groups. The results of the comparison of time of maximum concentration (T_{max}) between fasted and fed groups suggested that high-fat food may delay the absorption of moxidectin. Only 1 adverse event (AE) higher than grade 2 was reported in this study (enteritis due to food poisoning [grade 3] in the 36 mg fasting group) and was considered unrelated to study drug. The most common treatment emergent AEs (TEAEs) were headache (35%) and infection (29%). Only half of the headaches reported and none of the infections reported were regarded as study drug related. The reported infections, including type of infection, time of occurrence after moxidectin administration, and dose group were: upper respiratory tract infection (URTI) on Day 19 and Day 63 (same subject) and viral URTI on Day 14 in the 3 mg fasted group; toe infection on Day 52 in the 9 mg fasted group; URTI on Day 30 and Day 78 (different subjects) in the 9 mg fed group; tooth abscess on Day 47 and head cold on Day 50 and Day 66 (different subjects) in the 36 mg fasted group; cold on Day 42 and cold-like symptoms on Day 59 (same subject) in the 36 mg fed group. No SAEs were reported. Four (4) subjects discontinued from the study (1 before receiving study drug and 3 after dose administration [in the 3 mg fasting, 9 mg fed, and 36 mg fasting groups]).

The withdrawal from the study was unrelated to AEs. Overall, moxidectin appears to be safe at the doses evaluated in this study.

In another study (protocol 3110A1-101-EU) the relative bioavailability of a tablet (to be used in this study) and a liquid formulation (used in the first study in healthy subjects; protocol 3110A1-100-EU) of moxidectin at the 10-mg dose strength were compared. This was an open-label, randomized, single-dose, parallel-design study conducted in 58 young healthy male subjects. Subjects' mean age (32 years, range 20 – 45 years) and weight (81 kg, range 57 – 107 kg) were similar for those receiving the tablet formulation (n = 29) and those receiving the liquid formulation (n = 29). Each subject received 1 orally administered dose of moxidectin, either as five 2-mg tablets, or as a liquid. In both cases, moxidectin was administered under fasting conditions. Subjects were followed for 180 days.

During the course of the study, there were no SAEs and no subjects discontinued the study due to an AE.

A total of 36 (62.1%) subjects had TEAEs during the study, with the same number and percentage of subjects (18; 62.1%) reporting TEAEs in both the moxidectin liquid and tablet groups. The most commonly reported (by $\geq 5\%$ of subjects) TEAEs were flu syndrome (17.2% and 20.7% in the liquid and tablet groups, respectively), headache (17.2% and 13.8% in the liquid and tablet groups, respectively), infection (13.8% and 6.9% in the liquid and tablet groups, respectively), diarrhea (10.3% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group).

A total of 19 of 58 (32.8%) subjects reported TEAEs on or prior to day 7 post treatment (during the inpatient period) including 10 of 29 (34.5%) subjects in the group receiving moxidectin liquid and 9 of 29 (31.0%) subjects in the group receiving moxidectin tablets. The most commonly reported (by $\geq 5\%$ of subjects) TEAEs during this period were asthenia (10.3% in the tablet group), headache (13.8% and 6.9% in the liquid and tablet groups, respectively), infection (6.9% in the liquid group), diarrhea (6.9% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group).

A total of 22 (37.9%) subjects reported TEAEs during the outpatient period of the study (after study day 7 and up to study day 180) including 10 (34.5%) subjects in the liquid group and 12 (41.4%) subjects in the tablet group. The most commonly reported events were flu syndrome (17.2% and 20.7% in liquid and tablet groups, respectively), headache (6.9% in the tablet group), and infection (6.9% in the tablet group).

All of the TEAEs that were reported during the study were mild to moderate in intensity, and none were considered to be related to treatment. No clinically relevant abnormalities were observed in vital sign measurements, ECGs or laboratory tests during the study.

The data from the normal subject studies (protocol 3110A1-100-EU and 3110A1-101 EU) suggests that progression to a safety and tolerability study in subjects with different degrees of severity of infection with *Onchocerca volvulus* as described in this protocol is warranted. Based on the preclinical pharmacology data, moxidectin may be microfilaricidal and in addition may eliminate the reproductive capacity of the macrofilaria or be macrofilaricidal. If moxidectin has either of these effects on the macrofilaria, it has the potential to cure the disease in the trial subjects who are recruited from an area without onchocerciasis control, i.e. areas without vector control or ivermectin distribution. If moxidectin does not have either this effect on macrofilaria or a microfilaricidal effect, subjects will benefit from participating in the protocol by the nodulectomies performed, which will free them of all palpable nodules and reduce the number of macrofilaria in their bodies that can generate microfilariae.

Route of Administration, Dosage and Treatment Period

In this study, a tablet formulation will be available for both ivermectin and moxidectin. A single dose regimen was chosen for this study, as well as for the whole development program, because a longer dosing regimen is not compatible with the ultimate use of moxidectin within onchocerciasis control programs.

Moxidectin dose selection (2 mg, 4 mg and 8 mg) was based on comparison of the maximum plasma levels obtained during the first study in human subjects (protocol 3110A1-100-EU liquid formulation, 3 mg : mean 22 ng/mL range 17.1-28.5 ng/mL; 9 mg: mean 54-58 ng/mL, range 38.9 – 66.5ng/mL, Protocol 3110A1-101-EU tablet formulation, 10 mg 67.1 ng/mL) with those of the approved dose of ivermectin (mean 46.6 ng/mL after a 12 mg dose, equivalent to 150 µg/kg for an 80 kg adult), and on the pre-clinical pharmacology data on the relative efficacy of moxidectin and ivermectin. The frequency and severity of AEs after ivermectin treatment are related to the amount of microfilariae killed. Most of the serious and/or severe AEs after ivermectin treatment occur within the first 72 hours after dosing. To reduce the risk associated with AEs related to microfilaria killing after moxidectin treatment, three measures have been included in this protocol: (1) the initial dose of moxidectin in subjects was chosen to

be only 2 mg, (2) subjects are enrolled at each dose level sequentially by increasing severity of infection and (3) subjects are hospitalized during the first 18 days post treatment (see section 11).

11. TRIAL DESIGN

11.1 Description

This is a randomized, ivermectin-controlled, double-blind, single-ascending-dose, parallel design, inpatient/outpatient study of moxidectin administered to subjects of both sexes with different degrees of severity of *O. volvulus* infection. A total of 192 subjects will be enrolled in consecutive cohorts and will receive a single oral dose of moxidectin or a standard dose of ivermectin. Moxidectin is available in 2 mg TIC (tablets in capsules). Three (3) dose levels of moxidectin will be studied: 2 mg, 4 mg, and 8 mg. Therefore, the dose of moxidectin will be either 1 TIC for the 2mg, 2 TIC for the 4 mg, or 4 TIC for the 8 mg dose group.

Ivermectin will be dosed according to the approved weight based dosing schedule (see section 17.1).

To ensure blinding, moxidectin-treated and ivermectin-treated subjects may receive a number of placebo capsules so that each subject receives 4 capsules. All doses will be given after an overnight fast and breakfast will be delayed for about 2 hours.

Enrollment will be by dose and severity of infection as indicated below. The intensity of infection will be based on the mean of the densities at the iliac crests and calves. At each dose level, subjects with > 0 and < 10 microfilariae/mg of skin must have no ocular involvement; subjects with 10-20 microfilariae/mg. of skin must have not more than 10 microfilariae in both eyes.

- Cohort 1: 2 mg, 16 subjects with > 0 and < 10 microfilariae/mg of skin
- Cohort 2: 2 mg, 16 subjects with 10-20 microfilariae/mg of skin with ≤ 10 microfilariae in both eyes
- Cohort 3: 2 mg, 32 subjects with > 20 microfilariae/mg of skin with or without ocular involvement (this cohort will be enrolled in two groups of 16 subjects due to the capacity of the site)
- Cohort 4: 4 mg, 16 subjects with > 0 and < 10 microfilariae/mg of skin

- Cohort 5: 4 mg, 16 subjects mg, with 10-20 microfilariae/mg of skin with ≤ 10 microfilariae in both eyes
- Cohort 6: 4 mg, 32 subjects with > 20 microfilariae/mg of skin with or without ocular involvement (this cohort will be enrolled in two groups of 16 subjects due to the capacity of the site)
- Cohort 7: 8 mg, 16 subjects with > 0 and < 10 microfilariae/mg of skin
- Cohort 8: 8 mg, 16 subjects with 10-20 microfilariae/mg of skin with ≤ 10 microfilariae in both eyes
- Cohort 9: 8 mg, 32 subjects with > 20 microfilariae/mg of skin with or without ocular involvement (this cohort will be enrolled in two groups of 16 subjects due to the capacity of the site)

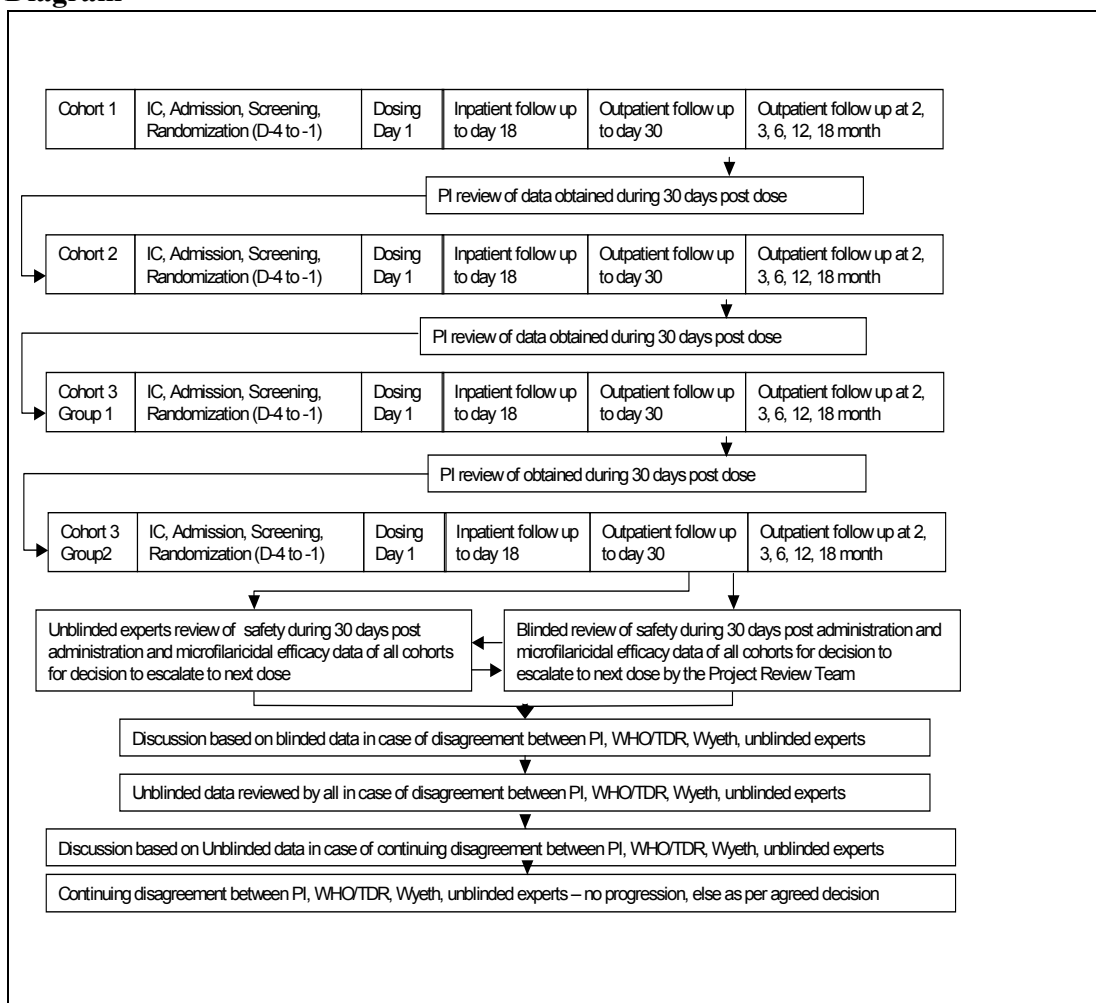
The decision to move to the next cohort within one dose group will be made by the PI based on evaluation of all blinded data obtained during the first 30 days post treatment of the previously enrolled cohort(s).

The decision to move to the next higher dose group, will be made based on blinded review of the safety and microfilaricidal data obtained during the first 30 days post treatment of all previously enrolled cohorts. The PI will submit a recommendation to proceed or not to proceed after a detailed examination of the blinded data. The Wyeth Medical Monitor, the WHO Clinical Monitor and the WHO Project Manager will conduct their separate review of the blinded data. Wyeth will include a representative of its safety surveillance group in addition to the medical monitor for purposes of review. WHO may include its Clinical Coordinator in the review.

The Project Review Team (PRT), consisting of Wyeth and WHO/TDR reviewers and the PI, will discuss the blinded data and formulate a recommendation to progress or not. The recommendation will be provided together with the rationale for this recommendation to the Clinical Expert Review Team (CERT) consisting of three clinical experts (not otherwise associated with the conduct of the study) who have access to the randomized dose assignments and have reviewed the data in parallel with the PRT. If there is a difference of opinion within the PRT regarding the dose progression recommendation, the different recommendations and their rationale will be provided to the CERT. The CERT will provide their recommendation to PRT. If there is not unanimous agreement among the CERT, they will provide their differing recommendations and their rationale. If there is not unanimous agreement on proceeding to the next dosing cohort between the PRT, and a majority of the CERT, the data will be discussed in a blinded fashion. If no agreement can be reached, unblinded data will be made available to the PRT and discussed. If upon discussion of the unblinded data there is no unanimous agreement to proceed to the next higher dose group, dose progression will not occur.

The diagram below provides an overview of the process from enrollment of the first cohort (2 mg) to decision to progress to the 4 mg dose as well as treatment and study participation for each subject. The same process will be followed for the cohorts in the 4 mg dose group and the decision to move to the 8 mg dose.

**Enrollment Process and Dose Progression Decision
Diagram**



A schematic presentation of procedures is provided in the subject flowchart (section 9).

12. STUDY OBJECTIVES

12.1 Primary

The primary objective of this study is to determine the safety and tolerability of orally administered moxidectin in subjects with *O. volvulus* infection, as measured by the incidence of clinical AEs and clinically significant laboratory test results.

12.2 Secondary

The secondary objectives of this study are:

1. To determine doses that effectively eliminate microfilariae and prevent their reaccumulation in the skin as measured by the skin microfilarial loads at days 8, 30, 60, 90, and 180, and at 12 and 18 months after treatment.
2. To determine the viability and fertility of adult worms at 18 months.
3. To assess the pharmacokinetics of moxidectin in adult male and female subjects.

13. SELECTION OF STUDY POPULATION

This study will be conducted in otherwise healthy subjects with *O. volvulus* infection from the OCRC study area in the basin of River Tordzi, located in the forest area of south-eastern Ghana and within a 2 to 2½ hours journey from Hohoe, the location of the study site. The Onchocerciasis Control Programme (OCP) had established in 1988, during the southern extension of the program, that transmission of onchocerciasis in the area involved forest vectors exclusively and hence no control activities were instituted. The area was also not included in the ivermectin distribution program launched by the Directorate for Onchocerciasis Control of the Ministry of Health since the area is largely hypoendemic for onchocerciasis. Extensive clinical, ophthalmologic and parasitological surveys carried out by the OCRC showed that morbidity due to onchocerciasis was low. The vast majority of adults had no skin or ocular lesions. Where ocular lesions were found they were mainly non-onchocercal. This was in line with the observation during initial contact with the area that most villages had never heard of onchocerciasis, the *Simulium* fly, or of ivermectin and very few had attended any health institution for skin or ocular problems or for the excision of nodules. Thus the OCRC only offered individualized treatment with ivermectin to those found during surveys to have significant

onchocercal lesions. The communities were informed of the existence elsewhere of mass treatment with ivermectin and the availability of the drug at nearby centers.

Subjects will be members of a “grand cohort” who were previously prescreened in their villages and the hospital and who have been dormant, pending further testing and enrollment in the appropriate clinical trial.

The ‘grand cohort’ was identified previously in a step-wise process consisting of (1) identification of potentially suitable villages based on entomological data collected by the Onchocerciasis Control Programme, and/or indirectly via OCRC out-patients with high skin microfilaria counts from these villages, and/or known breeding sites of *Simulium* close to these village and/or village residents reporting a high prevalence of onchocerciasis and *Simulium* bite rates, (2) an initial meeting with the village chief, elders and opinion leaders during which the information provided in a ‘generic information sheet’ (e.g. background on onchocerciasis, purpose of the OCRC, purpose and procedures for screening, general purpose and procedures for three types of studies (clinical drug efficacy and safety study, ‘ex vivo’ study of the efficacy of drugs on the macrofilariae, PK study) is presented and discussed, (3) a meeting with the community in which the same information was presented and discussed, after the village chief, elders and opinion leaders had provided their agreement to such a meeting, (4) a village survey, after the community had agreed to that, (5) a screen at Onchocerciasis Chemotherapy Research Centre in the Government Hospital at Hohoe for those subjects that, based on the village survey, had onchocerciasis, were 18-60 years old, had no obvious exclusion factors, and had agreed to the hospital screen. The results of the screening were communicated to the subjects. Subjects who could potentially qualify for a clinical trial form the ‘grand cohort’ from which subjects for future studies will be recruited. Informed consent was obtained at all stages of contact with the communities listed above. The “generic” informed consent form was the basis for the transfer of information and the subsequent discussions. The consent prior to the hospital screening phase was verbal and involved thousands of people in the initial stages and a few hundred in the hospital-screening phase.

For recruitment for this study, subjects on the ‘grand cohort’ list will be asked to come for screening per cohort, based on position of their name on the list, gender and microfilaria counts. If a subject asked to come for screening for a particular cohort meets all inclusion criteria and has none of the exclusion criteria, but has a microfilaria count too high or too low for that cohort, they will be offered the choice between (1) enrollment into the next cohort for which they qualify based on their microfilaria count or (2)

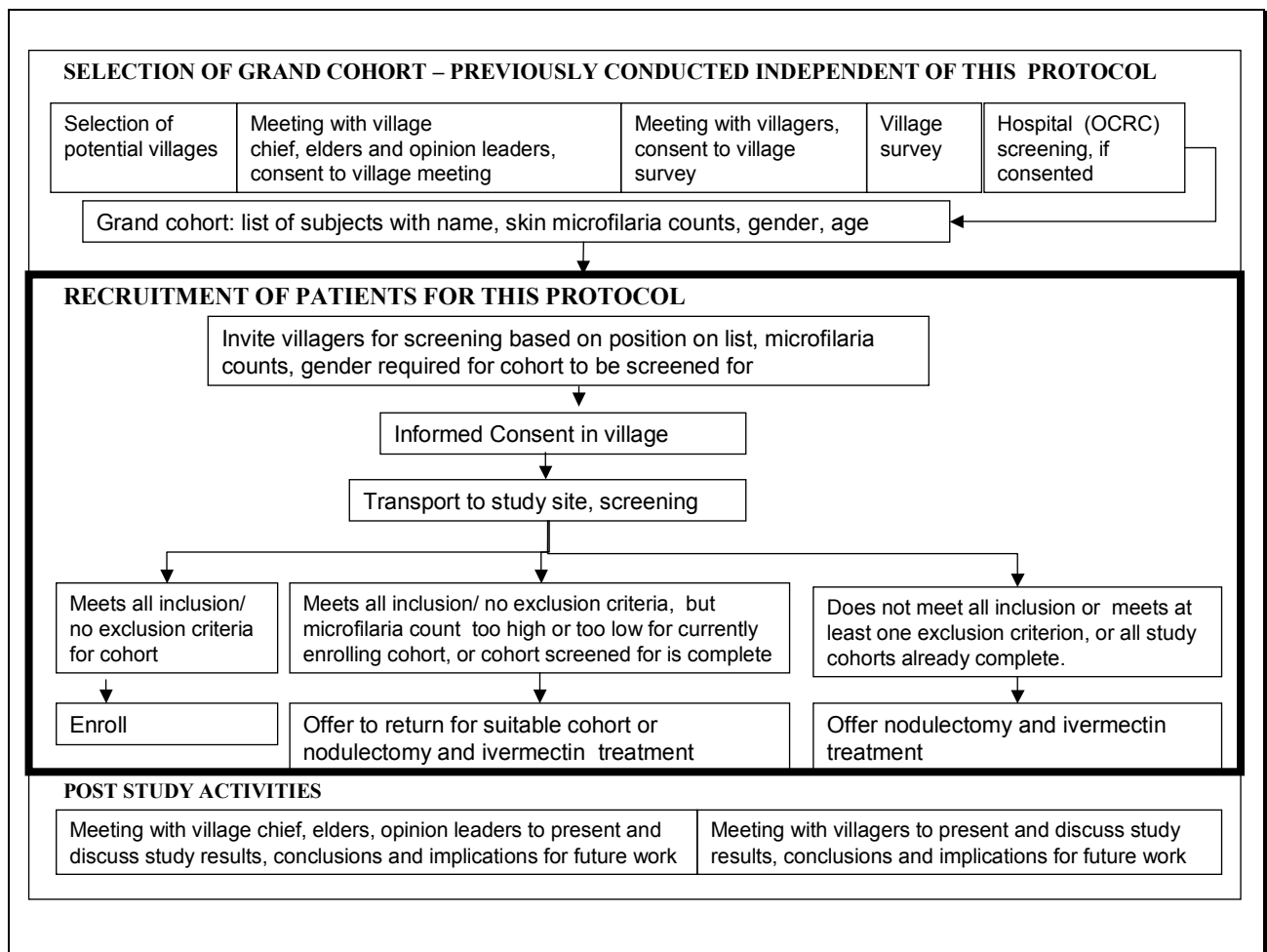
nodulectomy and ivermectin treatment. If their microfilaria count is too low or too high for any cohort planned in the future, they will be offered nodulectomy and ivermectin treatment. The same will happen, if they do not meet one of the other inclusion criteria or meet an exclusion criterion (see figure below) or if 16 subjects higher on the grand cohort list have already qualified for the study.

All members of the grand cohort who are invited for this study participate in a written and signed or thumb printed informed consent process. During this process, the PI or co-investigator informs the subjects of all the elements specific to the study. An information sheet that is specific to the study and is available in English and the local language replaces the generic information sheet. Adequate time is then allowed, as during the earlier discussion, for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including transport to the study site and screening, will be performed until the subject has signed or thumb printed and dated an ethics committee (EC) approved informed consent form. The form will be witnessed by a member of the community (impartial witness) and countersigned by the investigator. A copy will be given to the subject. The study begins at the time the first subject is admitted to the hospital for the study. Subjects must meet all the inclusion and none of the exclusion criteria to be enrolled in the study.

OCRC informs each subject individually about the details of the study, which concern him/her from the time of enrollment to completion. This includes AEs, lab results etc. and the final status. If there are any outstanding medical issues, further advice is given.

Following completion of the study, the PI and his staff seek an appointment with the chiefs and the elders and discuss the overall findings and conclusions of the study with them. Subsequently, study results and conclusions are presented and discussed at a village durbar. The discussions with chiefs and elders as well as those at the village durbar include the implications of the study results for future studies on moxidectin as well as other research.

Consent Process Diagram



13.1 Inclusion Criteria

Ivermectin-naïve men and women in good general health, with *O. volvulus* infection and:

- a) Written, signed (or thumb-printed), and dated informed consent
- b) Aged 18 to 60 years, inclusive
- c) Body weight ≥ 40 kg for women and ≥ 50 kg for men
- d) Nonpregnant, nonbreastfeeding women. Women of child-bearing potential must agree to use birth control during the first 150 days after treatment.
- e) Healthy, as determined by a physician on the basis of a physical examination, ECG, and a thorough review of the medical history and clinical laboratory results
- f) No previous exposure to moxidectin
- g) Adequate hematologic, renal, and hepatic function, defined as:
 - 1) White blood cell (WBC) count $\geq 2,800$ and $\leq 11,800$ cells/mL
 - 2) Hemoglobin: ≥ 11.0 g/dL for men and ≥ 10.0 g/dL for women
 - 3) Platelet count: $\geq 110,000$ mm³
 - 4) Serum creatinine: ≤ 1.25 x upper limit of normal (ULN)
 - 5) Total bilirubin: ≤ 1.25 x ULN
 - 6) AST/SGOT: ≤ 1.25 x ULN
 - 7) AP: ≤ 1.25 x ULN
 - 8) Prothrombin time WNL
 - 9) Urinalysis WNL
- h) Skin microfilarial density within the required range for the cohort

13.2 Exclusion Criteria

- a) Participation in any studies other than purely observational ones, within 4 weeks before test article administration.
- b) Any vaccination within 4 weeks before test article administration
- c) Acute infection requiring therapy within the last 10 days before test article administration
- d) Administration of any medication (with the exception of medication required to treat any reactions during the screening fluorescein angiography or paracetamol) or herbal preparation within 10 days prior to test article administration or any condition currently requiring regular medication

- e) Clinically significant ECG abnormalities or history of cardiac abnormality
- f) Subjects with orthostatic hypotension at the screening evaluation
- g) History of drug or alcohol abuse or regular use of ≥ 3 cigarettes per day
- h) Use of alcohol or other drugs of abuse within 72 hours before test article administration
- i) Any condition, in the investigator's opinion, that places the subject at undue risk
- j) Subjects who have donated blood within 8 weeks before study entry
- k) Subjects with ocular onchocerciasis in cohorts intended to enroll subjects with mild infection. Ocular onchocerciasis is defined by presence of live or dead microfilariae, onchocercal punctate opacities, onchocercal lesions of the posterior segment or lesions that mimic those seen in onchocerciasis.
- l) Subjects with hyperreactive onchodermatitis
- m) Antifilarial therapy within the previous 5 years,
- n) Coincidental infection with *Loa Loa*
- o) Female subjects of childbearing potential with a contraindication to DMPA if not on Norplant
- p) Any other condition which the investigator feels would exclude the subject from the study

Subjects who are excluded from the study or subjects who are withdrawn from the study for medical reasons will be advised where to seek assistance.

13.3 Number of Subjects

One hundred and ninety-two (192) subjects including both sexes, aged 18 to 60 years are expected to enroll in this study. There will be 9 cohorts. The first 2 cohorts at each dose level will comprise 16 subjects while the third cohort will comprise 32 subjects, which will be enrolled in 2 successive groups of 16. The study will aim to enroll equal numbers of men and women at each dose level and intensity of infection.

13.4 Screen Failures

Subjects who sign an informed consent form and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. All screen failures should be recorded in the screening and enrollment log. A copy of the log should be retained in the investigator's study files. No case report forms (CRFs) will be

completed for screen failures. Subjects who are excluded on medical grounds will be advised where to seek assistance.

14. PRIOR TREATMENT

Reasonable efforts will be made to determine all relevant treatment received by the subject within 10 days prior to study drug administration. All relevant information, including the names of any procedures, drugs, or herbal or dietary supplements used will be recorded in the subject's CRF. Include the name of the procedure or drug and other information required on the CRF. Subjects must not have taken any medication, prescription or over-the-counter (OTC), within 10 days before administration of the study drug (with the exception of medication required to treat any reactions during the screening fluorescein angiography or paracetamol). Subjects must also have discontinued use of herbal and dietary supplements at least 10 days before study drug administration.

15. CONCOMITANT TREATMENT

15.1 Additional Required Drugs

Depo-medroxyprogesterone acetate (DMPA), 150 mg, will be administered twice to all women of childbearing potential. The first dose will be given on study day 11 and the second dose will be at month 2 (± 1 week). Women who have contraceptive protection by the Norplant system will be excluded from the DMPA injections. Dosing will be collected on the CRF.

15.2 Permitted Treatment

All medication given after admission to the hospital will be documented in the CRF.

15.3 Prohibited Treatment

Smoking, the ingestion of alcoholic beverages, grapefruit, or grapefruit juice, and the use of non-prescribed drugs will not be permitted during the 18 day admission period. Treatment with other anthelmintic agents including ivermectin will be prohibited for the duration of the study. If anthelmintic treatment has been taken for any reason, the subject will be withdrawn from the study.

16. TREATMENT OF SUBJECTS

16.1 Procedures

See flowchart(s) for the procedures to be performed at each visit.

16.1.1 Days -4 to -1 (Visit 1)

Subjects will be admitted to the OCRC at the beginning of this period and the following procedures and evaluations will be performed:

- Informed consent will be obtained prior to transport of the potential study participants from the village to the study center and before any study-related procedures are performed.
- Demographics (age, tribal origin, gender), medical history, medication history (all prescription and over-the-counter medications taken within 10 days prior to study drug administration) will be recorded.
- A complete physical examination, including the subject's height and weight, and a review of body systems, will be performed by a licensed physician.
- A twelve-lead ECG will be performed (See section 16.3.3, Special Methods, Electrocardiograms).
- An ocular examination, including fundus colour photography and fluorescein angiography for all subjects..
- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken up to 12 times throughout this screening period.
- An evaluation of any AEs will be conducted during waking hours as other activities permit.
- A complete laboratory evaluation including hematology with prothrombin time and G6PD, hemoglobin electrophoresis, serum chemistry (first morning fasted values) and a routine urinalysis (see section 16.3.5, Special Methods, Laboratory Evaluations/Specimen Collection).
- Skin snips will be taken from both iliac crests and calves to determine microfilarial density.

16.1.2 Day -1 (Visit 2)

On day -1, the final list of study participants will be drawn up.

- A pregnancy test (serum β -hCG) will be performed for all women of childbearing potential and the results known prior to study drug administration.
- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature).

- Adverse events assessment
- Randomization (once all screening data have been completed, and the subject meets the inclusion/exclusion criteria, a subject will be randomly assigned to receive moxidectin or ivermectin therapy).
- Packaging, dispensing and labeling of test articles. These will be locked up until the morning of day 1.

16.1.3 Day 1 (Visit 3)

On day 1, the following evaluations/procedures will be performed:

- A pre-treatment blood sample for PK analysis (obtained within 2 hours before drug administration)
- Test articles administration at 0700 $\pm$ 1 hours
- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 3 times in the 24 hour period.
- Adverse events assessment
- Blood samples for PK analysis at 1, 2, 4, and 8 hours (each time point $\pm$ 15 minutes) post study drug administration
- Interim physical examination including weight
- Twelve-lead ECG approximately 4 hours after dose administration
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis.

16.1.4 Day 2 (Visit 4)

On day 2, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Interim physical examination including weight
- Twelve-lead ECG

- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis. For the WHO substudies, blood and urine samples will be filtered and examined for microfilariae.
- Blood sample for 24 hour (± 15 min) post study drug administration for PK analysis.

16.1.5 Day 3 (Visit 5)

On day 3, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Interim physical examination including weight
- Twelve-lead ECG
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography

16.1.6 Day 4 (Visit 6)

On day 4, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Interim physical examination including weight
- Blood sample for 72 hour (± 15 min) post study drug administration for PK analysis.
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis.

16.1.7 Day 5 (Visit 7)

On day 5, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment

- Interim physical examination including weight

16.1.8 Day 6 (Visit 8)

On day 6, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Interim physical examination including weight

16.1.9 Day 7 (Visit 9)

On day 7, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Interim physical examination including weight
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography.

16.1.10 Day 8 (Visit 10)

On day 8, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], repeated after standing for at least 2 minutes; respiratory rate, and oral temperature) will be taken approximately 5 times in the 24 hour period.
- Adverse events assessment
- Twelve lead ECG
- Interim physical examination including weight
- Blood sample for Day 8 (± 1 hour) post study drug administration for PK analysis.
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis.
- Skin snips

16.1.11 Day 9 (Visit 11)

On day 9, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs]; respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight

16.1.12 Day 10 (Visit 12)

On day 10, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight

16.1.13 Day 11 (Visit 13)

On day 11, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight
- DMPA injection to women of child bearing potential (except those protected by the Norplant system)

16.1.14 Day 12 (Visit 14)

On day 12, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight

16.1.15 Day 13 (Visit 15)

On day 13, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis. For the WHO substudies, blood and urine samples will be filtered and examined for microfilariae.
- Blood sample for Day 13 (± 1 hour) post study drug administration for PK analysis

16.1.16 Day 14 (Visit 16)

On day 14, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography.

16.1.17 Day 15 (Visit 17)

On day 15, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight

16.1.18 Day 16 (Visit 18)

On day 16, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.

- Adverse events assessment
- Interim physical examination including weight

161.19 Day 17 (Visit 19)

On day 17, the following evaluations/procedures will be performed:

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 2 times per day.
- Adverse events assessment
- Interim physical examination including weight

16.1.20 Day 18 (Visit 20)

On day 18, the following evaluations/procedures will be performed. Subjects will be discharged after all procedures are completed.

- Vital sign measurements (supine pulse rate and blood pressure [see section 16.3.2 Vital signs], respiratory rate, and oral temperature) will be taken 1 time prior to discharge.
- Adverse events assessment
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Blood sample for Day 18 (± 1 hour) post study drug administration for PK analysis.

16.1.21 1-month (Visit 21)

At 1 month (± 1 week), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate [see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Skin snips

- Blood sample for Day 30 (± 1 week) post study drug administration for PK analysis.
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography.

16.1.22 2-Months (Visit 22)

At 2 months (± 1 week), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate [see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Skin snips
- Blood sample for Day 60 (± 1 week) post study drug administration for PK analysis.
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography
- DMPA injection to women of child bearing potential(except those protected by the Norplant system)

16.1.23 3-Months (Visit 23)

At 3 months (± 1 week), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate[see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Skin snips

- Blood sample for Day 90 (± 1 week) post study drug administration for PK analysis.
- Ocular examination for all subjects, including fundus colour photography and fluorescein angiography

16.1.24 6-Months (Visit 24)

At 6 months (± 1 month), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate [see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis.
- Skin snips
- Ocular examination for all subjects. Color fundus photography and fluorescein angiography only for subjects with lesions, or with visual function defect.
- Blood sample for Day 180 (± 1 month) post study drug administration for PK analysis

16.1.25 12-Months (Visit 25)

At 12 months (± 1 month), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate [see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Skin snips
- Ocular examination for all subjects. Color fundus photography and fluorescein angiography only for subjects with lesions, or visual function defect.

16.1.26 18-months (Visit 26)

At month 18 (± 1 month), subjects will return to the center for an outpatient visit. They will be questioned about their overall health, including any changes in health status and the indication for use of any medication. The following evaluations/procedures will be performed:

- Vital sign measurements (supine blood pressure and heart rate [see section 16.3.2 Vital signs], respiratory rate, and oral temperature)
- Adverse events assessment
- Physical examination including weight
- Laboratory evaluations including hematology with prothrombin time, serum chemistries (first morning fasted values), and routine urinalysis
- Skin snips
- Ocular examination for all subjects. Color fundus photography and fluorescein angiography only for subjects with lesions, or with visual function defect.
- Nodulectomy
- All subjects who have skin microfilariae will be treated with the approved dosage of ivermectin.

16.2 Discontinuation and Withdrawal of Subjects

- Subjects who withdraw their consent before administration of the test article will be replaced.
- Subjects cannot be withdrawn from therapy because this study involves only a single dose administration.
- A subject can be withdrawn from the study after test article administration if continued follow up jeopardizes the subject's health in the judgment of the principal investigator (e.g. an illness that contra-indicates follow up visits).
- A subject who terminates participation or is withdrawn from the study by the PI after test article administration will be considered as having discontinued from the study and will not be replaced unless the number exceeds 2 subjects in any 16 subject group and the terminations occur before day 7.
- PK data will not be collected on subjects who replace those who have withdrawn post drug administration.
- Replacement subjects will be assigned to the same cohort and treatment as the subjects leaving the study and will need to complete safety evaluations at day 30 (± 7) before subsequent cohorts are enrolled.

- Replacement subject numbers will be the number of the subject that they replace plus 10000. Subject numbers for the 9 cohorts without replacements are from 101-1216, replacements would be assigned numbers 10101-11216.

Subjects manifesting serious medical illnesses should be discussed with the clinical coordinator and medical monitor(s). The PI will be responsible for any decision regarding the subject's discontinuation from the study.

Subjects that terminate before the end of the study should have the procedures performed that are indicated for the 18-month visit on the study flow chart. Nodulectomy will be performed if the subject agrees but the results will not be collected on the CRF. A reasonable effort will be made to ascertain the reasons for withdrawal from the study or failure to return and these will be recorded in the CRF. This protocol only requires administration of one dose of study drug; therefore, subjects with AEs will not have to be withdrawn since no further study drug will be administered.

The administration of the test article(s) may be delayed for up to 2 days to permit all predose examinations to be performed on replacement subjects.

16.3 Special Methods

16.3.1 Physical Examinations and Medical History

A complete physical examination will be performed at baseline, and at 1, 2, 3, 6, 12, and 18 months. These will include height (cm, on admission only), weight (kg), vital signs, supine pulse rate and blood pressure, respiratory rate, and oral temperature, and a complete review of body systems. A summary of the dermatologic findings including nodules and onchocercal skin lesions will be entered in the CRFs.

Medical history will be obtained at baseline and will include a history of both systemic and ocular symptoms. These symptoms will be monitored for any changes in severity that could be attributed to test drug administration.

Interim physical examinations conducted during the admission period will include weight (kg), vital signs, and a review of body systems to determine whether there have been any significant changes since the previous examination.

At each post-discharge follow-up visit the subject will be questioned regarding any recent illness or changes in health status, and any medication taken and for what indication. All findings will be recorded, any significant changes investigated, and relationship to test drug administration defined.

16.3.2 Vital Signs

Vital signs including pulse rate, blood pressure, respiratory rate, and oral temperature (centigrade) will be measured after the subject has been in a supine position for at least 5 minutes. During the screening period and on Day 1 to Day 8, pulse rate and blood pressure measurements will be repeated after the subject has been standing for 2 minutes. Measurements will be taken up to 12 times during the 4 day screening period, approximately 3 times per day on day 1, 5 times per day on day 2 to day 8, and twice a day for the remainder of the inpatient period. Vital signs measurements including pulse rate, supine blood pressure, respiratory rate, and oral temperature (centigrade) will also be made at each outpatient visit.

16.3.3 Electrocardiograms

Twelve-lead ECGs will be performed during baseline and on day 1 (approximately 4 hours following test article administration) and on days 2, 3, and 8. A physician experienced in evaluating ECGs will provide the interpretations of all ECGs. This should include the rate, rhythm, length of the PR, QRS and Q-T intervals, and any abnormalities noted. The results will be recorded in the CRFs. Additional ECGs will be performed at the discretion of the investigator, or where clinically indicated.

16.3.4 Ocular Examination

Ocular examinations will include examination of visual acuity, visual fields using a calibrated Goldmann perimeter, color vision, external ocular structures, ocular mobility and pupillary reflex. The anterior segment will be examined with a Haag-Streit 900 slit-lamp. Microfilariae in the anterior chamber will be counted after head-down positioning for 5 minutes. Living and dead microfilariae in the cornea and punctate opacities will be counted. Intraocular pressure will be measured and the dilated fundus examined by direct and indirect ophthalmoscopy. Color fundus photography and fluorescein angiography (using 20% fluorescein sodium) will be done on all subjects before dosage and at days 3, 7, 14 days and 1, 3 months and will not be repeated unless lesions or visual function deficiencies are demonstrated. The

color photographs and fluorescein angiograms will be retained at the study site. Descriptive abnormalities will be recorded on the case report forms.

16.3.5 Laboratory Evaluations/Specimen Collection

Hematologic studies, including prothrombin time, a complete blood cell count (CBC), including hematocrit, hemoglobin, WBC with differential, and platelet count, will be obtained. A G6PD and hemoglobin electrophoresis will also be obtained with the screening CBC.

Serum chemistry tests will be performed, including sodium, potassium, chloride, bicarbonate, glucose, total protein, albumin, urea, creatinine, alkaline phosphatase, lactic dehydrogenase (LDH), total bilirubin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST/SGOT), and alanine aminotransferase (ALT/SGPT).

Routine urinalysis, using a 10-parameter dipstick (specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase) and microscopic evaluation will be performed.

All specimens for hematologic and serum chemistry tests will be obtained with subjects in the fasting state.

A pregnancy test (serum β -hCG) will be performed at baseline on all women of childbearing potential.

Blood samples for PK analysis for moxidectin will be collected in 10 mL collection tubes containing heparin as an anticoagulant. The plasma will be processed and separated into 2 tubes according to Attachment 2. One set of samples will be sent to the bioanalytical laboratory for analyses. The other set of samples will be stored at Hohoe until all analyses are complete. PK data will not be collected on subjects who replace those who have withdrawn post drug administration.

16.3.6 Skin Snips

A total of 4 skin snips will be taken at each time point (from iliac crests and calves) using a corneosccleral punch (Walser or Holth-type). Each snip will be weighed on an analytical balance and incubated overnight in isotonic saline in a well of a flat-bottomed microtitre plate. The microfilariae that have

emerged will be counted using an inverted microscope. The skin microfilarial density at each site will be documented as the number per mg of skin. One punch will be used per subject and punches will be sterilized between subjects using steam under pressure (autoclave).

17. TEST ARTICLE

17.1 Test Article(s) and Administration

Test article is administered only to subjects who have provided informed consent, fulfill all inclusion and exclusion criteria and have been assigned a randomization number by the unblinded third party pharmacist (see section 18.1). Once a randomization number and the associated test article has been assigned to a subject it must not be reassigned to another subject. All subjects will receive a total of 4 capsules. Matching placebo capsules will be administered as necessary so that each subject receives the same number of capsules independent of their treatment assignment.

The doses of moxidectin for this study are 2 mg, 4 mg, and 8 mg and will be administered to subjects in TIC, each HPMC capsule containing 2 mg moxidectin.

The moxidectin group will receive either 1, 2 or 4 moxidectin capsules based on the dosage for that group. (see Table 17.4.A and Attachment 4).

Ivermectin will be supplied as 3 mg tablets encapsulated in HPMC capsules and will be dosed according to the weight based dosing schedule approved for the treatment of onchocerciasis in the ivermectin package insert. (See Table 17.4.A and Attachment 4).

The recommended dosage of ivermectin in the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 µg/kg of body weight.

The capsules will be swallowed with water.

Ivermectin Weight based Dosing Schedule¹⁵	
Bodyweight (kg)	Dose Number of 3 mg tablets
26 to 44	Two
45 to 64	Three
65 to 84	Four

The doses of moxidectin for this study were selected based on safety data from an initial PK study in man and expected therapeutic blood levels based on those of ivermectin, a similar compound. The starting dose (2 mg or approximately 33 µg/kg for a 60 kg subject) is similar to the minimal effective dose of ivermectin (30 µg/kg).

17.2 Packaging and Labeling

The moxidectin tablets used in this study contains the following ingredients:

Component	% w/w
Moxidectin solid	2.00
Microcrystalline Cellulose	44.625
Lactose, Anhydrous	44.625
Croscarmellose Sodium	5.00
Sodium Lauryl Sulfate	3.00
Colloidal Silicon Dioxide	0.25
Magnesium Stearate	0.5

The placebo contains all ingredients listed above except the moxidectin solid.

Each ivermectin tablet contains 3 mg of active drug. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, magnesium stearate, butylated hydroxyanisole, and citric acid powder (anhydrous).

For blinding purposes each 2 mg moxidectin tablet and each 3 mg ivermectin tablet was inserted into an HPMC capsule filled with a mixture of inert ingredients (lactose, microcrystalline cellulose, magnesium

stearate and sodium starch glycolate). Detailed instructions for the unblinded designated individual who prepares the drug are provided in Section 17.4 and Attachment 4.

The three capsules used in this study contain the following ingredients:

Component	Moxidectin	Placebo	Ivermectin
	% w/w		
Moxidectin 2 mg Tablet	1 Tablet	0	0
Ivermectin 3 mg Tablet	0	0	1 Tablet
Microcrystalline Cellulose	40	96.5	40
Lactose, Anhydrous	59	0	59
Sodium Starch Glycolate	0.5	0	0.5
Magnesium Stearate	0.5	0.5	0.5
Croscarmellose Sodium	0	3.0	0
Capsule #0 HPMC Opaque (Brown)	1 capsule	1 capsule	1 capsule

17.3 Storage and Stability

Moxidectin 2 mg TICs and Ivermectin 3 mg TICs as well as the placebo capsules should be stored at room temperature up to 30°C with protection from light.

17.4 Preparation

The drug will be prepared by an unblinded pharmacist on the day before dosing according to Table 17.4A and Attachment 4. The prepared drug, identified for each subject by subject name, initials, age, sex, weight, subject number and randomization number, will then be provided to the clinical study staff who will administer the drug.

Table 17.4.A: STUDY DRUG PREPARATION																		
Cohort	2 mg						4 mg						8 mg					
Treatment Assignment	Moxidectin			Ivermectin			Moxidectin			Ivermectin			Moxidectin			Ivermectin		
Capsule ^a	M	P	I	M	P	I	M	P	I	M	P	I	M	P	I	M	P	I
Weight	Number of Capsules																	
26-44 kg	1	3	0	0	2	2	2	2	0	0	2	2	4	0	0	0	2	2
45-64 kg	1	3	0	0	1	3	2	2	0	0	1	3	4	0	0	0	1	3
65-84 kg	1	3	0	0	0	4	2	2	0	0	0	4	4	0	0	0	0	4

a: M - Capsule containing 2 mg moxidectin tablet, P - Placebo capsule, I - Capsule containing 3 mg ivermectin tablet

17.5 Test Article Accountability, Reconciliation, and Return

The European Medicines Evaluation Agency (EMA), and Special Program for Research and Training in Tropical Diseases (TDR) require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. Storage conditions must also be documented. The PI is responsible for accounting for all unused test articles and all used test article containers.

Supplies will be shipped to the principal investigator site for the study initiation. The OCRC will use the relevant form to document test article disposition and record storage conditions from initial receipt through the completion of the study. This form will be completed by the unblinded third party pharmacist and kept locked in a cabinet accessible to no one else. Each time a dose is prepared for a subject, the following information will be recorded by the unblinded third party pharmacist:

- the subject's initials

- the subject number
- randomization number
- the total dose prepared
- the number and type of capsules
- the packaging control number (lot number) from which the different types of capsules were taken
- the initials of the person preparing the dose

At a minimum, drug accounting will be reviewed by an unblinded monitor not involved in subject treatment or dose progression decision after the 30 day safety review of the last cohort to be enrolled has been completed.

At the termination of the study, a final drug accountability review and reconciliation will be completed, any discrepancies will be investigated, and their resolution will be documented. All unused test articles will be returned to Wyeth or shall be properly disposed of at the direction of Wyeth, including all empty containers. The test article accountability, reconciliation, and return procedures also apply to all other test articles (i.e. comparator, placebo) that are required by the protocol and supplied by the sponsors.

17.6 Study Subject Compliance

The study staff will directly observe compliance. Moxidectin and ivermectin will be administered in a single oral dose under medical supervision in the hospital and administration recorded on the source documents and CRF.

17.7 Other Supplies

Wyeth will provide additional clinical supplies such as CRFs, SAE reporting forms, PK specimen tubes and PK specimen labels.

18. MEASURES TO MINIMIZE/AVOID BIAS

18.1 Subject Identification

Subjects will be enrolled by dose and severity of *O. volvulus* infection. The intensity of infection will be based on the mean of the densities at the iliac crests and calves. Each cohort will consist of 16 subjects

(12:4 moxidectin:ivermectin). They will receive a single oral dose followed by frequent safety monitoring over a 30-day period. There will be a total of 9 cohorts, based on the dose of moxidectin to be administered and the intensity of infection as follows:

- 2 mg: subjects with > 0 and < 10 microfilariae/mg of skin (16 subjects)
- 2 mg: subjects with 10-20 microfilariae/mg of skin (16 subjects)
- 2 mg: subjects with > 20 microfilariae/mg of skin with or without ocular involvement (32 subjects) to be enrolled in 2 consecutive groups of 16 subjects.
- 4 mg: subjects with > 0 and < 10 microfilariae/mg of skin (16 subjects)
- 4 mg: subjects with 10-20 microfilariae/mg of skin (16 subjects)
- 4 mg: subjects with > 20 microfilariae/mg of skin with or without ocular involvement (32 subjects) to be enrolled in 2 consecutive groups of 16 subjects.
- 8 mg: subjects with > 0 and < 10 microfilariae/mg of skin (16 subjects)
- 8 mg: subjects with 10-20 microfilariae/mg of skin (16 subjects)
- 8 mg: subjects with > 20 microfilariae/mg of skin with or without ocular involvement (32 subjects) to be enrolled in 2 consecutive groups of 16 subjects.

At the time of initiation of screening, each subject is assigned a unique subject number in the order in which they are scheduled for screening. Each subject randomized will keep this subject number for the duration of the study. Subject numbers will not be reassigned or reused for any reason. However, a subject who does not qualify for one cohort based on his/her skin microfilaria count or because the cohort currently being screened for is already complete, but qualifies for another cohort, can be re-screened prior to enrollment of the cohort for which he/she qualifies based on skin microfilaria counts and assigned the next subject number in sequence.

Screening evaluations (history, physical and ocular exam, ECG, lab evaluations, skin snip) will be performed during the 4-day screening period prior to administration of test article on day 1.

All subjects who are screened (including screen failures) will be recorded in an Onchocerciasis Chemotherapy Research Centre (OCRC) screening and enrollment log. Information to be collected includes:

- Date of screening
- Subject number
- Subject initials
- Ethnic origin
- Reason for screen failure (if applicable)

After completing the baseline investigations and qualifying for the study, each subject will be assigned a randomization number by an unblinded third party pharmacist. This number will automatically assign him/her to 1 of 2 treatment regimens (12:4 moxidectin:ivermectin) according to a predetermined schedule (section 18.2, Randomization). Subjects will be dosed according to the schedule in Table 17.4.A and Attachment 4. Treatment will be given after an overnight fast of at least 8 hours on day 1 under medical supervision. Breakfast will be delayed for 2 hours. Smoking, the ingestion of alcoholic beverages, grapefruit, or grapefruit juice, and the use of non-prescribed drugs will not be permitted during the 18-day admission period. Subjects will be encouraged to continue this practice at least until the day 30-31 follow-up and to maintain their normal exercise patterns.

The unblinded third party pharmacist will maintain confidentiality of the randomization number lists and prepare the test articles for administration. The PI will provide the unblinded third party pharmacist with the names, subject numbers, baseline severity and gender of those who are eligible for the trial.

Subjects should be identified to the sponsors only by their assigned numbers, initials, age, and sex. The investigator must maintain a list of subject names and the identifying information indicated above.

18.2 Randomization

Subjects will be assigned a randomization number by the unblinded third party pharmacist. The unblinded third party pharmacist will be supplied with 12 randomization schedules - one for each of the 3 severity levels (mild, moderate, severe) within each of the 3 dose cohorts (2 mg, 4 mg, 8 mg) and 3 additional schedules for the most severe (> 20 mf/mg of skin) subjects. Each randomization schedule will have 16 unique randomization numbers. The randomization numbers will be assigned by the unblinded third party pharmacist at the time of preparing the study medication and will be recorded on to the case report forms. Treatment groups will be blocked in groups of 4 with a 3 to 1 ratio of moxidectin to

ivermectin. When the first male subject is enrolled, the assigned treatment (randomization number) will be selected from the top of the randomization list that corresponds to the subject's assigned stratum. The treatment (randomization number) for the first female subject will be selected from the bottom of the randomization list that corresponds to the subject's assigned stratum. The second male subject will be assigned the next available treatment from the top of the randomization list that corresponds to the subject's assigned stratum. The second female subject will be assigned the next available treatment from the bottom of the randomization list that corresponds to the subject's assigned stratum. Assignment to treatment group will continue in this manner until the entire cohort has been assigned to a treatment group. A new randomization schedule should be used when a new cohort is started.

At the end of the study, the randomization numbers will be used to identify the treatment group assigned to the subject.

18.3 Blinding

The study monitor, the investigator(s), and the subjects at the site will be blinded to treatment assignment. The unblinded third party pharmacist will not participate in the evaluation of any study subject. This will permit all other participants to remain blinded. The unblinded third party pharmacist will prepare and label all treatments with the names and randomization numbers of the subjects based on the randomization list. Individuals who are unaware of the test article random assignment will administer the treatments to the subjects. Contact between the unblinded third party pharmacist and study subjects will be kept to a minimum. The investigator, sub-investigator, research nurse, and any study participants other than the unblinded third party pharmacist will not be allowed to know the treatment assigned to any study subject and will not have access to the randomization treatment records.

The subject's treatment will be unblinded only if an AE occurs that both the investigator, the Wyeth medical monitor and/or the WHO clinical coordinator and project manager believe requires identification of the treatment assignment. In this case, the unblinded third party pharmacist will inform the investigator, who will inform the Wyeth medical monitor of the subject's treatment assignment and the reason(s) for breaking the randomization code.

Emergency unblinding will be at the discretion of the Principal Investigator. The investigator must submit a written explanation describing the event to the sponsors within 5 working days. All randomization envelopes must be returned to the sponsors at the completion of the trial.

19. SAFETY

19.1 Safety Variables

All subjects enrolled in this study will be closely monitored for safety and evaluated for any AEs. Safety evaluation will include: symptoms, physical examinations, vital signs measurement, ECGs, ocular exams, and laboratory evaluations. All evaluations will be monitored as outlined in section 16.1, Procedures, and section 16.3, Special Methods. A key safety component of the study drug will be determined by the presence and severity of the Mazzotti reaction. An important consideration in the administration of microfilaricides to *O. volvulus* infected subjects is the potential for the combination of AEs due to the pharmacologic properties of the drug with the constellation of symptoms, signs and laboratory events that occur when microfilariae are killed (the Mazzotti reaction).¹⁶ These need to be differentiated one from the other and from any coincidental illnesses that may occur in temporal relationship with test drug administration. Common systemic clinical manifestations of the Mazzotti reaction include pruritus, rash, lymphadenitis, headache, myalgia, arthralgia, hypotension, fever and swellings of the face and limbs. Ocular events include epiphora, photophobia, conjunctival injection, limbitis, anterior uveitis, chorioretinitis and optic neuritis.

The clinical laboratory changes involve the peripheral blood leucocytes, aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) and sometimes lactate dehydrogenase (LDH) and gamma-glutamyl-transferase (GGT); microfilariae also appear in blood, urine, and other body fluids. The eosinophils exhibit the most prominent changes. There may be an initial eosinopenia followed several days later by a marked increase above pretreatment levels. A complete disappearance of eosinophils from the peripheral blood is the laboratory hallmark of a severe reaction. Lymphocyte counts may fall initially, followed by lymphocytosis, but not to the same extent as with eosinophils. Leucocytosis with neutrophilia is less common. Elevations in liver enzymes occur, but rarely exceed grade 2 and usually normalize by day 30. Levels of bilirubin and alkaline phosphatase are usually unchanged. Any deviation from this pattern of liver function abnormalities should prompt investigations for an intrinsic drug effect or a coincidental illness. Proteinuria may occur. Although the laboratory

changes per se have little clinical significance, they give indirect evidence of the death of microfilariae and may even indicate the severity of the reaction to the event.¹⁷

The factors that govern the Mazzotti reaction include the intensity of infection,¹⁸ the dose regimen, and the microfilaricide used. These determine the onset, evolution, reaction severity, extent of the laboratory changes, and whether the reaction is mono- or biphasic. A notable exception occurs in subjects with hyper-reactive onchodermatitis (Sowda),¹⁹ where severe, predominantly cutaneous adverse effects occur even with very low skin microfilarial counts.

For a given intensity of infection, the severity of the Mazzotti reaction to ivermectin is independent of dose within the range of 150 to 800 µg/kg (approximately 9 mg-48 mg).²⁰ Dangerous and alarming reactions result from the simultaneous occurrence of severe reactions in multiple systems.²¹ This phenomenon is rare with ivermectin. Biphasic reactions, characterized by a marked recrudescence of cutaneous or lymph node symptoms or the development of an acute febrile polyarthritis,²² several days after the initial reaction, have also not been observed with ivermectin. There is no reason to believe that the Mazzotti response to moxidectin would differ radically from those due to ivermectin. However, a more rapid elimination of microfilariae may result in an earlier onset, or a more severe reaction, for a given initial infection intensity.

Severe reactions can usually be aborted by the administration of 100 to 200 mg of hydrocortisone hemisuccinate intravenously aided by supportive therapy.

The clinical events will be graded according to the National Cancer Institute common toxicity table, version 2.0, with additions specific for this protocol summarized in Attachments 5 and 6.

More frequent safety evaluations may be made if clinically indicated or at the discretion of the investigator. All adverse effects (AEs) will be recorded in the CRFs throughout the entire study.

19.2 Safety Assessment Methods and Dose Progression Decision

The decision to move to the next higher dose group, will be made based on blinded review of the safety and microfilaricidal data obtained during the first 30 days post treatment of all previously enrolled cohorts.

The PI will submit a recommendation to proceed or not to proceed after a detailed examination of the blinded data. The Wyeth medical monitor, the WHO clinical monitor and the WHO Project Manager will conduct their separate reviews. Wyeth will include a representative of its safety surveillance group in addition to the medical monitor for purposes of review. WHO may include its Clinical Coordinator in the review.

The PRT will discuss the blinded data and the recommendation to progress or not. The recommendation will be provided together with the rationale for this recommendation to CERT who have access to the randomized dose assignments and have reviewed the data in parallel with the PRT. If there is a difference of opinion within the PRT regarding the dose progression recommendation, the different recommendations and their rationale will be provided to the CERT. The CERT will provide their recommendation to the PRT.

The experts will review the unblinded data with special focus on the following:

- The number of possibly, probably or definitively drug related non-CNS AEs $\geq$ grade 2 among moxidectin treated subjects.
- The number of subjects with possibly, probably or definitively drug related CNS AEs $>$ grade 1 that are not related to the efficacy of moxidectin (i.e. not characterized by the PI as Mazzotti reactions) among moxidectin treated subjects.
- Any moxidectin treated subject with a possibly, probably or definitively drug related SAE not related to the efficacy of moxidectin (i.e. not characterized by the PI as Mazzotti reactions).

The review will take the clinical significance of the AEs in the context of the control programs into consideration.

If there is not unanimous agreement among the CERT, they will provide their differing recommendations and their rationale. If there is not unanimous agreement on proceeding to the next dosing cohort between the PRT and a majority of the CERT, the data will be discussed in a blinded fashion. If no agreement can be reached, unblinded data will be made available to the PRT and discussed. If upon discussion of the

unblinded data there is no unanimous agreement to proceed to the next higher dose group, dose progression will not occur. A more detailed description of the procedures in the dose progression monitoring plan will be reviewed and approved by the PRT and the CERT.

19.3 Safety Laboratory Determinations

All clinical and laboratory evaluations that deviate from baseline values after study drug administration and are considered to be clinically significant will be repeated and followed until normalization. If normalization does not occur within 2 weeks or by day 30, the etiology will be identified, if possible, and the Wyeth medical monitor, the WHO clinical monitor, and the WHO project manager, will be notified.

20. EFFICACY

20.1 Efficacy Variables

Efficacy against the microfilariae will be determined by reductions from initial counts in skin and ocular microfilariae (where applicable).

20.1.1 Primary

This study will give initial indications of the efficacy of moxidectin against the microfilariae of *O. volvulus*. The primary efficacy variable will be:

- The change from baseline in the mean number of skin microfilariae per milligram of skin sampled at 4 body locations (right and left iliac crests, right and left calves) at 18 months after test article administration

20.1.2 Secondary

Secondary efficacy variables will include:

- The mean reduction from baseline, as well as the percentage of subjects with undetectable microfilariae, will be calculated by dose and severity of infection for each post treatment evaluation time point.

- The change from baseline in the mean number of skin microfilariae per milligram of skin sampled at 4 body locations (right and left iliac crests, right and left calves) at 12 months after test article administration.
- The change from baseline in the mean number of skin microfilariae per milligram of skin sampled at days 8, 30, 60, 90, and 180.
- The change from trough values to 12 months and 18 months post treatment in the mean number of skin microfilariae per milligram of skin sampled at 4 body locations (right and left iliac crests, right and left calves) to quantify the effect on the reproductive capacity of adult worms.
- The area under the curve (calculated by using the trapezoidal method through the 18 month visit)
- Ocular examination (time of maximum reduction of microfilariae and number (%) of subjects with complete clearance). The change from baseline in the mean number of ocular microfilariae measured in the anterior chamber. Living and dead microfilariae in the cornea and punctate opacities will also be counted. Retinal changes secondary to the disease will also be examined. Ocular examinations will be performed at baseline and on days 3-4, 7-8, 14-15, 30-31, 90-91, 180 and 12 and 18 months.
- Evidence of an effect on the viability and/or fertility of the macrofilaria will be obtained from the histologic examination of nodules excised at 18 months. Parameters to be evaluated include
 - a. Viability (number live, moribund, dead)
 - b. Calcification (presence/absence)
 - c. Reproductive status:
 - i. Females:
 - Proportion:
 - 1. Number producing embryos up to the microfilarial stage
 - 2. Degenerated microfilariae in uterus
 - 3. Relict embryos
 - ii. Males:
 - Proportion with:
 - 1. Spermatogenesis normal or abnormal
 - iii. Other criteria:
 - Proportion of nodules with:
 - 1. Microfilariae in the capsule
 - 2. No male worms

20.2 Efficacy Assessment Methods

- The maximal microfilaricidal effect on skin microfilariae will be determined by skin snips taken at days 8 and 30.
- Nodules will be processed at 18 months for histological examination and assessed by the OCRC parasitology department (blinded to the treatment).

21. PHARMACOKINETIC ANALYSIS

Blood samples for determination of moxidectin plasma concentrations will be collected within 2 hours prior to dosing (0 hr), and at 1, 2, 4, 8, 24, and 72 hours after study drug administration and on study days 8, 13, 18, 30, 60, 90, and 180. PK samples will be drawn from all subjects in all cohorts with the exception of the 2nd group of 16 subjects with > 20 microfilariae/mg of skin in cohorts 3, 6, and 9. Samples from subjects will be analyzed by a validated bioanalytical method.

A PK analysis will be performed using model independent methods to characterize the PK parameters of moxidectin, such as maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration vs. time curve (AUC) and the apparent terminal elimination half-life ($t_{1/2}$).

22. STATISTICAL ANALYSIS

22.1 Statistical Methods

This is a randomized, double-blind, active-control, dose-escalation trial comparing 3 doses of moxidectin (2, 4, and 8 mg) with ivermectin, stratified by microfilariae density (mild, moderate, severe) and gender. Subjects will be treated as in subjects for the first 18 days and as outpatients for the remainder of the 18 month study.

The primary analysis population for safety will be the intent-to-treat (ITT) population, which consists of all subjects who receive study medication. For efficacy, the primary analysis population will be the evaluable subject population, which is defined as all subjects who receive study medication and have

baseline and 18-month microfilariae count data. An ITT sensitivity analysis will also be performed to evaluate the effect on the efficacy results of dropouts occurring before 18 months.

The primary objective of the study is to evaluate the safety of escalating moxidectin regimens. Both the incidence of clinical AEs and clinically significant laboratory test results will be used to assess safety. The primary efficacy endpoint is the reduction from baseline in skin microfilariae at 18 months. Microfilariae count will be defined as the geometric mean of skin microfilariae/mg taken at 4 sites (iliac crests and calves).

In addition, important secondary endpoints are the reduction from baseline in skin microfilariae load at days 8, 30, 60, 90, 180 and at 12 months, area under the curve (calculated by using the trapezoidal method through the 18 month visit), ocular examination (time of maximum reduction of microfilariae and number (%) of subjects with complete clearance) and nodulectomy (viability and fertility of macrofilariae) at 18 months.

22.2 Methodology

Initially, an overall among-group test will be performed to determine if any significant differences exist among the 4 treatment groups (2 mg, 4 mg, 8 mg moxidectin, and ivermectin). For this analysis the ivermectin control will be pooled over all nine cohorts (three dose groups). Following a significant overall result, paired comparisons (i.e., each moxidectin group versus ivermectin) will be performed to characterize the results. Prior to pooling the nine cohorts the ivermectin response for the nine cohorts will be graphically evaluated to ensure that there is no time effect on the pooled ivermectin results. For safety, moxidectin will be compared with ivermectin with respect to the incidence of AEs by using the Fisher's exact test. Laboratory data will be analyzed by using the analysis of covariance, adjusting for baseline. For efficacy, the microfilariae counts will be logarithmically transformed (Mosteller and Tukey) and analyzed by using the analysis of covariance, adjusting for baseline counts and the number of sites from which the microfilariae were taken. The latter covariate will be used to adjust for subjects who have fewer than 4 microfilarial collection sites. Factors in the model will include treatment group, covariates, level of microfilariae density (mild, moderate, severe), and gender. Also, a sensitivity analysis will be performed to examine the effect on results of second-order interactions. Data results will be summarized as adjusted geometric means. If the assumptions of normality or log-normality are not met, the data will be analyzed by using the Friedman Test, blocking on baseline skin microfilariae density and gender. In

order to evaluate the robustness of the results, the microfilariae data will also be analyzed as a percent change from baseline. The proportion of subjects cured (i.e. with undetectable microfilariae) will also be evaluated.

For the analysis of microfilariae viability and fertility endpoints, proportions will be analyzed by using the Cochran-Mantel-Haenszel procedure blocking on baseline skin microfilariae density. If the overall test is significant, paired comparisons will be made comparing each moxidectin group with ivermectin.

For ocular microfilariae, time to maximum reduction will be analyzed by using the Friedman Test blocking on baseline skin microfilariae density. The proportion of subjects with complete clearance will be analyzed by the Cochran-Mantel-Haenszel procedure blocking on baseline skin microfilariae density. If the overall test is significant, paired comparisons will be made comparing each moxidectin group with ivermectin.

All tests will be performed as 2-sided tests with $\alpha = 0.05$.

22.3 Sample Size and Power

For the mild and moderate severity levels in each dose group, 16 subjects will be randomly assigned in a 3:1 ratio to either moxidectin or ivermectin, for the severe level in each dose group 32 subjects will be randomly assigned to treatment using the same ratio. The probability of detecting at least 1 AE of NCI grade 2 or higher among 12 moxidectin-treated subjects will be 0.114 and 0.718 when the true rates are 1% and 10%, respectively. The probability of detecting at least 1 AE of NCI grade 2 or higher among 24 moxidectin-treated subjects will be 0.214 and 0.92 when the true rates are 1% and 10%, respectively.

For efficacy, given that the subjects in the three severity levels within a moxidectin dose group can be pooled and that all ivermectin subjects can be pooled, there will be 48 subjects per moxidectin dose group and 48 subjects in the pooled ivermectin treatment group. With 48 subjects per treatment group there is 78.3% power to detect a statistically significant difference between a response (% of baseline microfilariae) of approximately 0.1% (moxidectin) and 20% (ivermectin) at 18 months after treatment.

23. CONTRAINDICATIONS, PRECAUTIONS, AND WARNINGS

Safety studies have been completed in mice, rats, dogs, sheep, cattle, horses, and humans. At toxic dose levels, events such as decreased activity, prostration, tremors, chromodacryorrhea, decreased respiration, diarrhea, hypersensitivity to touch and sound, and epistaxis were observed. However, the NTEs in all of the animal models were high multiples of the anticipated human dosage on the basis of body weight. Further information is given in the Moxidectin Investigator's Brochure provided. The data from the first study in man, a single ascending dose study in uninfected subjects followed for 80 days after dose administration show that moxidectin is safe and well tolerated at single doses between 3 mg and 36 mg. No SAEs and no grade 4 AEs were reported. Only 1 AE higher than grade 2 was reported in this study (enteritis due to food poisoning [grade 3] in the 36 mg fasting group) and was considered unrelated to study drug. The most common AEs were headache (35%) and infection (29%). Only half of the headaches reported and none of the infections reported were regarded as study drug related. The reported infections, including dose group, infection type and days after moxidectin administration, were: 3 mg fasted – upper respiratory tract infection (URTI) on Day 19 and Day 63 (same subject), viral URTI on Day 14; 9 mg fasted – toe infection on Day 52; 9 mg fed – URTI on Day 30 and Day 78 (different subjects); 36 mg fasted – tooth abscess on Day 47, head cold on Day 50 and Day 66 (different subjects); 36 mg fed – cold on Day 42 and cold-like symptoms on Day 59 (same subject). Four (4) subjects discontinued from the study (1 before receiving study drug and 3 after dose administration [in the 3 mg fasting, 9 mg fed, and 36 mg fasting groups]). The withdrawal from the study for these subjects was unrelated to AEs.

In a bioavailability study comparing the tablet and liquid forms of moxidectin (protocol 3110A1-101-EU) 58 healthy male subjects received a single dose of 10 mg of moxidectin either as the liquid formulation (29 subjects) used in the FIM study or as tablets (29 subjects) and were followed up for 180 days. During the course of this study there were no SAEs and no subjects discontinued the study due to an AE. A total of 36 (62.1%) subjects had treatment emergent AEs (TEAEs) during the study, with the same number and percentage of subjects (18; 62.1%) reporting TEAEs in both the moxidectin liquid and tablet groups. During the first 7 days post treatment, 10 subjects (34.5%) receiving liquid moxidectin and 9 subjects (31.0%) receiving tablet reported AEs, including asthenia (10.3% in the tablet group), headache (13.8% and 6.9% in the liquid and tablet groups, respectively), infection (6.9% in the liquid group), diarrhea (6.9% in the liquid group), myalgia (6.9% in the tablet group), and dizziness (6.9% in the tablet group).

Between day 8 and 180 of follow up, 10 subjects (34.5%) receiving liquid and 12 subjects (41.4%) receiving tablet reported AEs. The most commonly reported events were flu syndrome (17.2% and 20.7% in liquid and tablet groups, respectively), headache (6.9% in the tablet group), and infection (6.9% in the tablet group). All of the TEAEs were mild to moderate in intensity, and none were considered to be related to treatment. No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory tests during the study.

For a complete description of all (AEs) reported during the Phase 1 clinical studies with moxidectin, please refer to the most recent moxidectin Investigator's Brochure provided.

24. ADVERSE EVENTS

24.1 Definitions

The term "adverse event," as used by the sponsors, is synonymous with the term "adverse experience," which is used by the FDA.

An **adverse event** is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with a sponsor's test article, regardless of causal relationship. This includes the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of a sponsor test article whether accidental or intentional (ie, a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor's test article (ie, use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor's test article.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A **preexisting condition** is a clinical condition (including a condition being treated and AEs occurring between ICF signing to the subject's arrival at the clinic) that is diagnosed or occurs before the screening of the subject for this study is initiated in the hospital. A preexisting condition can be part of the subject's

medical history or part of baseline conditions and are recorded in the source records and on the appropriate page of the CRF (for randomized subjects).

Baseline conditions are all those clinical conditions, including those related to infection with *Onchocerca volvulus*, present at the time of screening. Medical history are all clinical conditions known to have been present prior to screening. A condition can be both part of the medical history and baseline conditions if the condition started prior to screening and is still present at screening (e.g. any condition related to infection with *Onchocerca volvulus*).

Adverse events occurring during and due to screening procedures will be recorded as adverse events.

AE collection on source documents starts on the date of subject's arrival at the clinic / start of screening. From this time point, any SAEs are reported to Wyeth within 1 business day from their occurrence.

The questions concerning whether the condition existed before the start of the active phase (i.e. treatment) of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE (TEAE). An AE is considered to be treatment emergent if (1) it was not present when the active phase of the study began and is not a chronic condition that is part of the subject's medical history, or (2) it was present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increased during the active phase.

The active phase of the study begins at the time of the administration of the test article and ends at the 18 month visit.

A ***serious adverse event*** (SAE) is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life threatening (see below)
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in cancer

- Results in a congenital anomaly or birth defect

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A **life threatening adverse event** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization is to be considered only as an overnight admission. Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating investigator should not report hospitalization or prolongation of hospitalization on a Serious Adverse Event form (a 7443 form). This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (eg, stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (eg, elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt whether the information constitutes an AE or SAE, the information is treated as an AE or SAE.

24.2 Timing for Reporting Serious Adverse Events

Any SAE, regardless of causal relationship, must be reported to the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (GNCP) (or their designees) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by faxing a completed serious adverse event form (form 7443) to the numbers indicated in the front of this protocol and then confirming by telephone that the faxes were received. Compliance with this time requirement is essential so that the sponsors may comply with their regulatory obligations.

Follow-up information relating to an SAE must be reported to the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (or their affiliates or designees) within 24 hours of receipt by the investigator by faxing a completed serious adverse event form (form 7443) to the numbers indicated in the front of this protocol and confirming by telephone that the faxes were received. The subject should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

Any emergency must be reported to the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (or their affiliates or designees) immediately (within 24 hours).

For all other inquiries and information about this study, contact a clinical scientist listed in the front of this protocol.

24.3 Reportable Events/Information

- An AE or SAE can occur from the time that the subject begins the hospital screening period to the completion of the final study visit at month 18; regardless of test article or protocol relationship. All

AEs and SAEs will be recorded on source documents. All AEs and SAEs for subjects who are not screen failures will be recorded in the CRFs. The investigator must follow up as is medically necessary on all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilizes.

For SAEs: The investigator will provide all documentation pertaining to the event (eg, additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc) to the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (or their affiliates or designees) in a timely manner. Reports relative to the subject's subsequent course must be submitted to the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (or their affiliates or designees) until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

- The following events will be recorded and reported in the same time frame and following the same process as for SAEs:
 1. All pregnancies that occur during the study and their outcome. If a pregnancy is confirmed during the study, the Wyeth medical monitor, the WHO clinical monitor, the WHO project manager and the Coordinator of the Ghana National Center for Pharmacovigilance (or their affiliates or designees) should be notified immediately. When possible, all reports of pregnancy must be followed up for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. The investigator will provide follow-up information concerning the outcome of the pregnancy to the sponsors and the Coordinator of the GNCP in a timely manner. This information will be provided regardless of whether the subject has discontinued participation in the study.
 2. Test article abuse and overdose (ie, use for nonclinical reasons) with or without AEs. An overdose is a dose higher than that prescribed by a health care professional for clinical reasons. It is up to the participating investigator to decide whether a dose was an overdose.
 3. Inadvertent or accidental exposure to test article with or without an AE.

- Poststudy test article-related SAEs.
- SAEs occurring after unauthorized or accidental use in persons not participating in the study.
- Abnormal biological or vital signs values that are considered clinically relevant by the participating investigator. These must be reported in the same time frame and following the same process as for an AE or an SAE.

24.4 Recording and Reporting

At each required study visit, all AEs that have occurred since the previous visit must be recorded in the adverse event record of the subject's CRF. The information recorded should be based on the signs and symptoms detected during the physical examination and clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

The following AE information must be included (when applicable): the specific condition or event and direction of change; whether the condition was preexisting (ie, an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (eg, in severity and/or frequency); the dates and times of occurrence; severity; causal relationship to test article; action taken; and outcome. The causal relation between an AE and the test article will be determined by the investigator on the basis of his or her clinical judgment and the following definitions:

- ***Definitely related:*** Event can be fully explained by administration of the test article.
- ***Probably related:*** Event is most likely to be explained by administration of the test article rather than the subject's clinical state or other agents/therapies.
- ***Possibly related:*** Event may be explained by administration of the test article or by the subject's clinical state or other agents/therapies.
- ***Probably not related:*** Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the test article.
- ***Definitely not related:*** Event can be fully explained by the subject's clinical state or other agents/therapies.

When assessing the relationship between administration of a test article and an AE, the following should be considered:

- Temporal relationship between administration of the test article and the AE
- Biological plausibility of relationship
- Subject's underlying clinical state or concomitant agents and/or therapies
- When applicable, whether the AE abates on discontinuation of the test article (dechallenge)
- When applicable, whether the AE reappears on repeat exposure to the test article (rechallenge)

SAEs that are not test article related may nevertheless be considered by the participating investigator or the medical monitor (or designee) to be related to the conduct of the clinical study, ie, to a subject's participation in the study. For example, a protocol-related SAE may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

The severity of AEs will be assessed according to the National Cancer Institute's common toxicity criteria (CTC), version 2.0, April 30, 1999.²³ Additions to this grading scale for ocular, hematological and biochemical adverse events can be found in Attachments 5 and 6 respectively

25. DATA QUALITY ASSURANCE

The sponsors perform quality control and assurance checks on all clinical studies that they sponsor. Before enrolling any subjects in this study, sponsors' personnel and the investigator review the protocol, the brochure for clinical investigators, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsors monitors the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded on the CRFs is verified against source documents. All data on the CRFs will have corresponding source records in patient charts or laboratory records. After the sponsors receive the CRFs, the data are entered into the database by using a double data entry procedure. The sponsors' medical monitor reviews the data for safety information. The sponsor clinical data associates review the data for legibility, completeness, and logical consistency. Additionally, the sponsors clinical data associates use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction are forwarded to the investigative site for resolution. A sample set of records from the final database will be fully audited against the corresponding CRFs.

26. INVESTIGATORS REGULATORY OBLIGATIONS

26.1 Independent Ethics Committee (GFDB/IEC) Approval

The protocol and the informed consent document must have the initial and at least annual (when required) approval of the GFDB/IEC. The signed GFDB/IEC approval letter must identify the documents approved (ie, list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Written information to be provided to the subject (eg, diary cards, instructions for test article administration) and any advertisement used to recruit subjects must also be reviewed by the GFDB/IEC. The sponsors will not ship clinical supplies until a signed approval letter from the GFDB/IEC has been received and a contractual agreement has been signed by the sponsors and the clinical site. Copies of the regulations relating to IECs are available from the sponsors.

26.2 Prestudy Documentation

The investigator must provide the sponsors with the following documents BEFORE enrolling any subjects:

- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the investigator, subinvestigators, and all key personnel listed on the clinical study information form.
- Copy of the GFDB/IEC approval letter for the protocol and informed consent. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the GFDB/IEC must also be provided to the sponsors. Any changes in this study or unanticipated problems involving risks to the subjects must be reported promptly to the GFDB/IEC. An investigator must not make any changes in a study without GFDB/IEC and sponsors approval except when necessary to eliminate apparent immediate hazards to the subjects. All protocol amendments must be submitted to the GFDB/IEC and approved.
- Copy of the GFDB/IEC-approved informed consent document to be used.
- When applicable, a list of the GFDB/IEC members and their qualifications, and a description of the committee's working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Fully executed clinical study agreement (CSA).

- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsors must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsors must be notified if normal values or units of measurement change.

26.3 Informed Consent

Regulatory agencies have issued regulations to provide protection for human subjects in clinical investigations and to describe the general requirements for informed consent.

A copy of your proposed informed consent document should be submitted to the sponsors for review and comment before submission to your IEC. The study should not begin until the document has been reviewed by the sponsors and must not begin until the document has been approved by the IEC. In some instances the study must not begin until the document has been approved by a regulatory agency.

The informed consent document shall contain all of the elements of informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the subject and/or inclusion of additional information in an informed consent document. Copies of the regulations relating to informed consent and the protection of human subjects in clinical studies are available from the sponsors.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, the PI should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

The delegation of investigator responsibilities including informed consent will be documented on the clinical study information form.

26.4 Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and the applicable regulatory requirements.

26.5 Case Report Forms

- 1) All data will be recorded on CRFs provided by the sponsors. Black ballpoint pens should be used.
- 2) The white and yellow originals, or the white originals for North American studies, must be returned to the sponsors; the investigator must retain the pink copy for his/her file. For some studies, the specified copy will be sent to the central lab.
- 3) CRFs and other pertinent records are to be submitted to the sponsors during and/or at completion or termination of the study. The investigator also must submit all incomplete CRFs that document subject experience with the test article, including retrievable data on subjects who withdraw before completion of the study.

26.6 Adverse Event Reporting

The investigator agrees to report all AEs to the sponsors as described in the Adverse Events section. Furthermore, the investigator is responsible for ensuring that any coinvestigator or subinvestigator promptly brings AEs to the attention of the investigator. The investigator is responsible for reporting any AE to the Ghana National Center for Pharmacovigilance (GNCP) and to send copies of all correspondence with the GNCP to Wyeth and the WHO. If applicable, the investigator also is responsible for informing the participating IEC of any SAEs.

26.7 Review of Source Records

The investigator agrees that qualified representatives of the sponsors and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the subject will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) will be included in the informed consent document:

Representatives of regulatory agencies GFDB/IECs, the sponsors, the WHO, the Review Board of the Ghana National Center for Pharmacovigilance, and your personal physician may review your medical records and all information related to this study as permitted by law. Identifying information will not appear on any record received by the sponsors. Your identity will remain confidential unless disclosure is required by law.

26.8 Monitoring of the Study

This study is monitored by a representative from the WHO. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by telephone and mail and e-mail may be used as needed to supplement site visits. The investigator and study personnel will cooperate with the sponsors, provide all appropriate documentation, and be available to discuss the study. The purpose of the site visits is to verify the following:

- 1) Adherence to the protocol. (The investigator should document and explain any deviation from the approved protocol.)
- 2) The completeness and accuracy of the CRFs and the dispensing and inventory record. (Adequate time and space for these visits should be allocated by the investigator.)
- 3) Compliance with regulations. The verification will require comparison of the source documents to the CRFs.

26.9 Protocol Amendments

Any significant change in the study protocol will require an amendment. The investigator will outline the reasons and justification for the amendment in line with the TDR SOP for clinical investigators, and will discuss with the WHO clinical monitor. The monitor will append his comments and recommendations to the document that will then be submitted to the Wyeth medical monitor and WHO Project manager. A protocol amendment will be generated and signed by the Wyeth medical monitor and the WHO Clinical Coordinator. A protocol amendment may be implemented at this stage. Where applicable, the amendment must receive a favorable opinion from the GFDB/IEC and SCRIHS.

A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment and submitted to the Ghana Food

and Drugs Board (IEC) and SCRIHS within 5 working days. The protocol amendment will be sent in the same time period to the Wyeth medical monitor and the WHO project manager.

26.10 Change in Investigator

If the investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the sponsors, GFDB/IEC, or another investigator. The sponsors must be notified of and agree to the change. The Ghana Food and Drugs Board will be notified with the appropriate documentation.

26.11 Termination of the Study

26.11.1 Termination by the Sponsors

Either sponsor may terminate the study at any time for any of the following reasons:

1. Failure to enroll subjects.
2. Protocol violations.
3. Inaccurate or incomplete data.
4. Unsafe or unethical practices.
5. Questionable safety of the test article.
6. Suspected lack of efficacy of the test article.
7. Administrative decision.

26.11.2 Termination by the Investigator

If the investigator terminates the study prematurely, the investigator does the following:

1. Returns all test articles, CRFs, and related study materials to the sponsors.
2. Provides the GFDB and the sponsors with a written statement describing why the study was terminated prematurely. Prompt compliance with this requirement is essential so that the sponsors may comply with its regulatory obligations.

26.12 Final Study Report

The investigator should complete a report notifying the GFDB of the conclusion of the clinical study. This report should be made within 3 months of completion or termination of the study.

The final report sent to the GFDB should also be sent to the sponsors and, along with the completed CRFs, constitutes the final summary to the sponsors, thereby fulfilling the investigator's regulatory responsibility.

26.13 Confidentiality

All unpublished information that the sponsors give to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the sponsors.

When the sponsors generate reports for presentations to regulatory agencies, the investigator may be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the sponsors unless otherwise specified in the CSA.

26.14 Records Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for the longer of:

- i. 2 years after the last marketing authorization for the study drug has been approved or the sponsors have discontinued its research with respect to such drug or
- ii. Such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify in writing the sponsors of its intent to destroy all such material. The sponsors shall have 30 days to respond to the investigator's notice, and the sponsors shall have a further opportunity to retain such materials at the sponsor's expense.

26.15 Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The principal investigator shall submit reports, abstracts, manuscripts and or other presentation materials to the sponsors for review prior to submission for publication or presentation. The sponsors shall have 60 calendar days to respond with any requested revisions, including without limitation, the deletion of confidential information. The principal investigator shall act in good faith upon such requested revisions, except the principal investigator shall delete any confidential information from such proposed publication. The principal investigator shall delay submission of such publication or presentation materials for up to an additional 90 calendar days in order to have a patent application(s) filed.

26.16 Subject Injury

In general, if a subject is injured as a direct result of the test article, the sponsors will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the sponsors shall comply with such law or regulation. Where applicable, the sponsors have taken specific national insurance.

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ATTACHMENTS

**ATTACHMENT 1. RESPONSIBILITIES OF THE UNBLINDED THIRD PARTY
PHARMACIST**

1. The unblinded third party pharmacist signs a statement (Wyeth form 6732C) that assures Wyeth Research and the regulatory authorities that he or she understands his or her obligations and responsibilities as specified in the protocol, ie, correct preparation of the study medication and the manner in which it is to be administered. The original signed statement is forwarded to the Wyeth Research clinical scientist. Copies of this statement are retained by the unblinded third party pharmacist and the investigator.
2. The unblinded third party pharmacist is responsible for all clinical materials provided by Wyeth Research, such as the study medication, randomization chart, drug accountability and dispensing forms, and any other supplies.
3. The unblinded third party pharmacist will be responsible for maintaining the confidentiality and security of the randomization chart.
4. The unblinded third party pharmacist will
 - a. Identify the correct treatment for the subject based on the randomization chart generated by Wyeth Research and prepare the doses according to the detailed instructions provided (see Attachment 4).
 - b. Adhere to good preparation practices, eg, clear an appropriate space; minimize distractions; open only 1 medication container at a time.
 - c. Prepare medication that is appropriately labeled with the subject or subject number and initials, and the randomization number (include other label requirements specific to the protocol).
 - d. Safely and efficiently deliver the prepared drug directly to the investigator or his or her designee.
 - e. Complete all drug accountability and dispensing information on the drug accountability and dispensing records, including any amount returned by the subject or investigator. Quantities that are wasted or discarded must also be recorded.
 - f. Return the randomization chart to the Wyeth Research Clinical Pharmacy Section.
 - g. Not participate in the evaluation of any subject or subject.
5. The unblinded third party pharmacist may not administer the medication to the subjects. Contact between the unblinded third party pharmacist and subjects should be kept to a minimum.

ATTACHMENT 2. COLLECTION, PREPARATION, AND LABELING OF PLASMA SAMPLES

1. Plasma (for drug concentration data):

- Collect 10 mL of blood into a single evacuated blood tube containing sodium heparin.
 - Invert the tubes gently 4 or 5 times (avoid shaking).
 - Blood must be placed on ice immediately, and centrifuged (at 1500g for 10 minutes) in a refrigerated centrifuge within 15 minutes following collection.
 - Aliquot into **two** watertight, labeled polypropylene containers. Distribute plasma evenly between containers
 - Store frozen in an upright position at about -70°C until shipped.
2. Pre-printed labels with a bar code will be provided by Wyeth which will identify each sample with the analyte to be assayed, protocol number, investigator name, subject number, matrix (plasma) and protocol day and time of sample collection. Hand writing information on the labels is not required, but in the event that it should be necessary to hand write information, only indelible ink should be used. Additional information handwritten on a computer-printed label **must not obscure the bar code**.
3. Apply preprinted labels to tubes at room temperature at least 2 hours before refrigerating or freezing. Adequate adhesion cannot be guaranteed if the labels are applied to cold tubes.
4. Apply the labels along the length of the tube with the colored bar at the top. Do not spiral or wrap around the circumference of the tube as this interferes with reading the bar code.
5. Secure the labels by wrapping with clear tape.

ALL SAMPLES MUST BE KEPT FROZEN AT APPROXIMATELY -70°C AFTER COLLECTION AND UNTIL SHIPMENT IS INITIATED.

ATTACHMENT 3. INSTRUCTIONS FOR SHIPPING FROZEN SAMPLES

1. The shipping list is included as the white page of the PK shipping worksheet from the case report form. If a separate shipping list is used, be sure to include the same information collected on the tube label.
2. Place the watertight plastic transfer tubes from each subject in watertight plastic bags, preferably 1 to 10 tubes per bag. Place the plastic bags in an insulated shipping container with the appropriate completed case report form shipping page(s). Fill the container with sufficient dry ice to maintain the samples in the frozen state for at least 48 hours (72 hours for international shipments), and seal with tape.
3. Label the containers as clinical specimens. If further information is needed, contact the WHO monitor.
4. Ship the sealed containers in sturdy outside packaging in accordance with the shipper's guidelines.
5. Make shipments as early in the week as possible - not later than Wednesday noon. They never should be made on a Friday or two days before a holiday. Consult your analytical laboratory representative for the dates of site-specific holidays.
6. Choose the carrier in collaboration with the WHO monitor.
7. Be sure that the carrier will pick up the container from your office. If they do not, however, a member of your staff should deliver the containers to the carrier's office.
8. It is extremely important that the airway bill prepared by the shipping agent contain the exact instructions and address given on the package label. The fact that the shipment contains a frozen biological packed in dry ice should be noted on the airway bill.
9. At the time shipment is initiated, notify the recipients (see instruction 11) and the clinical scientist (see instruction 12) by fax and (if appropriate) e-mail with the following information:
 - Carrier, Airway bill number, Expected time of arrival, Number of pieces in the shipment, Protocol number, and your name and fax number.
 - Note: The e-mail notification described here serves as an adjunct to the fax notification but does not replace it.

10. Ship plasma samples for moxidectin to:

Dr. Larry Fleckenstein
College of Pharmacy
University of Iowa
Iowa City, IA 52242

Phone: +1 (319)-335-8804
Fax: +1 (319)-353-5646

11. The recipient will acknowledge receipt of the sample shipment by fax and (if appropriate) e-mail within 24 hours to the responsible party at the clinical site, with a copy to the clinical scientist. Any irregularities in the shipment received will be promptly and duly noted by the recipient in the sample receipt notification.
12. Similarly, the status of delayed or missing shipments will be communicated within 24 hours of the expected time of arrival. Such issues will be resolved by follow-up communication between the responsible clinical site personnel and the recipient.
13. If you have any questions regarding shipment, please do not hesitate to call:

Beth Morse RN, BSN
Senior Clinical Scientist
Wyeth Research-US
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E-mail: kehsJ@wyeth.com

ATTACHMENT 4. INSTRUCTIONS FOR PREPARATION OF STUDY DRUG

1. The drugs are encapsulated moxidectin 2 mg tablets (TIC), encapsulated 3 mg ivermectin tablets (TIC) or matching placebo capsules. Moxidectin 2 mg TIC is the only strength available. Therefore, 1 TIC is required for the 2 mg dose; 2 TICs are required for the 4 mg dose; 4 TICs are required for the 8 mg dose.
2. Three dose regimens of moxidectin (2 mg, 4 mg, 8 mg) will be studied at 3 levels of intensity of infection (mild, moderate, severe). The weight-based ivermectin dosing schedule approved for the treatment of onchocerciasis will be used. The first 2 cohorts at each moxidectin dose level will comprise 16 subjects while the third cohort will comprise 32 subjects enrolled in 2 successive groups of 16. Thus, one hundred and ninety-two (192) subjects including both sexes are expected to enroll in this study; and will be admitted in 12 groups.
3. Subjects will be assigned a number on admission (subject number). The unblinded third party pharmacist will be supplied with 12 randomization schedules (one for each of the three severity levels within each of the three treatment strata and 3 additional schedules for the most severely infected subjects). Each randomization schedule will contain the 16 randomization numbers, as well as the corresponding treatment assignments. Treatment groups will be blocked in groups of 4, with a 3 to 1 ratio of moxidectin to ivermectin. Where there are less than 16 subjects enrolled, the leftover randomization numbers will be ignored and a new randomization schedule will be used when a new cohort is started.
4. The PI or clinical assessor will provide the unblinded third party pharmacist with a list of subjects who qualify for enrollment, and will identify the cohort for which drug is to be prepared by the dose group and the severity of infection. For the severely infected cohorts, the PI will add the information whether this is the first or the second 16 subject group to be treated. For each subject, the name, initials, age, sex, weight and subject number will be stated. The unblinded third party pharmacist will assign the randomization numbers at the time of preparing the study medication. Each randomization number will be matched with the corresponding subject number and, **WITH THE EXCLUSION OF ALL PREPARATION INFORMATION**, be provided to the PI to be placed onto the Case Report Form. At the end of the study, they will be used to identify the treatment group assigned to the subject.

5. The drugs will be prepared the night before administration (day –1). Moxidectin/ivermectin/placebo capsules will be stored locked at room temperature up to 30°C.

Materials

Moxidectin capsules (containing 2 mg tablets)
Ivermectin capsules (containing 3 mg tablets)
Matching placebo capsules
Plastic cups (about 600 mL) with lids
Ordinary tap water
Markers
Sterile Disposable gloves
Refrigerator with key
Metal cabinet with key
Teaspoon (to dispense the tablets)
Dispensing tray
Small plastic envelopes for dispensing tablets
Medium sized envelopes (opaque)
Medium size trays-2
Self adhesive labels
Disposal Bin

Procedure

A. Day –1.

1. Treatment Allocation (Unblinded Third Party Pharmacist)

Using the randomization schedule supplied by Wyeth Research and the subject list provided, allocate each subject to the appropriate treatment regimen.

- Select the first male subject to be enrolled from the top of the randomization list that corresponds to the subject's assigned stratum. Similarly, select the first female from the bottom of the randomization list that corresponds to the subject's assigned stratum.
- Assign the second male subject to the next available treatment from the top of the randomization list that corresponds to the subject's assigned stratum. Assign the second female subject to the next available treatment from the bottom of the randomization list that corresponds to the subject's assigned stratum. Continue in this manner until the entire cohort has been assigned to the relevant treatment group.

- Complete the treatment allocation on the drug accountability form.

THIS FORM MUST NOT BE AVAILABLE TO ANYONE EXCEPT THE UNBLINDED MONITOR UNTIL THE END OF THE STUDY.

2. Preparing and Dispensing the Study Drugs (Unblinded Third Party Pharmacist)

- Label 16 medium size envelopes (one for each subject) with the subject's identification i.e. name, subject number, randomization number, age, sex, and date of drug administration.
- Wear the disposable gloves.
- Using the teaspoon and dispensing tray, dispense the appropriate number of moxidectin, placebo and/or ivermectin capsules for each subject into the small plastic envelopes and seal them. There should be a total number of 4 capsules in each envelope as per the tables below:

Cohort	2 mg					
Treatment Assignment	Moxidectin			Ivermectin		
Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule
Subject Weight	Number of Capsules					
26-44 kg	1	3	0	0	2	2
45-64 kg	1	3	0	0	1	3
65-84 kg	1	3	0	0	0	4

Cohort	4 mg					
Treatment Assignment	Moxidectin			Ivermectin		
Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule
Subject Weight	Number of Capsules					
26-44 kg	2	2	0	0	2	2
45-64 kg	2	2	0	0	1	3
65-84 kg	2	2	0	0	0	4

Cohort	8 mg					
Treatment Assignment	Moxidectin			Ivermectin		
Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule	Moxidectin Capsule	Placebo Capsule	Ivermectin Capsule
Subject Weight	Number of Capsules					
26-44 kg	4	0	0	0	2	2
45-64 kg	4	0	0	0	1	3
65-84 kg	4	0	0	0	0	4

- Put the small envelopes containing the tablets capsules into the corresponding labeled medium size envelopes. Seal the envelopes. Lock them up in a small cabinet at $\leq 30^{\circ}\text{C}$ and keep the key.
- Dispose of all used disposable items (e.g. gloves, facemask) into a bin provided for that purpose.

- Prepare a list with the name, initials, age, sex, weight, subject number, and randomization number.

B. Day 1.

1. Morning of Drug Administration (Unblinded Third Party Pharmacist)

- Remove the medium size envelopes containing the capsules from the cabinet. Re-check all the labeling and arrange them according to subject numbers on the tray.
- Hand over the tray to the clinical staff in-charge of administering the drugs. Ensure he/she acknowledges receipt.
- Hand over the list with the name, initials, age, sex, weight, subject number and randomization number to the PI.
- After administration of the drugs, collect all the empty drug envelopes from the personnel that has dispensed the drugs. Check that all have been handed over.
- Write the name, subject number, randomization number, age, sex, weight, treatment regimen and date for each subject on a piece of paper and insert into the corresponding opaque envelope. Ensure that each tightly sealed envelope has been locked in a cabinet by the hospital pharmacist only to be opened if required for emergency unblinding.
- Record the drugs dispensed on the “Drug Stocks, Distribution and Accountability” Form.
- Lock up all documents in the cabinet for drug accounting purposes.

2. Administration of Study Drugs (Clinical Staff)

The study drugs will be administered after an overnight fast. Breakfast will be delayed for about 2 hours.

- Retrieve the drug envelopes for the subject from the tray. Put them in a kidney dish.
- Half fill the 600 mL plastic cups with ordinary tap water.

- With the assistance of one or more nurses, check the labeling on the drug envelopes containing the capsules. Ensure that the subject name and number correspond with those on the board above the head of the bed. Check the date.
- Call out the name on the label and listen to the subject verifying that he/she is the named individual.
- Open the drug envelope and give the capsules and the plastic cup containing about 300 mL of tap water to the subject.
- Observe the subject swallow the capsules and inspect the mouth to ensure compliance.
- Record the date and time in the source documentation that the capsules were swallowed.

ATTACHMENT 5. RECOMMENDATIONS FOR GRADING OF OCULAR EXAMINATIONS

Toxicity	0	1	Grade	2	3	4
SYMPTOMS						
Ocular discomfort	None	Mild: not interfering with function	Moderate: interfering with function, but not with ADL	Interfering with ADL	----	----
Ocular itching	None	Mild: not interfering with function	Moderate: interfering with function, but not with ADL	Interfering with ADL	----	----
Tearing (watery eyes)	None	Mild: not interfering with function	Moderate: interfering with function, but not with ADL	Interfering with ADL	----	----
Photophobia	None	Mild: not interfering with function	Moderate: interfering with function, but not with ADL	Interfering with ADL	----	----
Discharge	None	Present	----	----	----	----
Vision- blurred vision	Normal	Mild, not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	----	----
VISUAL ACUITY						
(uncorrected) Snellen/ illiterate E	Unchanged or 6/4-6/6	Loss of 1 line	Loss of 2 lines	Loss of 3 lines	Loss of >3 lines	
COLOUR VISION						
	Normal	Abnormal	----	----	----	----
VISUAL FIELDS^a						
IV/4e kinetic	None	1-12	13-24	25-48		
I4/e kinetic	None	1-12	13-24	25-36		49-72
I/2e	None	1-12	13-20	21-28		37-60
						29-36
^a Note: Based on the number of missed targets						
PUPILLARY REFLEX						
	Normal	Abnormal	----	----	----	----
EXTERNAL EXAMINATION						

Toxicity	0	1	Grade		2	3	4
Eyelids	Normal	Abnormal		----		----	----
Conjunctiva	Normal	Abnormal		----		----	----
Cornea	Normal	Abnormal		----		----	----
Iris	Normal	Abnormal		----		----	----
Ocular movement	Normal	Abnormal					
ANTERIOR SEGMENT INFLAMMATION							
Conjunctivitis	None	Hyperaemia		Chemosis		-	
Limbitis							
Vascular changes	None	Mild: not interfering with		Moderate: interfering with		Interfering with ADL	
Globular infiltrates	None	function		function but not with ADL			
Anterior chamber							
Flare	None	Mild		Moderate		Severe	
Cells	None	Mild		Moderate		Severe	
POSTERIOR SEGMENT							
OPTIC DISC							
Hyperaemia	None	Sectorial		Overall		-	-
Swelling	None	-		-		Sectorial	Overall
MACULA	Normal	Mild: not interfering with		Moderate: interfering with		Interfering with ADL	----
		function		function, but not with ADL			
PERIPHERAL RETINA							
Retinitis	Absent	Present		----		----	----
Hemorrhage	Absent	Present		----		----	----
Vasculitis	Absent	Present		----		----	----
Cotton wool spots	Absent	Present		----		----	----
RETINAL PHOTOGRAPHY							
Optic atrophy							
Colour film	None	Linear nerve fibre loss		Sectorial atrophy		Overall atrophy	Atrophy with pigment
Red free	None	Linear nerve fibre loss		Sectorial fibre loss		Total loss	Total loss with pigment
Pigment epithelial atrophy							
Distribution	None	Temporal to macula		More than temporal		Continuous round macula	Whole of macula
Intensity	None	RPE mottling only		RPE mottling with <50% atrophy		RPE mottling with ≥50% atrophy	RPE mottling with hypertrophy

Toxicity	0	1	Grade	2	3	4
FLUORESCCEIN ANGIOGRAPHY						
Optic disc leakage						
Within disc margin	None	Sectorial	Overall			
Beyond disc margin	None			Sectorial		Overall
Optic atrophy						
Red free	None	Linear nerve fibre loss	Sectorial fibre loss	Total loss		Total loss with pigment
Pigment epioithelial atrophy						
Distribution	None	Temporal to macula	More than Temporal	Continuous round macula		Whole of macula
Intensity	None	RPE mottling only	RPE mottling with <50% atrophy	RPE mottling with ≥50% atrophy		RPE mottling with hypertrophy
Note: Once an event has occurred the score is retained at subsequent visits whether the lesion persists or not.						

Modified from Hero, M., A. C. Bird & K. Awadzi. (1992). *Quantification of the ocular reactions to microfilaricides in the chemotherapy of onchocerciasis*. Eye 6(Pt 1): 93-96.

ATTACHMENT 6. POTENTIAL MAZZOTTI LABORATORY MANIFESTATIONS

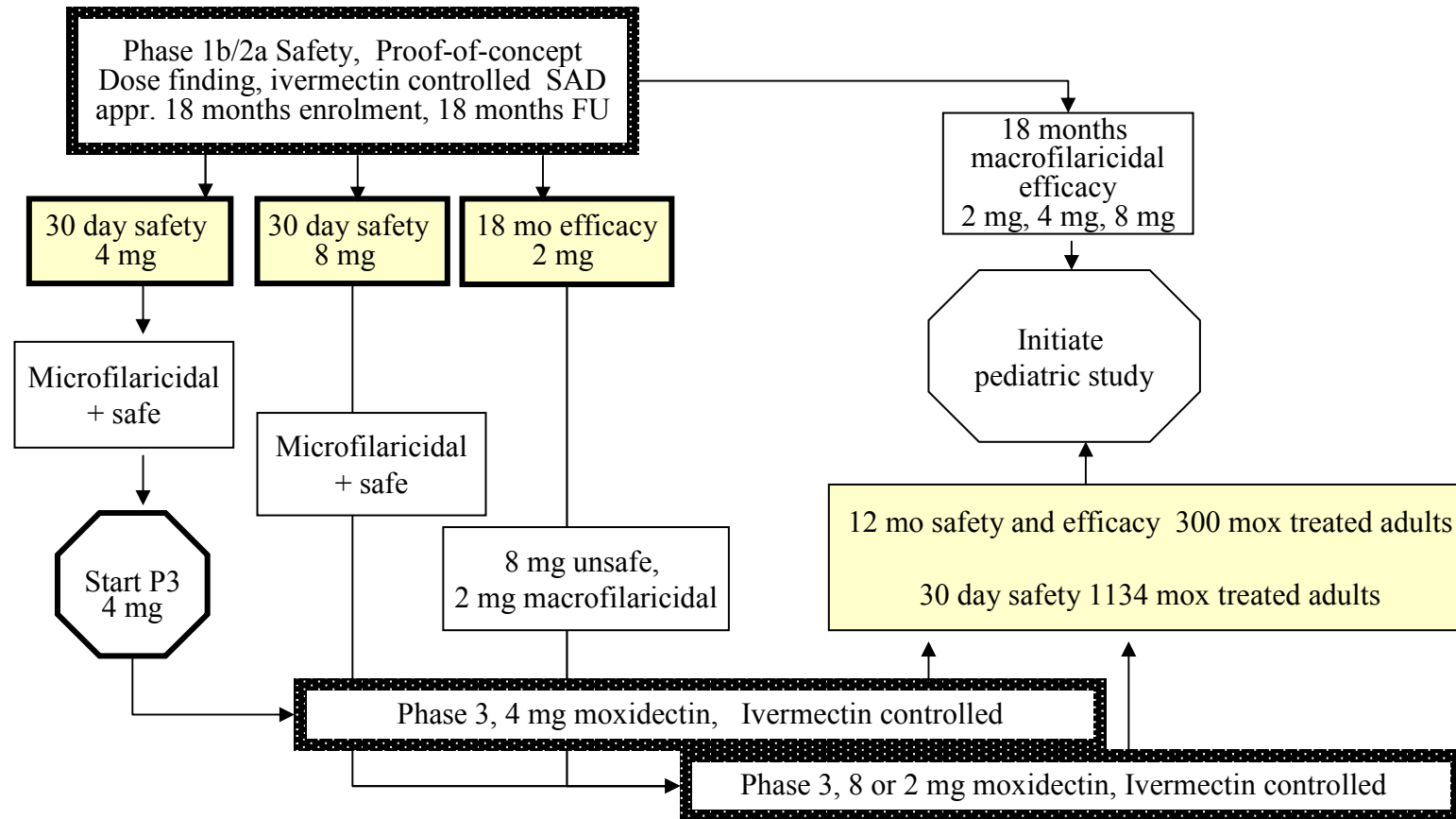
Toxicity	0	1	Grade 2	3	4
HEMATOLOGICAL					
G6PD (Additional)	Normal	Partial defect	Total defect		
Hemoglobin (Hgb)	WNL	< LLN – 100 g/L	80 - < 100 g/L	65 – 80 g/L	< 6.5 g/dl
Leukocytes (total WBC)	WNL	< LLN - 3.0×10^9 /L	≥ 2.0 - $< 3.0 \times 10^9$ /L	≥ 1.0 - $< 2.0 \times 10^9$ /L	< 1.0×10^9 /L
	WNL	> 9.5-19.0 $\times 10^9$ /L	>19.0-38.0 $\times 10^9$ /L	>38.0-57.0 $\times 10^9$ /L	> 57.0 $\times 10^9$ /L
Note: Contributory factors include Mazzotti reaction (leucocytosis), coincidental infection (exclude) drug effect					
Neutrophils/granulocytes (ANC/AGC)	WNL	≥ 1500 - $< 2000/\text{mm}^3$	≥ 1000 - $< 1500/\text{mm}^3$	≥ 500 - $< 1000/\text{mm}^3$	< $500/\text{mm}^3$
	WNL	>6080-12160/ mm^3	>12160-24320/ mm^3	>24320-36480/ mm^3	>36480/ mm^3
Note: Contributory factors include Mazzotti reaction (neutrophilia), coincidental infection (exclude) drug effect					
Lymphocytes	WNL	<LLN – 1000/ mm^3	≥ 500 - $< 1000/\text{mm}^3$	<500/ mm^3	-
	WNL	>636 5-12730/ mm^3	>12730-25460/ mm^3	>25460-38190/ mm^3	>38190/ mm^3
Note: Contributory factors include Mazzotti reaction (initial lymphopenia, lymphocytosis), coincidental infection (exclude) drug effect					
Eosinophils	WNL	20-26/ mm^3	≥ 14 -19/ mm^3	≥ 7 -13/ mm^3	<7/ mm^3
	WNL	>1425-2850/ mm^3	>2850-5700/ mm^3	>5700-8550/ mm^3	>8550/ mm^3
Note: Contributory factors include Mazzotti reaction (initial eosinopenia, eosinophilia), coincidental infection (exclude) drug effect					
Platelets	WNL	< LLN - $< 75.0 \times 10^9$ /L < LLN – 75000/ mm^3	≥ 50.0 - $< 75.0 \times 10^9$ /L ≥ 50000 - $< 75000/\text{mm}^3$	≥ 10.0 - $< 50.0 \times 10^9$ /L ≥ 10000 - $< 50000/\text{mm}^3$	< 10.0×10^9 /L < 10000/ mm^3
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	None	Only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	Evidence of red cell destruction and $\geq 2\text{gm}$ decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)

Toxicity	0	1	Grade 2	3	4
BIOCHEMICAL					
Hyponatremia	WNL	<LLN – 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	
Hyperuricemia Note: Also consider Renal failure, Creatinine, Potassium.	WNL	> ULN - ≤ 590 micromol/L without physiologic consequences	-	>ULN - ≤ 590 micromol/L with physiologic consequences	> 590 micromol/L
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase) Note: Elevations occur as part of the Mazzotti reaction but rarely reach 5 x ULN and usually last for less than 30 days	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGOT (AST) (serum glutamic oxaloacetic transaminase) Note: Elevations occur as part of the Mazzotti reaction but rarely reach 5 x ULN and usually last for less than 30 days	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
GGT (γ - Glutamyl transpeptidase) Note: Elevations occur as part of the Mazzotti reaction but rarely reach 5 x ULN and usually last for less than 30 days	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
LDH (Lactate dehydrogenase) Note: Elevations occur as part of the Mazzotti reaction but rarely reach 5 x ULN and usually last for less than 30 days	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Hypoalbuminemia	WNL	<LLN - 30 g/l	≥20 - <30 g/l	<20 g/dl	-

Toxicity	0	1	Grade 2	3	4
Hypoglycemia	WNL	<LLN - 3.0 mmol/L	2.2 - < 3.0 mmol/L	1.7 - < 2.2 mmol/L	< 1.7 mmol/L
Hyperglycemia	WNL	> ULN - 8.9 mmol/L	> 8.9 - 13.9 mmol/L	> 13.9 - 27.8 mmol/L	> 27.8 mmol/L or ketoacidosis
Hypercholesterolemia	WNL	> ULN - 7.75 mmol/L	> 7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	> 12.92 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN

Toxicity	0	1	Grade 2	3	4
URINALYSIS					
Proteinuria	Normal or Trace	1+	2+ to 3+	4+	Nephrotic syndrome
Hematuria (in absence of vaginal bleeding)	None	Microscopic only	Intermittent gross bleeding	Persistent gross bleeding or clots; may require catheterization or instrumentation or transfusion	Open surgery or necrosis or deep bladder ulceration

Link OCRC study to subsequent studies



Interim analysis requiring
third party unblinding

Strategic
Decision
Point

Note: 'Macrofilaricidal efficacy' denotes either macrofilaricidal activity
or permanently macrofilaria-sterilizing activity