

**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.<sup>1</sup>

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.

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<sup>1</sup> 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<sup>®</sup>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<sup>®</sup>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<sup>®</sup>6 recommended against the re-introduction of ProHeart<sup>®</sup>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<sup>®</sup>6, and ProHeart<sup>®</sup>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.<sup>2</sup>

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.<sup>3</sup>

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

<sup>3</sup> 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<sup>®</sup>6 or ProHeart<sup>®</sup>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<sup>®</sup>6***

On the basis of the documentation and presentations provided for the January 2005 FDA VMAC meeting on ProHeart<sup>®</sup>6, the data and events relating to ProHeart<sup>®</sup>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<sup>®</sup>6 or ProHeart<sup>®</sup>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<sup>®</sup>6 was regarded with particular concern in the context of the objectives of this meeting. (There are no records of ProHeart<sup>®</sup>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<sup>®</sup>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<sup>®</sup>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<sup>®</sup>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<sup>®</sup> tablets. Some 846 379 oral ProHeart<sup>®</sup> 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<sup>®</sup>6 and observed AEs may be related to the formulation of injectable ProHeart<sup>®</sup>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<sup>®</sup>6.

Since the planned study in subjects infected with *Onchocerca volvulus* will use an oral tablet, not ProHeart<sup>®</sup>6, the ProHeart<sup>®</sup>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 (IC<sub>50</sub> 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  $\geq 50$  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  $\geq 50$  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<sup>®6</sup> 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<sup>®</sup>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<sup>®</sup>6 tablets as compared to ProHeart<sup>®</sup>6 point to the formulation rather than the drug substance as the basis for any possible or probable causal relationship between ProHeart<sup>®</sup>6 and the reported AEs. This conclusion is supported by the fact that the FDA-CVM asked the company to recall ProHeart<sup>®</sup>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<sup>®</sup>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<sup>®</sup>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

**Prof Albert AMOAH**, Chairman, Ghana Health Service Ethics Committee, Deputy Provost, College of Health Sciences, University of Ghana, Top Floor, Library Building, Korle Bu Teaching Hospital, Korle Bu, Accra, GHANA.

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**Dr John GYAPONG**, Director, Health Research Unit, Ghana Health Service, PO Box GP-184, Accra, GHANA.

**Dr Ben BOTWE**, Head, Drugs Division, Food and Drugs Board, PO Box CT2783, Cantoments, Accra, GHANA (Morning of 5 May).

**Mr Eric Karikari BOATENG**, Senior Regulatory Officer, Food and Drugs Board, P O Box CT2783, Cantoments, Accra, GHANA.

**Mr Enoch AMPRAWUM**, Food and Drugs Board, PO Box CT2783, Cantoments, Accra, GHANA, (Observer).

**Mr Delese DARKO**, Food and Drugs Board, PO Box CT2783, Cantoments, Accra, GHANA (Observer, Morning of 5 May).

## APOC TCC Representatives

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## **Secretariat**

### **WHO/TDR**

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### **WHO Country Office**

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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<sup>®</sup>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

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





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