CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	210867
Priority or Standard	Priority
Submit Date	10/13/17
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Division/Office	Division of Anti-Infective Products/Office of Antimicrobial Products
Reviewer Name	Hiwot Hiruy, MD, PhD
Review Completion Date	04/06/2018
Established/Proper Name	Moxidectin
(Proposed) Trade Name	Not proposed
Applicant	Medicines Development for Global Health
Dosage Form	2mg Tablet
Applicant Proposed Dosing Regimen	8mg (Four 2mg Tablets) Single Oral Dose
Applicant Proposed Indication(s)/Population(s)	Treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Treatment of onchocerciasis due to Onchocerca *volvulus* in patients aged 12 years and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Moxidectin belongs to the milbemycin group of the macrocyclic lactone anti-helminthic drugs. It is a new molecular entity (NME) for human use, but is approved and has been used in veterinary medicine. The proposed indication is treatment of onchocerciasis, and the proposed dosing regimen is 8 mg single oral dose.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The results of one Phase 2 and one Phase 3 trial provided substantial evidence of moxidectin' s superiority over ivermectin, the current FDA- approved treatment for onchocerciasis. Both studies demonstrated a statistically significant reduction in the number of skin *Onchocerca volvulus* microfilariae at 12 months post-treatment. Additionally, both studies showed a higher proportion of moxidectin-treated patients having undetectable skin microfilariae count at 12 months. With these findings, it is concluded that moxidectin is effective for the treatment of onchocerciasis.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The Applicant has provided substantial evidence to support the safety and efficacy of moxidectin administered at a single oral dose of 8 mg in treatment of onchocerciasis. The efficacy of moxidectin was demonstrated in two adequate and well controlled trials comparing moxidectin with ivermectin, the only FDA-approved treatment for onchocerciasis. Both trials demonstrated a statistically significant decrease in the number of *Onchocerca volvulus* microfilariae (a microscopic larval stage of the parasite) in the skin at 12 months post-treatment. Because symptoms of onchocerciasis are caused by inflammatory reactions to microfilariae in the human tissue, microfilarial burden is considered a meaningful measure of moxidectin efficacy. Additionally, both trials showed a higher proportion of moxidectin-treated patients having undetectable skin microfilariae count at 12 months. With these findings, it is concluded that moxidectin is effective for the treatment of onchocerciasis.

There were no major imbalances in serious adverse events and deaths between moxidectin-and ivermectin-treated patients. Most the treatment emergent adverse events noted in the moxidectin-treated patients were related to Mazzotti reaction, immune response elicited by the dying microfilariae. These reactions encompassed, among other symptoms, itching, rashes, muscle pains, fever, tender lymph nodes, hypotension, tachycardia, and eosinophilia. There were higher incidences of adverse events related to Mazzotti reaction in the moxidectin- as compared to ivermectin-treated patients. Of note, there was higher incidence of symptomatic orthostatic hypotension, inability to stand without support after lying down for 5 minutes, in the moxidectin-treated patients. There was also higher incidence of transient hyperbilirubinemia without concurrent elevation in transaminases in the moxidectin-treated patients.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Onchocerciasis is caused by *Onchocerca volvulus*, a parasitic worm transmitted to humans by the black fly. Adult worms produce microfilariae that reside in the skin and eye and cause inflammatory reaction in these tissues.	Onchocerciasis is a debilitating disease affecting millions of people globally.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Onchocerciasis is the second-leading infectious disease cause of blindness worldwide. • It affects 18 million people, most residing in sub-Saharan Africa, with a few additional foci in South America and the Middle East.	
Current Treatment Options	• Ivermectin is the only FDA-approved drug for the treatment of onchocerciasis. Ivermectin is considered the drug of choice for treatment of onchocerciasis. • Ivermectin is a microfilaricidal drug, and does not kill the adult *O. volvulus.* • Doxycycline, treatment targeting the endosymbiotic bacteria *Wolbachia* that are needed for survival and reproduction of adult *O. volvulus*, is used in non-endemic areas or in areas of low transmission. Doxycycline causes death of the adult worms and a 6-week treatment course is commonly used. However, doxycycline is not used in areas of ongoing *O. volvulus* transmission because repeated treatment courses would be required; repeat dosing of ivermectin is used in these areas.	Ivermectin, is the only FDA-approved drug for onchocerciasis. Additional treatment options with higher efficacy against *O. volvulus* are needed to expand the treatment armamentarium.
Benefit	• The dose-ranging, ivermectin-controlled Phase 2 trial and the larger ivermectin-controlled Phase 3 trial both demonstrated higher efficacy of moxidectin in decreasing skin microfilariae at 12 months. Because symptoms of onchocerciasis are caused by inflammatory reactions to microfilariae in the human tissues, the reduction in microfilarial burden is considered a meaningful measure of moxidectin efficacy. • There were also higher proportion of moxidectin-treated patients	The results of the Phase 2 and Phase 3 trials demonstrate substantial evidence of the superiority of moxidectin over ivermectin in reducing skin microfilarial burden.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with undetectable *O. volvulus* skin microfilariae when compared to ivermectin-treated patients in both the Phase 2 and Phase 3 trials.	
Risk and Risk Management	• There were no imbalances in serious adverse events and deaths noted in moxidectin and ivermectin-treated patients. • Most common treatment-emergent adverse events noted in the moxidectin arm were due to Mazzotti reaction, an immune response to dying microfilariae. • Overall, moxidectin-treated patients had higher incidence of adverse events related to Mazzotti reaction as compared to ivermectin. • Symptomatic orthostatic hypotension occurred more frequently in the moxidectin- as compared to ivermectin-treated patients. • There were higher incidences of transient hyperbilirubinemia (without concurrent elevation in transaminases) in the moxidectin as compared to ivermectin arm. • Moxidectin, like ivermectin, is a microfilaricidal drug and does not kill the adult worm; hence, a single treatment with moxidectin will not be curative. Repeated courses of moxidectin have not been studied.	There is no clear explanation for the higher incidence of transient hyperbilirubinemia seen in the moxidectin-treated patients. Clinicians should be aware of the higher incidence of adverse events related to Mazzotti reaction in moxidectin-treated patients. Particularly, there was higher incidence of symptomatic orthostatic hypotension in the moxidectin-treated patients that resolved with lying down. Similar to other microfilaricidal drugs, moxidectin does not kill the adult worm, although it reduces the fecundity of the female worm. Since the life expectancy of the adult ranges up to 10-15 years, moxidectin may need to be given repeatedly. However, there are no data regarding the safety of repeated doses of moxidectin.

1.4. Patient Experience Data

There were no patient experience data submitted for this application.

2. Therapeutic Context

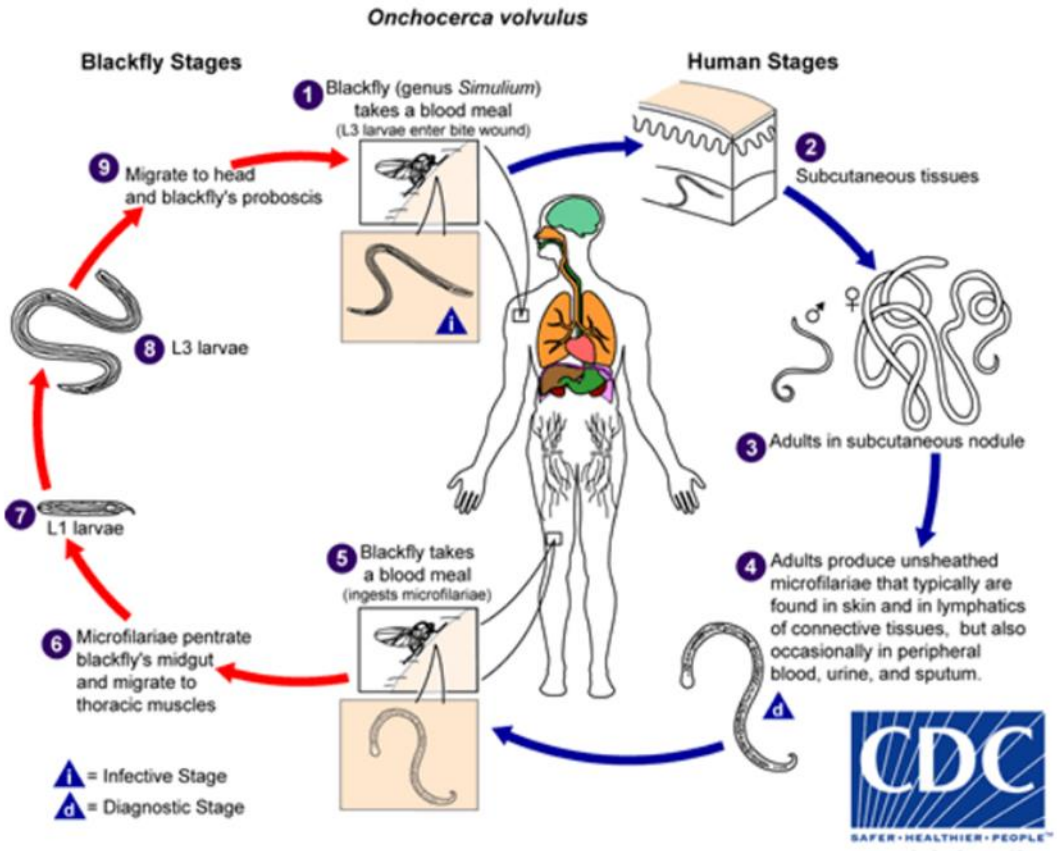
2.1. Analysis of Condition

Onchocerciasis, also known as river blindness, is caused by the filarial nematode, *Onchocerca volvulus*. It is the second-leading infectious disease cause of blindness worldwide and affects nearly 18 million people worldwide[1]. Although most of these affected individuals reside in Africa, the disease has small foci in the Middle East (Yemen) and southern and central America.

Onchocerciasis is transmitted by a bite of a black fly in the genus *Simulium* that is abundant near riverbeds. Prevalence of infection rises with age, with reported 1-2% detection of larvae (microfilariae) in the skin of children ≤ 5years of age, to about 90% by age 15.[2] After age 30, higher rates of microfilariemia and morbidity are reported in men than in women. This variation by age and gender may reflect exposure to the vector. Figure 1 shows the 5-stage life cycle of *O. volvulus.*

[1] http://www.who.int/mediacentre/factsheets/fs095/en/
[2] Fox L (2012). Blood and Tissue *Nematodes*. In S.S. Long, L.K. Pickering LK, C.G. Prober (Eds). *Principles and Practices of Pediatric Infectious Disease* (4th ed) (pp 1344-1346). Elsevier Saunders

Figure 1: Life Cycle of *Onchocerca volvulus*



Source: CDC website-https://www.cdc.gov/dpdx/onchocerciasis/index.html

As depicted in Figure 1, a bite of the blackfly deposits infective third-stage larvae into the human skin. These larvae mature into adult parasites, macrofilariae, over the next 6 to 12 months within the subcutaneous tissue. The adult female can measure 20-80 cm in length while the adult male measures 3 to 5 cm. The females live in a subcutaneous or deeper intramuscular tissue and are surrounded by a fibrous capsule. The males migrate between nodules to fertilize females. Adult worms can live inside these skin nodules for up to 15 years.

After maturation, adult females start releasing about 1600 microfilariae per day.[3] Microfilariae

[3] Mawson AR, Wakabongo M. Onchocerciasis-associated morbidity: hypothesis. Trans R Soc Trop Med Hyg. 2002 Sep-Oct;96(5):541-2.

measure 220-360 µm in length and can live for 12-18 months. Microfilaria reside primarily in the skin and will be transmitted to the black fly after a bite of the human host, perpetuating the cycle of transmission. Microfilariae can also migrate to the mammary glands, lymph nodes and have special predilection to the eyes.[4]

Upon their death, the microfilariae provoke inflammatory response in the skin and eyes that is the hallmark of the disease. In the skin, this response results in intense itching, papular dermatitis, and over time, lichenified onchodermatitis. Left untreated, it can result in the chronic presentations of onchocerciasis that include depigmentation, loss of skin elasticity and structure. Rarely, a subset of infected individuals experience hyperactive immune response, known as hyper-reactive onchodermatitis (sowda) present with severe sign and symptoms with very low intensity of infection (low microfilariae count).[5] Of note, an endosymbiotic gram-negative bacterium, *Wolbachia*, is implicated in some of the inflammatory response that results in damage to the skin and eyes.

The most severe consequence of onchocerciasis, ocular onchocerciasis, initially starts with anterior segment lesions such as punctate keratitis around the dead microfilariae. Chronic exposure can result in sclerosing keratitis and iridocylitits leading to severe visual impairment and blindness, which are more common in individuals older than 40 years. Microfilariae can also result in posterior segment involvement when they migrate to the retina and optic nerve, and can a result in lesions within these structures.[6] Immune phenomena in response to dying microfilariae and *Wolbachia* are hypothesized to contribute to posterior segment abnormalities such as chorioretinopathy, optic nerve atrophy, and eventual blindness.

The standard diagnostic mode for onchocerciasis is demonstration of microfilariae in skin snips. These skin snips are taken from the iliac crest, scapula and the lower extremities using a sclerocorneal punch biopsy needles. Each skin snip usually weighs about 2 mg. The skin snips are incubated in normal saline at room temperature for up to 24 hours to allow the microfilariae to emerge, and subsequently, microfilariae can be identified and counted microscopically. Of note, the sensitivity of skin snips is limited in early infection prior to maturation of the larvae to adult, which can last for the12- 18 months. Sensitivity can also be limited in low intensity infections.

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[4] Crump A, Morel CM, Omura S. The onchocerciasis chronicle: from the beginning to the end? Trends Parasitol. 2012 Jul;28(7):280-8.
[5] Kazura K, Tissue nematodes (Trichinellosis, dracunculiasis, Filariasis, Loiasis, and Onchcerciasis) (2015). In Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases* (8th ed)(pp 3208-3215). Elsevier Saunders
[6] Udall DN. Recent updates on onchocerciasis: diagnosis and treatment. Clin Infect Dis. 2007 Jan 1;44(1):53-60.

Other diagnostic methods include excision of subcutaneous nodules and identification of the adult worms, and presence of microfilariae in the anterior chamber of the eye on slit-lamp examination. The so-called "patch test", a topical application of a topical preparation of diethylcarbamazine (DEC) to a small area of skin, can also be used diagnostically to provoke local skin reaction with death of microfilariae. Other investigational tests such as skin snip PCR, and rapid tests based on antibody detection have been reported in the literature but are not widely used.[2,4,6,7,8]

2.2. Analysis of Current Treatment Options

Ivermectin, an avermectin macrocylic lactone, is the only FDA-approved drug and is the mainstay therapy for onchocerciasis. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels in muscles and nerve cells of the microfilariae. This results in hyperpolarization of the cell leading to paralysis and death of the parasite.[9] The approved treatment regimen is a single dose at 150 µg/kg dose. Ivermectin is a microfilaricidal drug, and reduces cutaneous microfilariae density by 85% to 95% within the first two months after a single dose; ocular microfilariae densities decline more slowly.[2] Of note, ivermectin does not eradicate adult worms. It is also not approved for pregnant women and children who weigh <15kg.

Like other microfilaricidal drugs, most of the adverse effects of ivermectin are related to the immune reaction to dying microfilariae, the so-called Mazzotti reaction. Mazzotti reaction was initially described in patients treated with DEC[10]. The clinical presentation Mazzotti reaction includes:

- Physical sign/symptoms
  - Dermatology: Pruritus, urticaria
  - Ocular: Conjunctival irritation, chorioretinitis, uveitis, photophobia, optic neuritis
  - Musculoskeletal: Myalgia, arthralgia, facial and extremity swelling
  - Neurological: Headache, dizziness
  - Lymphatic: Lymph node pain and tenderness

[7] Weil GJ, Steel C, et al. A rapid-format antibody card test for diagnosis of onchocerciasis. J Infect Dis. 2000 Dec;182(6):1796-9
[8] Burbelo PD, Leahy HP, et al. A four-antigen mixture for rapid assessment of *Onchocerca volvulus* infection. PLoS Negl Trop Dis. 2009;3(5):e438.

[9] Stromectol®(Ivermectin) oral Tablets label. Merck &Co, Inc, Whitehouse Station, NJ, 2009
[10] Mazzotti, L., 1948. Onchocerciasis in Mexico. Proc. 4th Int. Congr. Trop. Med. Malaria (session 1 of Section 6) Washington, DC

    - General: Influenza-like illness
- Vital sign changes
    - Fever
    - Tachycardia and orthostatic tachycardia
    - Hypotension and orthostatic hypotension
    - Tachypnea
- Laboratory changes
    - Initial eosinopenia with subsequent eosinophilia
    - Initial lymphopenia with subsequent lymphocytosis
    - Liver enzyme elevation (ALT, AST, GGT)
    - Blood lactate dehydrogenase (LDH) elevation
    - Eosinophils in urine

Mazzotti reaction is described as biphasic, with the initial manifestation starting within hours to 24 hours post administration of microfilaricidal drug, followed by a secondary phase which may occurs 2-6 days, with fever and joint complaints (arthralgia, arthritis) dominating this phase. The pathophysiologic basis for the Mazzotti reaction are presumed to be due to "mobilization" of microfilariae from the cutaneous tissue to the blood, and other body fluids, including CSF and urine[11,12]. There is also significant initial eosinopenia early after treatment as peripheral eosinophils migrate to the cutaneous tissue to contain microfilarial mobilization, as evidenced by formation of micro-abscesses in cutaneous tissue. The early eosinopenia is followed by significant eosinophilia. It is hypothesized that release of *Wolbachia* from dying microfilariae may contribute to induction of innate immune response that contributes to these symptoms.[4,13]

Mazzotti reactions seen with DEC were severe and some even fatal. The severity of Mazzotti reaction after DEC treatment was associated with microfilariae density (intensity of infection) and dose used. Less severe reactions are seen with ivermectin treatment as compared to DEC.

Of note, in areas where onchocerciasis is co-endemic with loiasis, treatment with ivermectin is not recommended as it may precipitate encephalopathy in patients with high levels (>8000 mf/mL) of *Loa loa* microfilaremia.[2,4,5]

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[11] Francis H, Awadzi K, Ottesen EA. The Mazzotti Reaction Following Treatment of Onchocerciasis with Diethylcarbamazine: Clinical Severity as a Function of Infection Intensity. Am J Trop Med Hyg. 1985 May;34(3):529

[12] Ottesen EA. Description, mechanisms and control of reactions to treatment in the human filariases. Ciba Found Symp. 1987;127:265-83

[13] Keiser PB, Reynolds SM, Awadzi K, Ottesen EA, Taylor MJ, Nutman TB. Bacterial endosymbionts of Onchocerca volvulus in the pathogenesis of posttreatment reactions. *J Infect Dis*. 2002 Mar 15;185(6):805-11

Suramin and DEC have been previously used in treatment of onchocerciasis; however, both are not recommended due to significant toxicity and adverse effect associated with them. Suramin has rapid impact against adult *O. Volvulus* parasites. DEC only acts against microfilariae[6].

In recent years, doxycycline, an antibacterial with anti-*Wolbachia* activity, has become drug of interest in treatment of Onchocerciasis. Studies have shown that administration of doxycycline three months prior to ivermectin results in reduced embryogenesis in the female worm and enhanced killing of adult female worms. [14,15,16]

Table 1 summarizes drugs used in treatment of onchocerciasis.

Table 1: Drugs used for Treatment of Onchocerciasis

Class	Agent	1° Mechanism on Microfilariae	Effect on Macrofilariae	
			Fecundity	Viability
Macrocytic lactone	Ivermectin*	GluCl inhibition	Yes	No
Piperazine	Diethylcarbamazine (DEC)**	Arachidonic acid pathway	Yes	No
Tetracycline	Doxycycline[#]	Anti-*Wolbachia*	Yes	Yes
Benzanilide	Suramin**	No	Yes	Yes

GluCl: Glutamate-gated chloride channel
*Only FDA-approved drug for treatment of Onchocerciasis.
**DEC and Suramin are not suitable for mass drug administration due to toxicity and severe side effects (WHO Expert Committee on Onchocerciasis Control 1995)
[#] Not standard of therapy
Source: Modified from Sponsor's Table 1 in Integrated Summary of Safety report

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

[14] Hoerauf A, Specht S, Marfo-Debrekyei Y, et al. Efficacy of 5-week doxycycline treatment on adult Onchocerca volvulus. *Parasitol Res* 2009; 104:437–47
[15] Hoerauf A, Specht S, et al. Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. *Med Microbiol Immunol* 2008; 197:295–31
[16] Debrah AY, Specht S, et al. Doxycycline Leads to Sterility and Enhanced Killing of Female Onchocerca volvulus Worms in an Area with Persistent Microfilaridermia After Repeated Ivermectin Treatment: A Randomized, Placebo-Controlled, Double-Blind Trial. *Clin Infect Dis*. 2015 Aug15;61(4):517-26

Moxidectin is a NME, and is not currently marketed in or outside of the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Moxidectin has been in development for human use since 1999. Its development was initiated as a collaborative effort between the World Health Organization/Special Program for Research and Training in Tropical Diseases (WHO/TDR) and Wyeth/Pfizer in 1999. Sponsorship of moxidectin was transferred from Pfizer to TDR/WHO in 2011 and subsequently to the current sponsor, MDGH, on October 14, 2014.

Moxidectin was granted Orphan Drug designation for the treatment of onchocerciasis on September 29, 2010. Pre-investigational new drug (Pre-IND) 126876 was opened in the U. S. on 07/07/2015 for the treatment of onchocerciasis.

A type C clinical meeting was held on 03/23/2016. The following points were discussed at the meeting:

- The primary efficacy outcome measure for the Phase 3 study, skin microfilariae density at 12 months. The sponsor included literature support for the Phase 2 and Phase 3 primary efficacy endpoint. Details of the discussion are presented in section 6.1.
- The agency agreed that the completed active-comparator controlled, randomized, Phase 2 and Phase 3 trials appear to be adequate and well-controlled trials.
- The agency recommended that the thorough QT study be completed before the NDA submission.

An IND was opened on 11/16/2016. The agency received protocol MDGH-MOX-1008 for a randomized, double-blind, placebo-controlled, parallel group study to evaluate the potential effect of single oral dose of up to 36mg moxidectin on the cardiac QT interval of healthy volunteers, and sent response for the study to proceed on 12/21/2016.

Pre-NDA meeting was scheduled for 02/14/2017 but the request was withdrawn as the agency's preliminary responses adequately addressed the sponsor's questions. A Chemistry Manufacturing and Control (CMC) meeting was held on 02/15/2017. Details of the discussion as it pertains to product quality are discussed in section 4. 2.

The NDA for moxidectin was filed on 10/13/2017, with the prescription drug user fee act (PDUFA) goal date of 06/13/2018.

3.3. Foreign Regulatory Actions and Marketing History

4. There have not been foreign submissions for marketing status.

Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The site-specific data for the two studies did not reveal specific efficacy or safety concerns; however, because all four study sites were overseas, an Office of Scientific Investigation (OSI) consult was obtained. The contract research organization (CRO) for the NDA sponsor, the World Health Organization Special program for Research and Training in Tropical Diseases (TDR) located in Geneva, Switzerland and the study site in Hohoe, Ghana, were chosen for inspection. Results of the investigation are pending at this time.

4.2. Product Quality

No issues related to the moxidectin product quality and manufacturing facilities that may preclude approval of the product have been identified. Per the Office of Pharmaceutical Quality (OPQ) review, the applicant provided sufficient information to assure the quality of the proposed drug product, moxidectin tablets, and the manufacturing and testing facilities for this NDA are deemed acceptable. The reader is referred to the OPQ review for more detail.

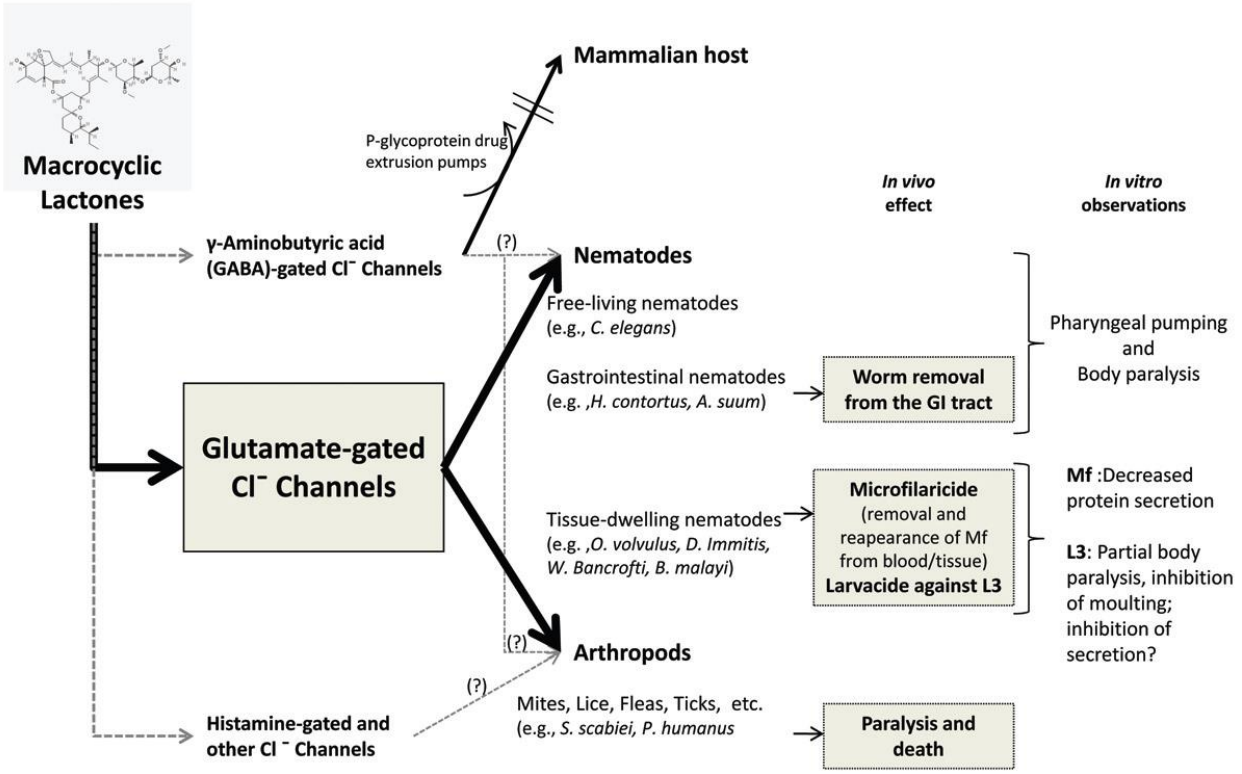
4.3. Clinical Microbiology

Moxidectin is a semi-synthetic compound chemically derived from nemadectin, a fermentation product of *Strepotmyces cyanogriseus*. It has been used as veterinary medicine as endectocide, and is registered worldwide for the prevention of canine heartworm and for treatment of parasites in cattle, sheep and horses.

Both moxidectin and ivermectin belong to the macrocyclic lactone class of anti-helminth; moxidectin is a member of the milbemycin group while ivermectin belongs to the avermectin group of macrocyclic lactones. Both moxidectin and ivermectin are microfilaricidal, and do not kill the adult worm. Of note, both have some effect on the adult worm's fecundity.

Moxidectin's mechanism of action against *O. volvulus* is not fully elucidated. Studies in other nematodes (e.g. *Brugia malayi*) suggest that moxidectin may have similar mechanism of action to ivermectin. The presumed mechanism of action for the macrocylic lactones is summarized in Figure 2. Briefly, it involves binding to glutamate-gated chloride channels (GluCl), and gamma aminobutyric acid (GABA) receptors leading to an increase in permeability, hyperpolarization, influx of chloride ions and muscle paralysis. In addition, treatment with moxidectin results in reduction in motility and decreased excretion of immunomodulatory proteins.

Figure 2: Mechanism of Action of Macrocylic Lactones



Source: Geary TG, Moreno, 2017[17]

4.4. Nonclinical Pharmacology/Toxicology

Long-term carcinogenicity effects for moxidectin have not been established. Moxidectin did not show genotoxicity in a battery of *in vitro* assays including a bacterial mutagenicity assay, mouse lymphoma cell mutagenicity assay, unscheduled DNA synthesis assay, and chromosome aberration assay, as well as *in vivo* in micronucleus assays in mice and rats.

[17] Geary TG, Moreno Y. Macrocyclic Lactone Anthelmintics: Spectrum of Activity and Mechanism of Action. *Curr Pharm Biotechnol*. 2012 May; 13(6): 866-72

In fertility evaluations, male and female mating and fertility indices were not inhibited by oral-dietary moxidectin doses of approximately 0.86 mg/kg/day, which is approximately equivalent to the recommended human dose based on body surface area comparison.

Moxidectin can potentiate mammalian GABA receptors, and although there has been no histological evidence for direct neurotoxicity, transient neurobehavioral effects and CNS-related clinical signs have been noted in nonclinical safety studies. In rats, at a single dose of 20 mg/kg (equivalent to approximately 24 times the recommended human dose based on body surface area comparison), moxidectin was associated with piloerection, reduced arousal and body tone, abnormal gait, slowed breathing, and impaired righting reflex. In dogs, repeated doses of 1.6 mg/kg/day moxidectin, (equivalent to approximately 7 times the recommended human dose based on body surface area comparison), were associated with lacrimation, languid appearance, tremors, slight salivation, and slight ataxia.

4.5. Clinical Pharmacology

Moxidectin belongs to the milbemycin group while ivermectin belongs to the avermectin group of macrocyclic lactones. The structural difference between the milbemycins and avermectins is that milbemycins are unglycosylated and protonated at carbon 13 (C13) of the macrocylic ring. In addition, moxidectin has a metoxime moiety at 23rd carbon(c-23) and olefinic side-chain at the 25th carbo (c-25). These changes make moxidectin more lipophilic with a larger volume of distribution than ivermectin.

The mechanism of action of macrocyclic lactones is summarized in Figure 2 in the clinical microbiology section (section 4.3) of this review. Briefly, it is hypothesized that it binds to glutamate-gated chloride channels (GluCl), and gamma aminobutyric acid (GABA) receptors leading to an increase in permeability, hyperpolarization, influx of chloride ions and muscle paralysis. In addition, it results in reduction in motility, excretion of immunomodulatory proteins and fertility of both male and female adult worms.

Pharmacokinetic Properties of Moxidectin

The pharmacokinetic parameters of moxidectin following a single 8 mg oral dose to healthy subjects and patients with onchocerciasis under fasted conditions are shown in Table 2 . Mean moxidectin C_{max} and AUC increased approximately proportionally to dose over a dose range of 2 to 36 mg (0.25 to 4.5 times the approved recommended dose) in healthy subjects under fasted conditions.

Table 2: Pharmacokinetic Parameters of Moxidectin Following a Single 8 mg Oral Dose in Healthy Subjects and Patients with Onchocerciasis under Fasted Conditions

PK Parameter	Healthy Subjects (N = 27)	Patients with Onchocerciasis (N = 31)
C_{max} (ng/mL), mean± SD	58.9 ± 12.5	63.1 ± 20.0
T_{max} (hours), median (range)	4 (2, 8)	4 (1, 4)
AUC_{inf} (ng•h/mL), mean± SD	3387 ± 1328	2738 ± 1606
Half-life (hours), mean± SD	784 ± 347	559 ± 525

Cmax = maximum plasma concentration; Tmax = time to reach Cmax; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity

Absorption

Moxidectin mean C_{max} and AUC increased on average by 34% and 39%, respectively, when administered with a standard high fat meal (900 calories, with a nutritional distribution of approximately 55% fat, 31% carbohydrates and 14% protein), compared to fasted conditions.

Distribution

The apparent mean (± SD) volume of distribution of moxidectin is 2421 (± 1658) L in patients with onchocerciasis. The plasma protein binding in humans is unknown.

Moxidectin is not a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein 1 (BCRP1).

In a Phase 1 study involving 12 healthy lactating women, the percentage of the 8 mg moxidectin dose excreted into the breast milk over 28 days was approximately 0.70% (approximately 0.056 mg).

Elimination

The mean terminal half-lives of moxidectin following a single 8mg dose were 23.3 days (559 hours) in onchocerciasis patients and 32.7 days (784 hours) in healthy volunteers.

The apparent mean (± SD) total clearance of moxidectin is approximately 3.50(± 1.23) L/hour in patients with onchocerciasis.

Metabolism

The hepatic metabolism of moxidectin is minimal. It is not a uridine 5'diphosphoglucuronosyltransferases (UGT) substrate. In vitro studies showed that moxidectin induces CYP3A4, but is not an inhibitor or substrate of CYP enzymes.

Excretion

Following administration of a single 8 mg oral dose to healthy subjects, 2% of the dose is eliminated unchanged in the feces within the first 72 hours. Renal elimination of intact drug is negligible.

Specific Populations

In clinical studies, no clinically significant differences in the pharmacokinetics of moxidectin were observed based on age (18 to 60 years), sex, weight (42.7 to 107.2 kg), or renal impairment (creatinine clearance (CrCL) 47 to 89 mL/min, estimated by Cockcroft-Gault). The pharmacokinetics of moxidectin in patients with CrCL less than 47 mL/min, including patients undergoing hemodialysis, is unknown.

Based on a population pharmacokinetic analysis and the fact that renal elimination of intact drug is negligible, mild (estimated CrCL 60 to 89 mL/min) and moderate (CrCL 30 to 59 mL/min) renal impairment is not likely to have an impact on the exposure of moxidectin. The effect of severe renal impairment (CrCL 10 to 29 mL/min) or of end-stage renal disease (patients undergoing hemodialysis) on the pharmacokinetics of moxidectin is unknown.

The pharmacokinetics of moxidectin in patients with hepatic impairment is unknown.

Pharmacodynamic Properties of Moxidectin

Results from a Phase 1 concentration-time study showed that at 36 mg dose, 4.5 times the 8 mg dose used in the Phase 2 and 3 studies, moxidectin did not prolong the QT interval to any clinically relevant extent. Please refer to section 8.4.8 for further details of the study.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to this NDA.

4.7. Consumer Study Reviews

This section is not applicable to this NDA.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 shows details of the two, randomized, ivermectin-controlled studies that were carried out to support efficacy and safety of moxidectin.

Table 3: Listing of Clinical Studies Relevant to the Support of Efficacy and Safety of Moxidectin

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
3110A1-2000	00300768	Randomized, double-blind, ivermectin controlled, single ascending dose study	**Mox**: 2, 4, and 8mg **Iver**: 150µg/kg	1°: Skin mf density (mf/mg) at month 18 2°: -Skin mf count at day 8, and months 1, 2, 3, 6, 12, and 18 -Proportion of patient with undetectable skin microfilariae at months 1, 12 and 18 -Time of maximum ocular mf reduction -Viability and fertility of macrofilariae (nodulectomy) at month 18	Single dose, follow up to 18months	**Mox:** 2mg=44 4mg=45 8mg=38 **Iver:** N=45	Adult population	Single center in Ghana, West Africa
3110A1-3000	00790998	Randomized, double-blind, ivermectin controlled, trial	**Mox**: 8mg **Iver**: 150µg/kg	1°: Skin mf density (mf/mg) at month 12 2°: Skin mf density at month	Single dose, follow up to 12 months for all patients,	**Mox**:978 **Iver**: 494	Included 77 pediatric patients between	4 study sites in West Africa: N=2 in the democratic

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				1, 6 and 18 -Proportion with undetectable levels of skin mf at month 1,6 12 and 18 -Percent reduction in mf levels in the anterior chamber at month 12 for patients with baseline sum of ocular mf count of >10	and up to 18months for subset of patients enrolled prior to amendment 3		the ages of 12-18 years (n=53 mox arm; n=24 iver arm)	republic of Congo (DRC); N=1 in Ghana, N=1 in Liberia

mf: microfilariae; Mox: Moxidectin; Iver: Ivermectin

5.2. Review Strategy

The review of the clinical efficacy and safety were primarily focused on the Phase 3 trial as 96% (n=978) of the data for moxidectin at the proposed dose was derived from the Phase 3 trial. The Phase 2 trial contributed 4% (n=38) data at the proposed dose. There were also differences in safety reporting between the Phase 2 and Phase 3 trial; hence, the data from these two studies is presented separately.

For the efficacy evaluation, the sponsor's results were evaluated and interpreted by the statistical reviewer, Dr. Edward Bein, and by the clinical reviewer, Dr. Hiwot Hiruy. Dr. Bein further analyzed the sponsor's data and the results included in section 6.3.2 are derived from Dr. Bein's analyses. Dr. Bein used R statistical software for his analyses.

For the safety review, pre-clinical and clinical studies performed during the development of moxidectin were reviewed by the clinical reviewer, Dr. Hiruy. As mentioned above, most the safety review is focused on the Phase 3 trial. The figures and tables in the safety portion are results of these analyses, unless stated otherwise.

In addition to the Phase 3 analyses, comprehensive summary of the pertinent findings from the Phase 1 and Phase 2 studies are included in the review.

For the clinical safety review, the analytical tools, JMPclinical, JReview and MAED were utilized.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Primary Endpoint for Phase 2 and 3 Trials

There were several discussions between the agency and the sponsor regarding the acceptability of the primary endpoint for the Phase 2 and Phase 3 trials, reduction in skin microfilariae. Note that both studies were conducted overseas previously and the agency did not have input in the design of the two trials. At a clinical meeting on 03/26/2016, the sponsor made the following points:

- There was regulatory precedence with the use of skin microfilariae count as the primary endpoint as the FDA approved ivermectin for the same indication based on reduction in skin microfilariae.
- The skin is the primary site of infection and serves as a reservoir for *O. volvulus*

- Presence of microfilariae in the skin is closely associated with clinical disease as clinical manifestations of onchocerciasis are due to death of the microfilariae and the ensuing inflammatory reaction

The sponsor provided literature to support these points. The agency noted that there are limited data available correlating reduction in microfilarial skin density and clinical benefit, especially effects on visual impairment, after a single dose of therapy. Most of the available data are from observational population-based studies conducted in the context of eradication campaigns and from expert opinions.

The agency reviewed the available literature to determine the acceptability of the primary endpoint. The agency also solicited expert advice from a special government employee (SGE) with expertise in the treatment of parasitic diseases. The SGE noted that reduction in skin microfilariae is a clinically relevant endpoint. In addition, the SGE pointed out that assessment of the proportion of patients with undetectable skin microfilariae and the time to reach undetectable skin microfilariae may be important endpoints from the public health perspective as these endpoints are relevant to the disruption of the *Onchocerca* transmission cycle.

Based on the totality of evidence including the current knowledge of the pathophysiology of onchocerciasis, the prior experience of using this endpoint in ivermectin trials, the literature review as well as input from the SGE, the reduction in skin microfilariae density appears to reasonably likely to predict clinical benefit and was considered acceptable as the primary efficacy endpoint.

6.2. Phase 2 Study (NCT00300768)

6.2.1. Study Design

Overview and Objective

The Phase 2 study was a randomized, double blind, ivermectin-controlled, single-center, single ascending dose study in patients with *O. volvulus* infection.

Trial Design

The trial was a single center study carried out at the Onchocerciasis Chemotherapy Research Center (OCRC) in Hohoe, Ghana. It compared 2mg, 4 mg, and 8mg single moxidectin dose to a single dose of ivermectin at 150 µg/kg.

Table 4 depicts the schedule of events for the study.

Table 4: Schedule of Events for the Phase 2 Trial

	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[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
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		Y[b]	X	X					X																
Ocular examination	X				X				X							X					X	X	X	X	X	X
Retinal Colour 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	X						
Hematology[d]	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
Skin snips	X									X											X	X	X	X	X	X
Randomization		X																								
Drug packaging and dispensing		X																								
Double-blind drug administration			X[e]																							
Moxidectin Plasma Samples		X[f]	X[g]	X		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[h]													X									X				
Discharge																				X						
Nodulectonmy																										Y[i]

a. Informed consent will be obtained in the village prior to transport of potential study participants to the study center and before any study-related procedures
are performed. Informed consent may be obtained prior to day -4.
b. ECG to be done approximately 4 hours after study drug administration. Can be repeated on days 4 through 7 if clinically indicated.
c. For all patients until month 3, then only in patients with lesions or visual defects.
d. All blood and urine samples will be filtered and stained for microfilariae.
e. Will be given after an overnight fast and 2 hours before breakfast.
f. Day -1 sample will be taken approximately 2 hours before drug administration.
g. Day 1 samples will be taken at 1, 2, 4, and 8 hours after drug administration.
h. Depo-medroxyprogesterone acetate (DMPA) on women of childbearing potential not already receiving a parenterally administered contraceptive.
i. All located nodules will be processed for histopathology and slides read by 1 or more blinded observers

Source: Sponsor's Statistical Methods and Interim Analysis plan for Phase 2

Study Endpoints

The primary endpoint for the study was mean reduction of skin microfilariae density at 18 months from baseline. Please refer to section 6.1 for discussion about acceptability of the primary endpoint.

The secondary endpoints included:

- Skin microfilariae levels:
  - Reduction form baseline at day 8, month 1, 2, 3, 6 and 12
  - Proportion of patients with undetectable skin microfilariae levels at month1, 12, and 18
- Ocular microfilariae count at days 3, 5, 14, and months 1, 2, 3, 6, 12 and 18
- Viability of macrofilariae at the month 18 visit
- Fertility of female macrofilariae at the month 18 visit
- Fertility of male macrofilariae at the month 18 visit

Statistical Analysis Plan

The primary objective of the Phase 2 study was to evaluate the safety of escalating single dose of moxidectin from 2mg to 8mg.

The primary efficacy analysis population included patients that received study medication and had baseline and 18-month microfilariae count data. For endpoint assessment, microfilariae count was defined as the geometric mean of skin microfilariae per mg (mf/mg) taken at four sites (iliac crests and claves).

The primary safety analysis population was defined as all patients that received study medication.

Protocol Amendments

The first 4 amendments occurred prior to initiation of the study in September 2006. The first amendment was done on 04/21/04 and pertained to (b) (4) (b) (4). The second amendment took place on 07/14/02 and was related changes in the informed consent form.

The third amendment took place on 10/27/05 and the main changes included:

- The sum of microfilariae in the 2 eyes must be < 10 for patients with moderate skin infection (10-20 microfilariae/mg of skin) in all doses
- Microfilarial migration into blood and urine will be used as indirect evidence of the speed of microfilaricidal activity (All blood and urine samples to be stained for microfilariae counts)

- PK sample added to the 12-month visit
- Primary analysis population changed to mITT
- Fluorescein angiography to be performed in all patients up to Month 3 and then only in patients with lesions or visual defects thereafter
- Initial clinical expert review team (CERT) review will be blinded, with the option to unblind patient/cohort
- All screen failures will be offered nodulectomy and ivermectin treatment
- Addition of microfilariae counts in blood and urine added to Mazzotti laboratory manifestations

The fourth amendment, carried out on 05/10/06, related some change in contact information of the international center for pharmacovigilance.

The fifth (01/10/07) and sixth (04/30/08) amendments took place after initiation of the study. The key points from these amendments were:

- Women already receiving parenterally administered contraceptive were excluded from the protocol-defined DMPA injection schedule
- All parts of the expanded Onchocerciasis Chemotherapy Research Center common toxicity criteria/Mazzotti toxicity criteria (OCRC/MTC) were included into the protocol as an attachment
- Change timing of ECG and fluorescein angiography from Day 4 to 2 to Day 1
- Changes to reference range for neutropenia to taking ethnic neutropenia in African population into consideration

Reviewer Comment: None of the amendments appears to have an impact on the interpretation of the results of the trial.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that the Phase 2 trial was conducted in compliance with the guidelines of Good Clinical Practice (GCP) and the Declaration of Helsinki. The study protocol was approved by the site independent ethics committee (IEC) and written informed consent was obtained from participants prior to study entry. The sponsor plans to archive all essential documents.

Reviewer Comment: The study appears to fulfill the requirements outlined in 2lCFR312.120 for foreign clinical studies not conducted under an IND.

Financial Disclosure

The previous sponsors, Wyeth Pharmaceuticals, Inc. and the World Health Organization, sponsored the Phase 2 trial. The current sponsor, MDGH, upon assuming sponsorship, collected financial certification/disclosure information for all clinical investigators and sub-investigators (including their spouses and dependent children) except for one investigator, Dr. Kwablah Awadzi, who died in 2011. Although a financial disclosure statement could not be obtained from Dr. Awadzi, MDGH states that they have reviewed Dr. Awadzi's contract and did not find information that would require disclosure under 21 CFR 54.4(a).

The sponsor states that none of the investigators were full or part-time employees of the previous study sponsors or of MDGH. None of the investigators has shares of MDGH as MDGH is registered as a charity and does not issue shares.

Patient Disposition

Table 5 summarizes disposition of the Phase 2 participants.

Table 5: Patient Disposition in the Phase 2 Trial

	Moxidectin			Ivermectin
	2 mg N=44 n, %	4 mg N=45 n, %	8 mg N=38 n, %	150 µg/kg N=45 n, %
Total treated	44 (100)	45 (100)	38 (100)	45 (100)
Completed the study	42 (95.5)	45 (100)	37 (97.4)	42 (93.3)
Discontinued	2 (4.5)	0	1 (2.6)	3 (6.7)
Death	1 (2.3)	0	0	0
Lost to follow-up	1 (2.3)	0	1 (2.6)	2 (4.4)
Patient request	0	0	0	1 (2.2)

Source: Modified from Sponsor's Table 8-1 in the Phase 2 Study Report

One patient in the moxidectin 2 mg arm died of snakebite.

Protocol Violations/Deviations

One patient in the ivermectin arm (patient (b) (6)) was enrolled prior to his 18th birthday. Other protocol deviations were mainly due to conduct of screening assessments on day 1 instead of day 4 to 2 and out of range laboratory findings.

Reviewer Comment: There were no protocol violations/deviations that appeared to affect the study endpoints.

Table of Demographic Characteristics

Table 6 shows the baseline characteristics of the study participants.

Table 6: Baseline Characteristics of the Phase 2 Participants

Demographic Parameters	Moxidectin			Ivermectin **150µg/kg** (N=45) n (%)
	2mg (N=44) n (%)	4mg (N= 45) n (%)	**8mg** (N=38) n (%)	
Sex				
Male	36 (81.8)	31 (68.9)	31 (81.6)	33 (73.3)
Female	8 (18.2)	14 (31.1)	7 (18.4)	12 (26.7)
Age				
Median (range) in years	38.5 (18-58)	35 (19-57)	28.5 (18-60)	34(17-58)
Region				
Africa	44 (100)	45 (100)	38 (100)	45 (100)
Race				
Black	44 (100)	45 (100)	38 (100)	45 (100)
Baseline Infection Intensity				
Mild (skin microfilariae 1 to <10, no ocular involvement)	10 (22.7)	11 (24.4)	12 (31.6)	12 (26.7)
Moderate (skin microfilariae 10 to <20 and sum of mf in two eyes >10)	11 (25)	11 (24.4)	11 (29)	12 (26.7)
Severe (skin microfilariae ≥ 20mf with or without ocular involvement)	23 (52.3)	23 (51.1)	15 (39.5)	21 (46.7)
Glucose 6 Phosphate Dehydrogenase				
Normal	38 (86.4)	37 (84.1)	27 (71.1)	40 (88.9)
Partial defect	2 (4.6)	2 (4.6)	5 (13.2)	2 (4.4)
Total defect	4 (9.1)	5 (11.4)	6 (15.8)	3 (6.7)
Missing	0	1	0	0

Source: Modified from the sponsor's Table 8-2's from the Phase 2 Clinical Study Report

Treatment Compliance and Concomitant Medications Use

Treatment Compliance
Each patient received a single dose of moxidectin or ivermectin based on randomization; hence, treatment compliance is not a factor for the study.

Concomitant medications

Table 7 depicts concomitant medications taken by ≥3% of study patients during the 180 days post administration of the study drugs.

Table 7: Summary of Concomitant Medications taken by >3% Study Participants during the 180 Days Post Administration of Study Drug

Generic name	Moxidectin			Ivermectin
	2mg N=44 n, %	4mg N=45 n, %	8mg N=38 n, %	150µg/kg N=45 n, %
Medroxyprogesterone	7 (15.9)	13(28.9)	7 (18.4)	12 (26.7)
Ciprofloxacin	2 (4.5)	1 (2.2)	0	0
Doxycycline	0	0	0	2(1.2)
Diclofenac	0	2 (4.4)	3 (7.9)	2 (4.4)
Turpentine oil	4 (9.1	0	0	0

Source: Modified from the sponsor's Table 8-3 in the Phase 2 Clinical Study Report

The list of concomitant medications used after the 180 days post study drug administration is similar to **Table 7**, except for use of doxycycline in 2 patients in the 8mg moxidectin arm.

Reviewer Comment: One potential concomitant medication that may affect the result of the study is doxycycline as it has activity against Wolbachia, the endosymbiotic bacteria necessary for the nematode. ***Table 7*** *and additional data from the sponsor show that only two patients in the moxidectin 8mg arm and 2 patients in the ivermectin arm were given doxycycline. Overall, the use of concomitant medications did not seem to affect the interpretation of the study result.*

Efficacy Results – Primary Endpoint

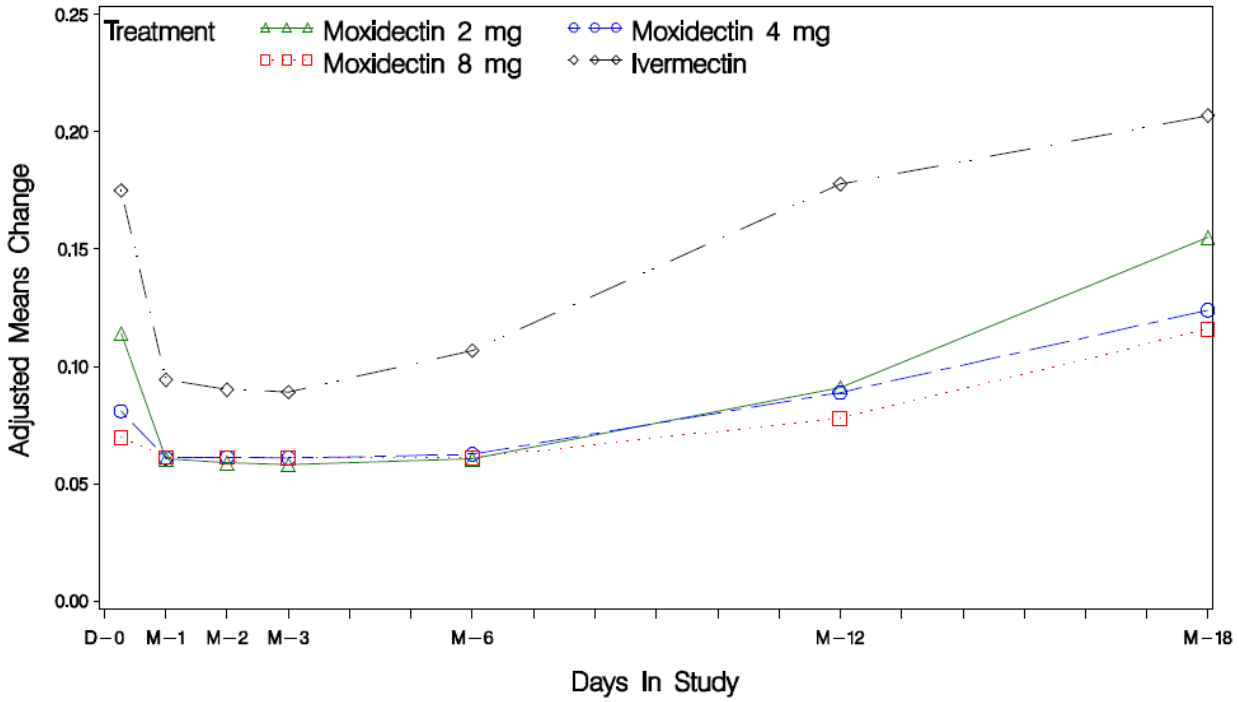
The main analysis population for the efficacy analysis was the efficacy-modified intention to treat (e-mITT) population, which was defined as patients who received the study drug and had baseline and month 18 microfilariae count data.

The efficacy analyses used adjusted mean skin microfilariae count, which was the anti-log of the logarithmically transformed (y=log(y+1)) skin microfilariae count. The primary efficacy analysis showed a statistically significant reduction in skin microfilariae count at 18 months with pairwise comparison of the 4 mg and 8 mg moxidectin arms to ivermectin. The adjusted mean change from baseline when comparing the 4 mg moxidectin to ivermectin was 0.6 (95% confidence interval 0.4 to 0.8, p-value of 0.0035), and the adjusted mean change from baseline was 0.6 (95% confidence interval of 0.4-0.8, p-value of 0.0009) when comparing the 8 mg moxidectin arm to ivermectin. Figure 3 below depicts the change in skin microfilariae count by

study visit for each arm of the study.

Of note, the moxidectin 2 mg arm also showed higher reduction from baseline adjusted mean skin microfilariae count at 18 month when compared to ivermectin, but the change did not reach statistical significance (p-value of 0.08).

Figure 3: Adjusted Mean Change in Skin Microfilariae Density at Month 18



NOTE: Adjusted mean change was calculated by taking the anti-log of the logarithmically transformed (y=log(y+1)) skin microfilariae count

Source: Sponsor's figure 9-1 in the Phase 2 Clinical Study Report

Reviewer Comment: It appears that compared to ivermectin, the two higher doses moxidectin, the 4mg and the 8mg, yielded statistically significant superiority in reducing skin microfilariae at month 18; the 2mg moxidectin showed numerically higher reduction compared to ivermectin, but it did not reach statistical significance.

Data Quality and Integrity

Office of Scientific Integrity (OSI) was consulted for this application. The Phase 2 trial site was also one of the study sites for the Phase 3 trial. The OSI consult is pending at this time, and findings will be amended to this review.

Efficacy Results – Secondary and other relevant endpoints

Percent of Patients with Undetectable Levels of Skin Microfilariae
The number of patients with undetectable levels of skin microfilariae were statistically significantly higher with pairwise comparison of moxidectin 4 mg and 8 mg arms to ivermectin (p values <0.01 using Cochran Mantel Hostel method) for day 8, months 1, 2, 3, 6 and 12 time points. Detailed look at the two later time points, the 6 month and 12 month, show that the 8 mg dose had the highest proportion of patients with undetectable skin microfilariae (36//38=95%) when compared to 4mg (39/45=87%) and 2mg (31/44=71%) at month 6. Similarly, the 8 mg moxidectin resulted in the highest percentage of patients with sustained undetectable skin microfilariae at 12 month (53%) when compared to the 4mg (40%) and 2mg (34%).

The pairwise comparison of moxidectin 2 mg arm to ivermectin also showed statistically significantly higher number of patients with undetectable skin microfilariae for the months 1, 2, 3, 6, and 12 time points.

None of the pairwise comparison of each of the three moxidectin arms to ivermectin had statistically significant difference for the 18 month time point.

Change from Baseline Skin Microfilariae Density at Time point Other than Month 18
The secondary efficacy endpoints included skin microfilariae densities at time-point other than month 18, and included day 8, months 1,2,3,6 and 12. Using mixed model analyses, each of the three moxidectin arms showed statistically significant higher reduction (p-value <0.003) in skin microfilariae at each time point when compared to ivermectin for the abovementioned time points.

Ocular Microfilariae
There were a small number of patients with baseline anterior chamber microfilariae in each study arm; there were 9 out 44, 10 out of 45, and 10 out of 38 for the 2 mg, 4 mg, and 8 mg moxidectin arms, respectively. There were 8 out of 45 patients in the ivermectin arm with baseline anterior chamber microfilariae. In addition, there was significant variability in the maximum number of anterior chamber microfilariae noted in each arm at baseline. For the moxidectin arm, the maximum baseline microfilariae in the anterior chamber were 8, 39, and 5 for the 2 mg, 4 mg and 8 mg moxidectin arms, respectively. The maximum baseline anterior chamber microfilariae were 25 for the ivermectin arm.

The median time in days to maximum persistent reduction of anterior chamber microfilariae for the moxidectin arms were 31 (95% CI: 14 to 35), 30.5 (95% CI: 15 to 58), 4 (95% CI: 3 to 4) for the 2 mg, 4 mg and 8 mg moxidectin arms. The median time for the ivermectin arm was 33.5 days (95% CI 14 to 18).

Reviewer Comment: All three moxidectin arms showed statistically significant superiority over ivermectin for the secondary endpoints of mean changes from baseline at time points other than month 18 and percent of patients with undetectable microfilariae at months 6 and 12. There also appears to be a dose-response for these secondary endpoints, with the 8 mg single dose of moxidectin outperforming the 2 mg and 4 mg doses.

Drawing a conclusion about the ocular microfilariae endpoint is a challenge due to the small number of patients with eye involvement at baseline and the wide variability in the maximum baseline anterior chamber microfilariae count among the treatment groups.

Dose/Dose-Response

There was no difference in the efficacy primary endpoint for the 4 mg and 8 mg moxidectin. However, looking at the proportion of patients with undetectable skin microfilariae at months 6 and 12, there was a clear dose-response noted for the secondary endpoints of proportion of patients with undetectable skin microfilariae, with the 8mg dose showing the largest percentages of patients with undetectable skin microfilariae as compared to the 2 mg and 4 mg.

Durability of Response

Due to the small number of patients that received the 8 mg moxidectin dose in the Phase 2 trial, durability of moxidectin' s effect will be discussed in the Phase 3 trial results section, section 6.2.2.

Persistence of Effect

Due to the small number of patients that received the 8 mg moxidectin dose in the Phase 2 trial, persistence of moxidectin' s effect will be discussed in the Phase 3 trial results section, section 6.2.2.

6.3. Phase 3 Trial (NCT00790998)

6.3.1. Study Design

Overview and Objective

The Phase 3 trial was a large, randomized, double blind, multi-center, ivermectin-controlled study comparing single 8mg dose of moxidectin to ivermectin in patients with *O. volvulus* infection. The trial had two pre-specifications regarding the study participants. First, it targeted populations that

are naive to onchocerciasis treatment, i.e., areas where community directed treatment with ivermectin has not been implemented yet, or areas with low therapeutic coverage. Second, it excluded areas that were co-endemic with loaisis.

Trial Design

Phase 3 trial aimed to evaluate the efficacy and safety of a single 8 mg dose of moxidectin for the treatment of onchocerciasis. The trial was a superiority design, with a single-dose ivermectin at 150µg/kg as the active-comparator arm. The 8 mg moxidectin dose was selected based on the results of the single ascending dose Phase 2 trial discussed in section 6.1.

Participants were randomized in a 2:1 ratio to the moxidectin or ivermectin arm, respectively. The randomization was stratified by sex and by baseline microfilariae density (< 20 mf/mg skin vs. >= 20 mf/mg skin). Randomization was implemented manually, by an unblinded pharmacist, using applicant-generated tables of randomization codes with blocks of six.

Inclusion Criteria

1. Male or female patients ≥12 years of age and weighing ≥30 kg
2. Patients with *O. volvulus* infection, with at least 10 mf/mg by skin snip
3. Females of child bearing potential who have agreed to the use of a reliable method of birth control for 6 months after test article administration

Key Exclusion Criteria

1. Prior treatment with the anti-nematodal drugs, diethylcarbamazine (DEC), Suramin, ivermectin, albendazole or levamisole, within 6 months prior to planned administration of study drug
2. Pregnant or breastfeeding women
3. Patient unlikely to residency in the area (based on patient's assessment) over the next 20 months
4. Patients with loiasis
5. Patients with lymphatic filariasis (LF) with an intensity of infection >100 mf/mL
6. Acute or uncontrolled disease process (e.g., acute pneumonia requiring therapy or end-stage AIDS) within 7 days before study drug administration
7. Received any investigational drugs or investigational devices within 4 weeks before administration of study drug that may confound safety and/or efficacy assessments
8. Known or suspected allergy to moxidectin or ivermectin or other compounds related to these classes of medication
9. Any concomitant condition that, in the opinion of the investigator, would preclude an evaluation of a response or would place patient’s health at undue risk

Table 8 depicts the schedule of events for the Phase 3 trial.

Table 8: Schedule of Events for Phase 3 Trial

Study Procedures	D-30 to -1	D1	D2	D3	D4	D6 ± 1D	D14 ± 2D	M1 ± 5D	M3 ± 2W	M6 ± 1M	M12 ± 1M	M18* ± 2M
Demographics	X											
Medical history	X											
Medication history	X											
Assessment of *Loa loa* infection	X											
Pregnancy test[a]	X[j]							X[K]	X[K]	X[K]		
Skin snips[l]	X							X		X	X	X
Nodule palpation	X										X	X
Height	X											
Weight	X							X	X	X		
Complete PE	X[j]											
Interim PE		X	X	X	X	X	X	X	X	X	X	X
Vital signs[b]	X[j]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X[j]		X[c]									
Ocular examination	X			X[c]				X		X	X	X
Hematology[d]	X[j]					X	X	X	X	X		
Serum chemistry[e]	X[j]					X	X	X	X	X		
Urinalysis[f]	X[j]					X	X	X	X	X		
Lymphatic filariasis test [g]	X							X		X	X	X
Intestinal helminths infection[h]	X							X				
Study drug administration[i]		X										
Adverse events collection	X											

Abbreviations: ECG=electrocardiogram. PE Physical Examination, D = Day, M = Month

a. For women of childbearing potential, a negative urine pregnancy test result is required before randomization.
b. Vital signs on day 1 are performed before and after test article administration.
c. 12-Lead ECG on day 2 or day 3; ocular exam on day 3 or day 4.
d. Hematology includes complete blood count (CBC) (consisting of total white blood cell (WBC) count with differential, platelet count, hemoglobin, and hematocrit).
e. Serum chemistry includes sodium, potassium, chloride, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase (AP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), aspartate aminotransferase (SGPT) (AST), and alanine aminotransferase (SGPT) (ALT).
f. Urinalysis includes specific gravity, pH, albumin (protein), glucose, ketones, hemoglobin, bilirubin, urobilinogen, nitrite and leukocyte esterase. Microscopic evaluation of red blood cells (RBC), WBC, epithelial cells, bacteria, casts, and crystals is performed at Baseline and thereafter only at investigator's discretion as medically indicated.
g. Lymphatic filariasis (LF) evaluation in areas coendemic for LF or where endemicity is unknown. Pretreatment LF evaluation: immunochromatographic card test for Wuchereria bancrofti (ICT) in subjects without clinical signs and symptoms. If positive, these subjects (and all subjects with signs and symptoms of LF) will have nightblood evaluation for diagnosis and quantification of LF infection. Post-treatment LF evaluation (nightblood evaluation) only in subjects who are positive at Baseline (see protocol for more details for post-treatment follow up).
h. Collection of feces and evaluation for intestinal helminths is optional.
i. Drug administration after an overnight fast.
j. Test results should be obtained within 1 week before test article administration.
k. Pregnancy testing will be offered to women of reproductive potential. The active phase of this study begins with the administration of test article and ends 180 days after this dose administration. In order to assure follow-up of women who become pregnant during the active phase, all live births that occur during the 18-month follow-up period will be followed for the first year of the infant's life.
l. Skin snips may be obtained within the 30-day screening period or up to 2 months prior to test article administration.

* 18 months post treatment assessment for all subjects whose Month 18 visit was due prior to approval of Amendment 3, or 31 December 2011, whichever is the later date.

Study Endpoints

The primary endpoint for the Phase 3 trial was mean *O. volvulus* microfilariae density (mf/mg of skin) at 12 months. Please refer to section 6.1 for discussion about acceptability of the primary endpoint.

As discussed in section 2.1, the primary diagnostic mode for onchocerciasis is demonstration of microfilariae in skin snips. Skin snips were taken from four sites (right and left iliac crests and calves). Microfilariae from each site were counted and the average of the four counts was considered the mean microfilariae density. If microfilariae could not be counted at two or more sites, the mean microfilariae density was considered missing.

The secondary efficacy endpoints included:

- Mean microfilariae skin density at month 1, 6 and 18.
- Binary variable indicating whether skin microfilariae are detectable at month 1, 6, 12 and 18.
- For the subgroup of patient with baseline ocular involvement (sum of live or dead mf count

in of anterior chambers of >10), the percentage reduction in the sum of anterior chamber mf count at 12 months

Statistical Analysis Plan

Please refer to the biometrics review done by Dr. Edward Bein for full detail of the statistical analysis plan. Briefly, the Phase 3 trial was completed previously and the agency did not have input in the final statistical plan prior to study initiation.

The primary analysis population for the primary and secondary efficacy endpoint was the as-randomized modified intention to treat (AR-mITT) population, which was defined as all participants who received a single dose of the study medication. This was the same set of participants as the mITT, but it was analyzed as as-randomized as opposed to actual treatment received.

The sponsor used a mixed effect model, adjusting for baseline skin microfilariae density. The site-level was used as random intercept. The primary model contained baseline skin microfilariae density, treatment group, visit number, treatment by visit, and stratification variables, sex and study site. The skin microfilariae density data was $\log_e(y+1)$ transformed before analysis. The sponsor planned to use a non-parametric analysis if these data were neither normal nor log normal.

Reviewer Comment: The biometric reviewer, Dr. Bein, had concerns regarding the adequacy of the mixed effect model since the number of study sites were less than 10. He also had concerns regarding assumptions used in the secondary endpoint analyses. Please refer to his review for additional details.

Of note, there were no adjustments specified for the multiple secondary efficacy endpoints.
In regards to handling of missing data, the applicant assumed that missing data were missing at random (MAR), with the assumption the distribution of unobserved endpoint values is identical to the distribution of observed endpoint values.

There were no planned interim analyses.

Protocol Amendments

There were three protocol amendments; amendment 1 was made prior to start of the study in each country. The second and third amendments were made after start of the study. Key parts of each amendment are summarized below:

Amendment 1

- Addition of adolescents ≥12 years of age to the study
- Change of moxidectin dose to 8 mg only
- Screening skin snips allowed up to 2 months prior to administration of study drug
- Clarification of the active phase of the study for pregnancy follow-up, and timing of assessments

Amendment 2

- Clarification of prohibited treatment
- Clarification of skin mf/mg levels for randomization

Amendment 3

- Removal of the month 18 assessment visit with the caveat that month 18 visit to be carried out if it was due prior to this amendment's approval or 12/31/2011, whichever came later
- Clarification of prohibited concomitant medication
- Clarification of criteria for abnormal laboratory and ECG findings and adverse event reporting
- Change in sponsor and clarification of study procedures

Reviewer Comment: The abovementioned amendments do not appear to influence the results of the study. Removal of the month 18 visit did not influence the study result as the primary efficacy analysis was planned for month 12.

6.3.2. Study Results

Compliance with Good Clinical Practices

The sponsor has provided attestation that the study was conducted in compliance with the guidelines of Good Clinical Practice (GCP) and the Declaration of Helsinki. The sponsor plans to archive all essential documents. The study protocol was also approved by the site independent ethics committee (IEC) and written informed consent was obtained from participants prior to study entry.

Reviewer Comment: The trial appears to fulfill the requirements outlined in 2lCFR312.120 for foreign clinical studies not conducted under an IND.

Financial Disclosure

The Phase 3 trial was conducted by the previous sponsors, Wyeth Pharmaceuticals, Inc. (a subsidiary of Pfizer, Inc.) and the World Health Organization/Special Programme for Research and Training in Tropical Diseases (WHO/TDR). Upon assuming sponsorship of the moxidectin development program, MDGH states that they collected financial certification/disclosure information for all clinical investigators and sub-investigators (including their spouses and dependent children), except for an investigator, Dr. Kwablah Awadzi, who passed away in 2011.

MDGH states that although a financial disclosure statement could not be obtained from Doctor Awadzi, they were able to review Dr. Awadzi's contract and did not find information that would indicate that he received any compensation that would require disclosure under 21 CFR 54.4(a).

None of the investigators were full or part-time employees of the previous sponsors or of MDGH. MDGH does not issue shares, and hence none of the investigators held MDGH shares.

Patient Disposition

Table 9 summarizes the disposition of the Phase 3 participants.

Table 9: Patient Disposition in the Phase 3 Trial

	Moxidectin	**Ivermectin**
Randomized	997	502
Not dosed	20	7
Received study drug*	**978[#]**	**494[#]**
Completed the study**	927 (94.8%)	476 (96.4%)
Did not complete	51 (5.2%)	18 (3.6%)
Lost to follow-up	35 (3.6%)	13 (2.6%)
Death	11 (1.1%)	3 (0.6%)
Patient Request	4 (0.4%)	2 (0.4%)
Investigator Request	1 (0.1%)	0

*One patient randomized to moxidectin received ivermectin and 2 patients randomized to ivermectin received moxidectin
**Completion status for patients may have been month 12 or 18 relative to when the final amendment that removed the month 18 visit took effect; all patients that completed the study were followed for at least 12 months.
[#]The number of patients that received study drug for each arm was used as a denominator for percentage calculation.

Reviewer Comment: Overall, the completion rate for both arms was comparable. Looking at the study arms, no significant imbalance was noted in patients that did not complete the trial. There were a slightly higher proportion of deaths in the moxidectin arm (1.1%) as compared to the ivermectin arm (0.6%).

Protocol Violations/Deviations

The Phase 3 trial statistical analysis plan had outlined pre-specified deviations that may affect the efficacy and safety analyses of the study. For the efficacy analyses, the pre-specified deviations include incorrect study dose, missing informed consent, lack of skin microfilariae evaluation at month12, and treatment with anti-nematodal drugs. For the safety analyses, these include patients experiencing acute or uncontrolled disease process, receipt of other investigational drugs within 4 weeks prior to administration of study drug, administration of higher than planned dose of study drug, missing laboratory data up to month 6 and missing vital sign data up to month 1.

There were 130 major protocol deviations that may potentially affect the efficacy analyses, 91 (9.3%) in the moxidectin group and 39 (7.9%) in the ivermectin arm. The two main deviations were follow-up visits outside the protocol specified time windows (23/91 moxidectin, 8/39 ivermectin) and absence of *O. volvulus* skin microfilariae at month 12 (22/91moxidectin, 12/39 ivermectin).

In addition, 39 major protocol deviations that may potentially affect the safety analyses were reported; of these, 29 (3%) were in the moxidectin arm and 10 (2%) in the ivermectin arm. The two main deviations were missing supine blood pressure and pulse rate up to month 6 (15/29 moxidectin, 5/10 ivermectin) and missing hematology data at baseline or up to month 6 (12/29 moxidectin, 3/10 ivermectin).

Reviewer Comment: Overall, the protocol deviations that may affect the safety and efficacy results were balanced between the two arms.

Table of Demographic Characteristics

Table 10 shows the baseline characteristics of the primary efficacy and safety population.

Table 10: Baseline Characteristics of the Phase 3 Primary Efficacy and Safety Population

Baseline Characteristics	**Moxidectin** N=978 n (%)	**Ivermectin** N= 494 n (%)
Sex		
Male	626 (64)	313 (63.4)
Female	352 (36)	179 (36.2)
Age		
Mean years (SD)	41.6 (16.4)	42.9 (16.1)
Median (years)	42	44
Min, max (years)	12, 95	12, 86

Age Group		
12 to <18 years	53 (5.4)	24 (4.9)
≥18 to < 30 years	228 (23.3)	102 (20.6)
≥ 30 to <65 years	614 (62.8)	318 (64.3)
≥65 - < 75 years	64 (6.5)	37 (7.5)
≥ 75 years	19 (1.9)	13 (2.6)
Region		
Africa	978 (100)	494 (100)
Democratic Republic of Congo	620 (63.4)	312 (63.2)
Site 1	305 (31.2)	155 (31.4)
Site 2	315 (32.2)	157 (31.8)
Ghana	158 (16.2)	83 (16.8)
Liberia	200 (20.4)	99 (20)
Presence of Baseline Ocular Microfilariae (mf)	379 (38.8)	202 (40.9)
Ocular mf ≥10	152 (15.5)	86 (17.3)
Skin Microfilariae Density[1]		
< 20mf/mg	296 (30.3)	151 (30.6)
≥ 20 to < 50 mf/mg	444 (45.4)	185 (37.5)
≥ 50 to < 80 mf/mg	157 (16.1)	106 (21.5)
≥ 80 mf/mg	80 (8.2)	52 (10.5)

[1] One patient in the moxidectin arm did not have baseline microfilariae count

Reviewer Comment: Overall, the two study arms were well balanced in terms of sex, age, and number of patients at each study site. The majority of study participants in both arms were men. The proportion of patients with baseline skin microfilariae above 50 mf/mg was slightly higher in the ivermectin arm (32%) vs. the moxidectin arm (24.3%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline Co-infection with Other Helminths

Table 11: Phase 3 Baseline Co-infection with Other Helminths

	Moxidectin	Ivermectin

	Proportion, %	Proportion, %
Hookworm	499/959 (52)	263/482 (54.5)
Wuchereria bancrofti		
Immunochromatographic test	19/819 (2.3)	14/409 (3.4)
Night blood evaluation	0 /19	0/14
Roundworm	34/959 (3.5)	10/482 (2.1)
Schistosoma mansoni	146/959 (15.2)	68/482 (14.1)
Strongyloides stercoralis	4/958 (0.4)	0
Whipworm	13/959 (1.4)	6/482 (1.2)

NOTE: The number of patients tested for each helminth was used as denominator.

Reviewer Comment: The baseline co-infection with other helminths appears comparable between the two arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Each patient received a single dose of the study drug, moxidectin or ivermectin, based on randomization at the study sites; hence treatment compliance is not a factor for the study.

Concomitant Medication
While reviewing the data, it was noted that in addition to protocol-proscribed medications listed as part of the exclusion criteria in section 6.3.1, there were additional medication with potential for anti-nematodal and/or anti-*Wolbachia* activity that may affect the primary endpoint, skin microfilariae count at 12 months. The clinical reviewer expanded the list of proscribed medications to include mebendazole, doxycycline, and tetracycline. **Table 12** shows the number of patients that received these expanded proscribed medications with reference to the timing of administration of these drugs.

Table 12: Phase 3 Concomitant Medications that have Anti-nematodal or Anti-Wolbachia Activity

	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Patient that received anti-nematodal drugs at any time during the study*	56 (5.7)	25 (5.1)
Patients that received mebendazole from 6-month prior to day 1 to month12 visit	109 (11.1)	87 (17.6)
Patients that received anti-infective drugs with activity	60 (6.1)	31 (6.3)

against *Wolbachia***		
Those treated for ≥7days	14 (1.4)	6 (1.2)

**Anti-nematodal drugs include diethylcarbamazine, suramin, albendazole, levamisole and ivermectin; use of these drugs with 6 months prior to screening was an exclusion criteria.
**Anti-*Wolbachia* drugs included tetracycline and doxycycline

Reviewer Comment: Overall, the two arms were balanced in the use of proscribed medications. A sensitivity analysis with these patients that received the expanded proscribed medications that may interfere with the primary endpoint was carried out, and result of this analysis is presented in ***Table 17****.*

Efficacy Results - Primary Endpoint

Analysis of reduction in skin microfilariae at 12 month, using log-transformed or untransformed skin microfilariae count, yielded statistically significant results with p value < 0.0001 in favor of the superiority of moxidectin over ivermectin. The estimate of the untransformed average treatment effect is 8.04 fewer mf per mg skin using moxidectin vs. using ivermectin, with a 95% confidence interval of 7 - 9.1 fewer mf per mg skin. The corresponding estimated ratio of geometric means is 0.28, with a 95% confidence interval of 0.25 - 0.30.

Additional stringent analysis assuming "worst case scenarios" for missing data with assuming missing 12-month data as failures in moxidectin arm and successes in the ivermectin arm also yielded statistical superiority of moxidectin over ivermectin.

Table 13 summarizes these findings for the primary endpoint at month 12 with log-transformed and untransformed analyses.

Table 13: Phase 3 Primary Endpoint Analyses

Endpoint	**Moxidectin**	**Ivermectin**	**Difference in Means**
Mean mf density[a]	1.79 (1.35, 2.22)	9.83 (8.81, 10.85)	-8.04 (-9.11, -6.98) p < .0001
Mean mf density[a] "Worst Case"	2.56 (1.99, 3.13)	9.58 (8.59, 10.57)	-7.02 (-8.12, -5.91) p < .0001
			Ratio of Geometric Means
Log (mean mf density + 1)[b]	1.64 (1.56, 1.72)	5.92 (5.41, 6.47)	0.28 (0.25, 0.30) p < .0001

Log (mean mf density + 1)[b] "Worst Case"	1.77 (1.67, 1.87)	5.67 (5.17, 6.20)	0.31 (0.28, 0.35) p < .0001

Notes. N = 1472 (977 moxidectin/495 ivermectin)
Cells contain estimates and 95% confidence intervals.
"Worst case" refers to sensitivity analysis assuming patients with missing 12-month skin microfilariae count as failures in moxidectin arm and successes in the ivermectin arm
[a] Columns 2 and 3 contain estimates of arms' mean (untransformed) mean mf densities, and column 4 contains estimate of the average treatment effect (i.e., difference in means).
[b] Columns 2 and 3 contain estimates of arms' geometric means for 1+mean mf density, and column 4 contains estimate of ratio of arms' geometric means.

Data Quality and Integrity - Reviewers' Assessment

There were no inconsistencies in the data presented to raise suspicion about trial conduct issues that may have influenced the observed efficacy results.

Efficacy Results - Secondary and other relevant endpoints

Undetectable Skin Microfilariae at Month 1, 6, 12 and 18
All analyses at 1, 6, 12, and 18 months, including the "worst case" scenario sensitivity analysis assuming patients with missing skin microfilariae count as failures in moxidectin arm and successes in the ivermectin arm, yielded statistically significant results ($p < .0001$) in favor of the superiority of moxidectin over ivermectin. The estimate of the average treatment effect at 12 months is 40.4% more patients with undetectable skin microfilariae in the moxidectin arm as compared to ivermectin, with a 95% confidence interval of 36.7%-44.1%. The corresponding odds ratio estimate is 14.75, with a 95% confidence interval of 9.63-22.59 Table 14 summarizes the binary secondary endpoint of undetectable skin microfilariae at the month 1,6, 12 and 18 time points.

Table 14: Proportion of Phase 3 Patients with Undetectable Skin Microfilariae at Month 1,6, 12 and 18

Endpoint	Moxidectin	Ivermectin	Difference	Odds Ratio
1 month				
% Undetectable Skin Microfilariae	83.4% (81.0, 85.8)	42.9% (38.7, 47.1)	40.5% (35.7, 45.3) p < .0001	6.70 (5.26, 8.53)
% Undetectable Skin Microfilariae "Worst Case"	83.0% (80.7, 85.3)	43.2% (38.9, 47.4)	39.8% (35.0, 44.7) p < .0001	6.43 (5.07, 8.14)
6 months				
% Undetectable	91.0%	11.5%	79.6%	78.32

Skin Microfilariae	(89.2, 92.8)	(8.7, 14.2)	(76.3, 82.9) p < .0001	(54.93, 111.66)
% Undetectable Skin Microfilariae "Worst Case"	89.8% (87.9, 91.7)	11.6% (8.8, 14.5)	78.2% (74.8, 81.5) p < .0001	66.79 (47.38, 94.14)
12 months				
% Undetectable Skin Microfilariae	45.9% (42.7, 49.0)	5.4% (3.4, 7.5)	40.4% (36.7, 44.1) p < .0001	14.75 (9.63, 22.59)
% Undetectable Skin Microfilariae "Worst Case"	44.5% (41.6, 47.5)	7.8% (5.3, 10.2)	36.8% (33.0, 40.6) p < .0001	9.55 (6.65, 13.71)
18 months				
% Undetectable Skin Microfilariae	30.5% (26.8, 34.1)	4.9% (2.4, 7.4)	25.5% (21.2, 29.8) p < .0001	8.43 (4.75, 14.98)
% Undetectable Skin Microfilariae "Worst Case"	29.4% (26.0, 32.8)	6.8% (4.0, 9.6)	22.6% (18.2, 27.0) p < .0001	5.72 (3.52, 9.30)

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18. Cells contain estimates and 95% confidence intervals. Percentages are of participants with undetectable skin mf; i.e., mean mf density = 0.
"Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data.

Reviewer Comment: At all time points, the moxidectin arm had higher percentage of patients with undetectable skin microfilariae. The highest percentage of patients with undetectable skin microfilariae was seen at month 6, with 91% of the moxidectin-treated patients having undetectable skin microfilariae as compared to 11.5% of ivermectin-treated patients. It appears that the proportion of patients with undetectable skin microfilariae start to decline after month 6 for moxidectin arm to 45.9% and 30.5% at month 12 and 18, respectively. This observation goes along with the mechanism of action of moxidectin in that it kills the microfilariae and not the adult worms. One hypothesis is that after the initial killing of the microfilariae, the adult female worms will continue to release new microfilariae, hence the noticeable decline in the proportion of patients with undetectable skin microfilariae at the later time points.

Mean Microfilariae Density Endpoints at Month 1, 6 and 18

All analyses at 1, 6, and 18 months of the log-transformed and the untransformed skin microfilariae count, and the "worst case" scenarios sensitivity analyses (please see primary endpoint section for definition) yielded statistically significant results with p value < 0.0001 in favor of the superiority of moxidectin over ivermectin.

Percent Reduction in Ocular Microfilariae from Baseline to Month 12

Table **15** summarizes the percent reduction in ocular microfilariae for the subset of patients with baseline sum of anterior chamber mf count >10.

Table 15: Percent Reduction in Ocular Microfilariae from Baseline to Month 12 in the Phase 3 Trial

Endpoint	Moxidectin	Ivermectin	Difference in Means
Percent Reduction[a]	98.0% (96.0, 99.9)	97.8% (95.7, 99.9)	0.2% (-2.6, 2.9) p > .90
			Ratio of Geometric Means
Log (Percent Reduction + 1)[b]	1.97 (1.95, 2.00)	1.97 (1.95, 2.00)	1.00 (0.98, 1.02) p > .90

Notes. Analysis restricted to participants in AR-mITT sample with baseline ocular mf count >= 10.
N = 236 (151 moxidectin/85 ivermectin); there were 34 other participants with missing baseline ocular mf counts. 11 of the 236 participants had missing ocular mf counts at 12 months (4.7%).
Cells contain estimates and 95% confidence intervals.
[a] Columns 2 and 3 contain estimates of arms' mean untransformed ocular mf counts, and column 4 contains estimate of the average treatment effect (i.e., difference in means).
[b] Columns 2 and 3 contain estimates of arms' geometric means for 1+percent reduction in ocular mf, and column 4 contains estimate of ratio of arms' geometric means.

Subgroup Analyses by Site, Gender, Age Group and Baseline Skin Microfilarial Density
Sub-group analyses by site, gender, age group (<18 vs. >18) and baseline skin microfilariae density (<20 vs. ≥ 2mf/mg) all yielded statistically significant superiority of moxidectin over ivermectin. Results are summarized in **Table 16**.

Table 16: Subgroup Analyses by Site, Gender, Age Group and Baseline Skin Microfilarial Density for the Phase 3 Trial

	Subgroup	N N_M/N	Overall Baseline	Moxidectin	Ivermectin	Difference
Site[a]	Site 1	460 304/156	35.87	1.17 (0.49, 1.85)	8.05 (6.40, 9.70)	-6.88 (-8.57, -5.20) p < .0001
	Site 2	472 315/157	49.59	2.30 (1.24, 3.36)	13.85 (11.75, 15.94)	-11.55 (-13.82, -9.28) p < .0001
	Site 3	299 201/98	30.25	1.34 (0.69, 2.00)	4.99 (3.64, 6.34)	-3.64 (-5.12, -2.16) p < .0001
	Site 4	241 157/84	38.29	2.67 (1.91, 3.44)	10.97 (8.52, 13.42)	-8.30 (-10.77, - 5.82) p < .0001
Gender[b]	Female	531 352/179	37.71	0.55 (0.26, 0.84)	8.35 (6.73, 9.98)	-7.80 (-9.42, -6.19) p < .0001
	Male	941 625/316	40.55	2.54 (1.86, 3.22)	10.56 (9.25, 11.87)	-8.02 (-9.44, -6.59) p < .0001
Age Group[c]	Adolescent	77 53/24	28.62	2.94 (1.64, 4.25)	11.48 (6.40, 16.56)	-8.54 (-13.79, - 3.29) p = .0014
	Adult	1395 924/471	40.13	1.73 (1.25, 2.20)	9.73 (8.69, 10.78)	-8.01 (-9.11, -6.90) p < .0001
Baseline Skin mf Density [d]	Low (10 to < 20 mf/mg)	447 296/151	14.16	0.43 (0.27, 0.59)	3.40 (2.44, 4.37)	-2.97 (-3.94, -2.00) p < .0001
	High (≥20 mf/mg)	1024 680/344	50.60	2.27 (1.67, 2.87)	12.93 (11.43, 14.43)	-10.66 (-12.27, - 9.05) p < .0001

Notes. N = 1472 (977 moxidectin/495 ivermectin); NM-subgroup in moxidectin arm; NI-subgroup in ivermectin arm
Cells contain estimates and 95% confidence intervals. "Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data. Columns 5 and 6 contain estimates of arms' mean (untransformed) mean mf densities, and column 7 contains estimate of the average treatment effect (i.e., difference in means).

a. Site differences in efficacy are statistically significant, p < .0001. Site 1 is DRC, Butembo; site 2 is DRC, Rethy; site 3 is Liberia; and site 4 is Ghana.

b. Gender differences in efficacy are not significant, p > .8.

c. Age group differences in efficacy are not significant, p > .8.

d. Baseline infection level differences in efficacy are significant, p < .0001. Sample size sums to 1471 because one participant had missing baseline infection level.

Reviewer Comment: All of the subgroup analyses showed that moxidectin' s superiority over ivermectin in reducing skin microfilariae was maintained. Of note, there was no statistically significant difference in efficacy between adolescents and adults, and between men and women.

The comparison of efficacy between sites showed statistically significant difference among the sites; however, each site's analysis of moxidectin vs. ivermectin still yielded superiority of moxidectin.

Comparison of efficacy between patients with low (<20 mf/mg) vs. high (≥20mf/mg) baseline skin microfilariae density also resulted in statistically significant difference in efficacy. Even then, for each subgroup of patients, the moxidectin arm was superior to ivermectin.

Additional Sensitivity Analysis of Patients Who Received Proscribed Medications
This sensitivity analyses assumed patients that received these expanded proscribed medications as failures (12 month microfilariae density = baseline microfilariae density). In addition, any missing 12 month skin microfilariae count was considered a failure in the moxidectin arm and success in the ivermectin arm. This conservative analysis, with log-transformed and untransformed data, yielded statistically significant superiority of moxidectin over ivermectin. Table 17 summarizes the results of the analysis.

Table 17: Phase 3 Sensitivity Analysis of the Primary Endpoint Excluding Patients with Extended Proscribed Medications Use

Endpoint	Moxidectin	Ivermectin	Difference/ Ratio of Geometric Means
12 months			
Mean mf density:[a] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	6.43 (5.43, 7.44)	14.57 (13.03, 16.11)	-8.14 (-9.94, -6.34) p < .0001
Log (mean mf density + 1):[b] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	2.53 (2.34, 2.73)	7.74 (7.01, 8.54)	0.33 (0.29, 0.37) p < .0001

N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18. Cells contain estimates and 95% confidence intervals. "Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data.
[a] Columns 2 and 3 contain estimates of arms' mean (untransformed) mean mf densities, and column 4 contains estimate of the average treatment effect (i.e., difference in means).
[b] Columns 2 and 3 contain estimates of arms' geometric means for 1+mean mf density, and column 4 contains estimate of ratio of arms' geometric means.

[c] There were 203 participants who used the expanded proscribed medications between study entry and 12 months (118 in moxidectin arm, 85 in ivermectin arm). There were additionally 116 instances of proscribed medication use with missing start dates; these were assumed to have occurred prior to study entry.

Reviewer Comment: Moxidectin was superior to ivermectin even with the conservative sensitivity analysis of assuming all patients that received the extended proscribed medications as failures in the moxidectin arm and successes in the ivermectin arm.

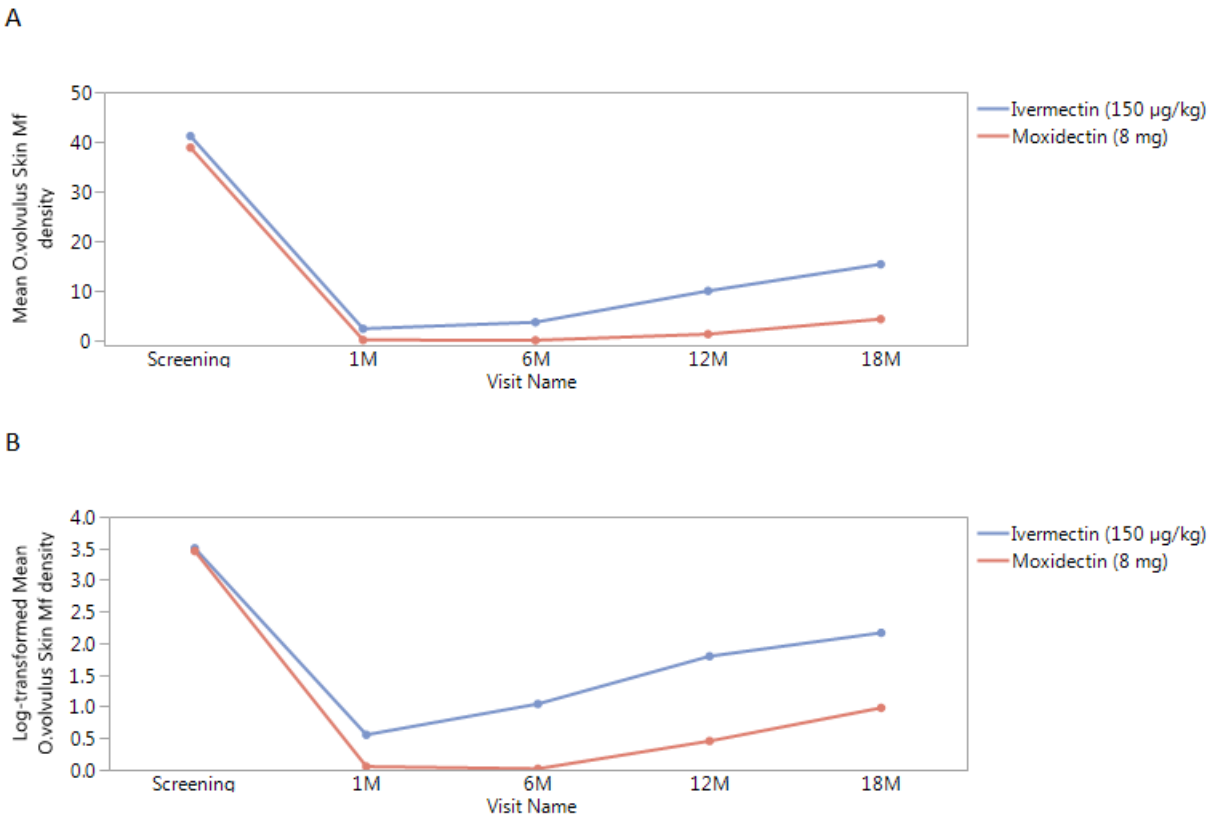
Dose/Dose Response

Single dose of 8 mg was used for the Phase 3 trial so evaluation of dose response is not applicable. Please refer to results of the Phase 2 trial in section 6.2.2 that compared 2 mg, 4 mg, and 8 mg moxidectin doses.

Durability of Response

As stated above, only single 8 mg dose of moxidectin was studied in the Phase 3 trial.
Figure 4 below shows the log- untransformed (A) and log-transformed (B) mean *O. volvulus* skin mf density (mf/mg) by study visits.

Figure 4: Log Untransformed (A) and Log-transformed Mean *O. volvulus* Skin Mf Density by Study Visit of the Phase 3 Trial



Reviewer Comment: Based on **Table 14** *and* Figure 4*, it appears that single 8 mg dose of moxidectin was able to suppress skin microfilariae density up to month 6 and there is a notable rise in skin microfilariae afterwards, albeit a much slower rise in skin microfilariae in moxidectin arm as compared to ivermectin*.

Persistence of Effect

Looking at the pathophysiology of the disease, since moxidectin is a microfilaricidal drug, and does not kill the adult worm, single dose of moxidectin will not be curative, and persistence of effect for a single dose may be limited to 6-12 months.

7. Integrated Review Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Both the Phase 2 and Phase 3 trials used skin microfilariae count as the primary endpoint; for the small Phase 2 trial, the primary endpoint was the skin microfilariae density at 18 months after administration of the study drug. The primary endpoint for the larger Phase 3 trial was skin microfilariae density at 12 months. Both were ivermectin-controlled trials. As detailed in sections 6.2.2 and 6.3.2, both yielded a statistically significant superiority of single 8 mg dose of moxidectin over ivermectin in reducing skin microfilariae. Both studies demonstrated a large effect size, with p-values <0.001 (<0.0009 for Phase 2 and <0.0001 for Phase 3).

Both studies were conducted in West Africa where > 98% of the burden of onchocerciasis is seen. Hence, the study results are pertinent to the target population with the disease.

Reviewer Comment: Of note, there are small foci of onchocerciasis in South America and Yemen; although the population in these areas may be different, the causative organism is the same nematode, O. volvulus. Hence, it is likely that the results of the two studies may be generalizable to these populations as well.

7.1.2. Secondary and Other Endpoints

Both studies had similar secondary endpoints including skin microfilariae density at time points different from the primary endpoint (month 1, 6 and 12 for Phase 2, month 1, 6, and 18 for Phase 3), and proportion of patients with undetectable microfilariae at these different time points. The Phase 2 trial demonstrated the single dose of 8mg had the best efficacy results for the secondary endpoints of proportion of patients with undetectable skin microfilariae as well as percent change from baseline skin microfilariae density when compared to the 2 mg and 4 mg moxidectin doses.

The larger Phase 3 trial only tested the 8 mg dose, and the results once again showed that moxidectin treatment yielded a statistically significant superiority over ivermectin for the abovementioned secondary endpoints.

In addition, both studies had ocular microfilariae density as a secondary endpoint and both studies had a small subset of patients with baseline ocular involvement. Neither of the studies was able to demonstrate a statistically significant superiority of moxidectin over ivermectin in reduction of ocular microfilariae.

Reviewer Comment: *Proportion of patients with undetectable microfilariae is of particular interest for the clinician as it can provide important public health information as to when a repeat dose of moxidectin may be needed if moxidectin were to be used in a mass-eradication type of setting.*

Both studies show that the 8 mg moxidectin dose was superior to ivermectin in suppressing skin microfilariae to a higher degree for a longer period of time.

7.1.3. Subpopulations

Subgroup analyses were performed for the Phase 3 trial since the single ascending dose Phase 2 trial only had 38 patients that received the proposed dose of 8 mg moxidectin. As noted in section 6.3.2, sub-group analyses by site, gender, age group, and baseline skin microfilariae for the Phase 3 trial all yielded statistically significant superiority of moxidectin over ivermectin.

7.1.4. Dose and Dose-Response

Data from the single ascending dose Phase 2 trial were utilized for exposure-response analyses; as a reminder, the trial compared 2 mg, 4 mg, and 8 mg moxidectin dose to the active control, ivermectin. There were no clear exposure-response differences between the doses when looking at the primary endpoint, mean reduction of skin microfilariae from baseline. However, when looking at the proportion of patients with undetectable skin microfilariae at month 6, the 8 mg dose had the highest proportion of patients with undetectable skin microfilariae (36/38=95%) when compared to 4 mg (39/45=87%) and 2 mg (31/44=71%). Similarly, the 8 mg moxidectin resulted in the highest percentage of patients with sustained undetectable skin microfilariae at 12 month (53%) when compared to the 4 mg (40%) and 2 mg (34%).

Please refer to the clinical pharmacology review by Dr. Yang He for details as well as for additional independent exposure-response analyses.

Reviewer Comment: Findings of the Phase 2 single dose ascending trial showing higher proportion of the 8 mg dose patients achieving undetectable skin microfilariae count provided evidence that the 8 mg dose was the most efficacious in resulting sustained reduction of skin microfilariae.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Only single dose moxidectin was studied for both the Phase 2 and Phase 3 trials. The two clinical trials showed that a single dose of 8 mg moxidectin was able to suppress skin microfilariae to a higher degree and for longer when compared to ivermectin.

Review of the results from the larger Phase 3 trial (please refer to Figure 4) shows that the effects of the single 8 mg dose of moxidectin on skin microfilariae are evident starting at month 1, and it appears that its effects continue to suppress skin microfilariae until month 6. After month 6, there is a slow rise in skin microfilariae, albeit at a much slower rate when compared to the ivermectin arm.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Similar to other microfilaricidal drugs, a single dose of moxidectin will not be curative as the adult worms can survive for 10 - 15 years. As previously mentioned, only a single dose of moxidectin was studied during the drug development program.

If moxidectin is to be used for mass administration in endemic areas in as semi-annual or annual basis, similar to ivermectin, there is no data on safety or efficacy of multiple doses. Post-marketing studies to elucidate the safety and efficacy of multiple doses of moxidectin will be of significant public health importance.

7.3. Integrated Assessment of Effectiveness

The Applicant has provided substantial evidence to support the efficacy of moxidectin administered at a single oral dose of 8 mg in treatment of onchocerciasis. The efficacy of moxidectin was demonstrated in two adequate and well-controlled trials comparing moxidectin with ivermectin, the only FDA-approved treatment for onchocerciasis. Both studies demonstrated a statistically significant reduction in the number of *O. volvulus* skin microfilariae at 12 months. The effect size for the noted efficacy was large with p-values of <0.0001. Of note, based on review of literature, expert opinion, and pathophysiology of the disease with symptoms of onchocerciasis mainly arising from inflammatory reactions to microfilariae in the human tissue, the primary endpoint for the Phase 2 and 3 trials, reduction in skin microfilarial burden, is considered a meaningful measure of moxidectin efficacy.

Additionally, both studies showed higher proportion of moxidectin-treated patients having undetectable skin microfilariae count at 12 months.

With these findings, it is concluded that moxidectin is effective for the treatment of onchocerciasis.

8. Review of Safety

8.1. Safety Review Approach

Safety of moxidectin was evaluated in one Phase 2 and one Phase 3 trial. In the Phase 2 trial, only 38 patients received moxidectin at the proposed dose of 8 mg. Hence, most of the safety data for the proposed 8mg moxidectin dose comes from the Phase 3 trial that had 978 patients

in the moxidectin arm and 494 patients in the ivermectin arm. Due to differences in frequency of adverse event reporting, the data for these two trials are presented separately.

Since moxidectin is a microfilaricidal drug, Mazzotti reaction (please refer to section 2.2 for description of Mazzotti reaction) was considered adverse event (AE) of special interest.

Of note, the sponsor highlighted the different approaches the previous sponsors took in reporting adverse events. To address changes in severity of ongoing AEs, the previous sponsor, Wyeth/Pfizer, considered an ongoing previously reported AE as "resolved" and created a new AE at the new toxicity grade rather than reporting the event once at the highest severity. Pfizer then transferred the Phase 3 study database to the next sponsor, the WHO's Special Programme for Research and Training in Tropical diseases (WHO/TDR). WHO/TDR chose the Luxembourg Institute of Health (LIH) to manage the data. The LIH required continuing AEs at each assessment to be marked "resolved" and then the same AE re-entered as new at each visit. Because of these two approaches, the numbers of AE events reported is higher compared with the usual approach of reporting a single event once only. The current sponsor, MDGH, stated that the safety databases for both studies were submitted without modification to these unusual approaches to maintain data integrity.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

During the development program for moxidectin, 1349 patients received a single dose of moxidectin at a dose ranging from 2 mg to 36 mg. Of these, 244 were healthy volunteers exposed to doses ranging from 3 mg to 36 mg, administered as a liquid or tablet formulation at fed and fasting states. More than 93% of these healthy volunteer patients were exposed to ≥ 8mg of moxidectin. There were 1105 patients with onchocerciasis exposed to moxidectin in the Phase 2 and 3 trials; of these, 1016 patients (n=38 from Phase 2, n=978 from Phase 3) were given the proposed 8mg dose of moxidectin.

Table 18 summarizes the number of patients in the safety database and their exposure to moxidectin.

Table 18: Safety Database and Overall Exposure to Study Drug in the Moxidectin Development Program

Clinical Trials	Moxidectin (n= 1349)	Ivermectin 150µg/kg (n=494)	Placebo (n= 16)
Healthy volunteers any dose	244	0	16
Phase 2 Study		45	
2mg	44		

4mg	45		
8mg	38		
Phase 3 Study			
8mg	978	494	0

There were some inter-study methodological differences between the Phase 2 and Phase 3 trials. These include:

- Longer in-patient stay to day 18 for Phase 2 as compared to up to day 6 for Phase 3 trial
- More intensive intra-a and inter-day assessments in the Phase 2 than Phase 3 trial
- Laboratory abnormalities were not reported as adverse events in Phase 2 trial

Reviewer Comment: Since only 38 patients received the proposed 8mg moxidectin dose in Phase 2, the main safety population will be the patients in the Phase 3 trial. Summary of the safety findings from the Phase 2 trial are presented separately. As seen in the table above, the Phase 3 study had more than 978 patients exposed to the dose and duration proposed for treatment. Hence, the safety database is considered adequate.

8.2.2. Relevant characteristics of the safety population:

Both the Phase 2 and Phase 3 trials were conducted in West Africa. The Phase 2 trial was conducted at a single site in Ghana while the Phase 3 trial was a multi-site trial with one site in Liberia and Ghana, each, and two sites in the Democratic Republic of Congo. Please refer to **Table 6** and **Table 10** for the baseline characteristics the participants in the Phase 2 and Phase 3 trial, respectively.

Reviewer Comment: Majority of the population at risk or affected by onchocerciasis live in West Africa. Hence, the sponsor's choice of study sites is acceptable. Since the same nematode causes disease in other parts of the world, the results of the study may be extrapolated to the other parts of the world affected by onchocerciasis such as South America.

8.2.3. Adequacy of the safety database:

Between the Phase 2 and Phase 3 trials, there have been 1016 onchocerciasis patients treated with the proposed single 8 mg moxidectin dose. As previously stated, these patients resided in West Africa, the main endemic area for onchocerciasis. Based on the above information, it is concluded that the Applicant has provided adequate safety database to evaluate the proposed

8 mg dose.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, the organization of the data was acceptable. There were no issues with completeness of the submitted information. To assess the quality of the original data and data integrity, the Office of Scientific Integrity was consulted to investigate a clinical site in Ghana and the Contract Research Organization (CRO) in Switzerland. The results of the inspections are pending at the time of this review.

8.3.2. Categorization of Adverse Events

The sponsor defined adverse events (AEs) as any untoward, undesired or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article. An AE included:

- Any clinical significant worsening of a pre-existing condition
- An AE occurring from overdose of a test article, whether accidental or intentional
- An AE occurring from abuse of a test article
- An AE that has been associated with the discontinuation of the use of a test article

AEs were reported by System Organ Class (SOC), as specified by the Medical Dictionary for Regulatory Activities (MedDRA). Clinical AEs were recorded in case report forms over 12months post administration of study drug for all patients. For patients that were enrolled prior to protocol amendment 3 that removed the 18-month study visit, AE were recorded up to 18 months. Physical exam and vital signs were recorded daily for the first 6 visits, and during each study visit afterwards (day 14 = study visit 7, month 1 = study visit 8, month 3 = study visit 9, month 6 = study visit 10, and month 12 = study visit 11). Electrocardiography was done at the screening and study visit 3 (study day 2). Laboratory assessments (hematology, chemistry, and urinalysis) were carried out during study visits 1, 6, 7, 8, 9, 10. Assessment of lymphatic filariasis was done at visits 1, 8, 10, 11 and 12. Assessment of intestinal helminth infections were done at visits 1 and 8.

In the Phase 3 study, treatment emergent AEs (TEAEs) were defined as AEs occurring in the first 180 days after test article administration, while AEs emerging after Day 180 were regarded as post-active phase AEs. In the Phase 2 study, TEAEs were defined in the protocol and Statistical Analysis Plan (SAP) as those emerging from the time of test article administration until the Month 18 visit. In the Phase 1 studies, TEAEs were reported for the duration of post-treatment follow-up.

Reviewer Comment: This reviewer does not agree with the definition of TEAE in the Phase 3 trial. One of the sponsor's premises regarding the improved efficacy of moxidectin is that because of the more lipophilic nature of moxidectin, it stays in the body for longer as evidenced by significantly longer plasma elimination half-life (t ½); this characteristic allows moxidectin to suppress microfilariae for longer periods compared to ivermectin. The sponsor states that they chose the 180 days for TEAE reporting since this time covers 5 times the plasma half-life of the drug. However, given its lipophilic nature, moxidectin may most likely be present in tissues after 180 days. For this reason, Phase 3 TEAEs in this review will be defined as AEs that occur up to and including the 12-month follow-up visit.

AE severity was categorized into mild, moderate, and severe. In addition, a serious AE (SAE) was defined as any AE occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in or prolongs an existing inpatient hospitalization
- Is a congenital anomaly/birth defect
- Is a cancer
- Is associated with an overdose
- Is another important medical event

As described in section 2.2, a unique set of adverse events related to death of microfilariae, Mazzotti reaction is common to microfilaricidal drugs such as moxidectin. The Applicant recorded and flagged these AEs.

8.3.3. Routine Clinical Tests

Please refer to

Table 4 and
Table 8 for the schedule of the study procedures, including the routine clinical tests for the Phase 2 and 3 trials, respectively.

Reviewer Comment: Overall, the safety assessment schema appears reasonable. Since moxidectin is a microfilaricidal drug, having intense follow-up in the first week post administration of the drug is critical, and the sponsor has done so by having patients remain in the study site for the first week after administration of study drugs.

8.4. Safety Results

8.4.1. Deaths

Phase 1 and 2 Studies

No death occurred in any of the Phase 1 studies. One death occurred in a patient that received 2 mg moxidectin in the Phase 2 study. The Phase 2 study participant died of snake bite on study day 310.

Phase 3 Clinical Trial

There were 14 deaths in the Phase 3 trial, 11/978 (1.1%) in the moxidectin and 3/494 (0.6%) in the ivermectin arm. Of these, 10 (n=8 moxidectin, n=2 ivermectin) occurred during the 12-month follow-up period after administration of study drugs, and 4 more deaths (n=3 moxidectin, n=1 ivermectin) occurred by the 18-month follow-up. Table 19 summarizes the timing and causes of deaths.

Table 19: Summary of Deaths in Phase 3 Patients

Patient Study ID number	Study Drug	Age	Sex	Study Day of AE Onset	Study Day of Death	Reported Cause of Death
(b) (6)	Mox	60	F	59	59	Peritonitis and cardiac arrest after surgery for vesico-vaginal fistula
	Mox	69	M	128	131	Acute asthmatic attack
	Mox	43	M	190	190	Hypoglycemia
	Mox	47	M	208	211	Hiccups in the context of prolonged hospitalization for malarial infection and left hemiplegia
	Mox	58	M	235	245	Viral hepatitis (clinically diagnosed)
	Mox	32	M	248	249	Hemoptysis
	Mox	59	M	291	291	Sudden death
	Mox	54	M	286	294	Sepsis (clinically diagnosed)
	Mox	62	F	Unknown	396	Anemia in the context of acute illness (fever, vomiting, diarrhea, lower extremity swelling)
	Mox	66	M	451	462	Cardiac failure
	Mox	58	F	Unknown	483	Diarrhea
	Iver	65	F	64	73	Sepsis and severe malaria
	Iver	63	F	73	79	Diabetic ketoacidosis hyperglycemic coma in the context of severe malarial infection

Patient Study ID number	Study Drug	Age	Sex	Study Day of AE Onset	Study Day of Death	Reported Cause of Death
(b) (6)	Iver	70	M	375	375	Hypoglycemia
Mo: Moxidectin; Iver: Ivermectin; M: Male; F: Female; AE: Adverse Events						

Of note, one additional patient in the moxidectin arm, patient (b) (6) died after he was withdrawn from the trial by the investigator after the patient had ingested herbal medicine. A brief narrative of patient (b) (6) is provided in section 8.4.3

Reviewer Comment: Review of the causes of death in the Phase 3 trial did not reveal any cluster of organ system as cause of death. Overall, the deaths appeared to be due to co-morbidities and other infectious causes and not related to moxidectin.

8.4.2. Serious Adverse Events

Phase 1 Studies
There were no serious adverse events (SAEs) reported in the five Phase 1 studies.

Phase 2 Trial
There were 8 patients who experienced at least one SAE in the phase 2 trial, 5 in the moxidectin 2 mg arm, 1 in the moxidectin 4 mg arm, and 2 in the moxidectin 8 mg arm. No patients in the ivermectin arm had SAE. Table 20 summarizes the SAEs reported in the Phase 2 trial.

Table 20: Serious Adverse Events in the Phase 2 Trial by MedDRA System Organ Class (SOC) and Preferred Term

System Organ Class [a] Preferred Term	Moxidectin 2 mg N=44	Moxidectin 4 mg N=45	Moxidectin 8 mg N=38	Ivermectin N=45	Total N=172
Any serious adverse event	5 (11.4)	1 (2.2)	2 (5.3)	0	8 (4.7)
General disorders and administration site conditions	1 (2.3)	0	0	0	1 (0.6)
Pyrexia	1 (2.3)	0	0	0	1 (0.6)
Infections and infestations	3 (6.8)	0	2 (5.3)	0	5 (2.9)
Appendicitis	0	0	1 (2.6)	0	1 (0.6)
Malaria	0	0	1 (2.6)	0	1 (0.6)
Pneumonia	1 (2.3)	0	1 (2.6)	0	2 (1.2)
Typhoid fever	2 (4.5)	0	0	0	2 (1.2)
Injury, poisoning and procedural complications	1 (2.3)	1 (2.2)	0	0	2 (1.2)
Injury	0	1 (2.2)	0	0	1 (0.6)
Snake bite	1 (2.3)	0	0	0	1 (0.6)
Nervous system disorders	2 (4.5)	1 (2.2)	0	0	3 (1.7)
Coma	0	1 (2.2)	0	0	1 (0.6)
Grand mal convulsion	1 (2.3)	0	0	0	1 (0.6)
Headache	1 (2.3)	0	0	0	1 (0.6)
Psychiatric disorders	1 (2.3)	0	0	0	1 (0.6)
Schizophrenia	1 (2.3)	0	0	0	1 (0.6)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
a. Totals for the No. of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
N: number of subjects in a given reporting group.

Reviewer Comment: All eight SAEs in the Phase 2 occurred in the moxidectin arms. Five of the 8 AEs occurred in the 2mg moxidectin arm. Hence, there does not appear to be a dose-related increase in AEs. Looking at the details of the SAEs, most appear to be due to other infectious and non-infectious conditions.

Phase 3 Trial

Among the 1472 individuals in the safety population, 89(6%) experienced SAEs, with the 282 SAE reported. Table 21 and Table **22** summarize SAEs by MedDRA System Organ Classification (SOC) and preferred term (PT), respectively.

Table 21: Serious Adverse Events in the Phase 3 Trial by MedDRA System Organ Class (SOC)

System Organ Class (SOC)	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Patient with at least one SAE	60 (6.1)	29 (5.9)
Infection and infestation	39 (4)	18 (3.6)
Gastrointestinal disorders	9 (0.9)	7 (1.4)

System Organ Class (SOC)	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Patient with at least one SAE	60 (6.1)	29 (5.9)
Injury, poisoning & procedural complications	7 (0.7)	1 (0.2)
Nervous system disorders	4(0.4)	2 (0.4)
Cardiac disorders	3 (0.3)	0 (0)
Respiratory, thoracic& mediastinal disorders	3 (0.3)	1 (0.2)
Musculoskeletal & connective tissue disorders	3 (0.3)	0
General disorders & administration site conditions	2 (0.2)	4 (0.8)
Blood & lymphatic disorders	2 (0.2)	0 (0)
Metabolism & nutritional disorders	2 (0.2)	1 (0.2)
Hepatobiliary disorders	2 (0.2)	0 (0)
Skin & subcutaneous tissue disorders	1 (0.1)	0 (0)
Eye disorders	1 (0.1)	0 (0)
Reproductive systems & breast disorders	1 (0.1)	0 (0)
Vascular disorders	0	1 (0.2)

Table 22: Serious Adverse Events Experienced by ≥2 Moxidectin-Treated Patients in the Phase 3 Trial by MedDRA Preferred Term

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Patient with at least one SAE	60 (6.1)	29 (5.9)
Malaria	27 (2.8)	15 (3)
Diarrhea/gastroenteritis/enteritis	7 (0.7)	3 (0.6)
Anemia	2 (0.2)	0 (0)
Cardiac arrest	2 (0.2)	0 (0)
Cardiac failure *	2 (0.2)	0 (0)
Abdominal pain**	2 (0.2)	1 (0.2)
Gastritis	2 (0.2)	2 (0.4)
Gastrointestinal hemorrhage	2 (0.2)	0 (0)
Hepatitis (chronic or viral)	2 (0.2)	0 (0)
Skin abscess/cellulitis	3 (0.31)	0 (0)

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Patient with at least one SAE	60 (6.1)	29 (5.9)
Loss of consciousness	2 (0.2)	0 (0)

*Cardiac failure included both cardiac failure and congestive cardiac failure
**Abdominal pain included all terms with abdominal pain (upper, lower)

In addition, there were 2 patients in the moxidectin arm with serious adverse events that led to death. The first patient, patient (b) (6) was reported to have sudden death on day 291 of the study. The second patient, patient (b) (6), was reported to have a serious fatal adverse event of hepatic failure/cirrhosis on day 415 due to herbal ingestion. Brief narrative for patient (b) (6) is presented in section 8.4.3.

Reviewer Comment: Malaria appears to contribute to almost half of the SAEs seen in each arm. Review of the reported SAEs did not reveal a specific pattern/organ system involvement that may be secondary to the effect of the study drugs.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no patients who discontinued the study drug in either the Phase 2 or Phase 3 trial as both trials featured a single dose of moxidectin or active comparator ivermectin. No patients discontinued from the study due to an adverse effect related to study drug.

Table 23 summarizes the overall patient disposition in the Phase 3 trial. Of note, one patient randomized to moxidectin received ivermectin and 2 patients randomized to ivermectin received moxidectin by error.

Table 23: Patient Disposition in the Phase 3 Safety Population

	Moxidectin	Ivermectin
Randomized	997	502
Not dosed	20	7
Received study drug	**978**	**494**
Completed the study*	927 (94.8%)	476 (96.4%)
Did not complete	51 (5.2%)	18 (3.6%)
Lost to follow-up	35 (3.6%)	13 (2.6%)
Death	11 (1.1%)	3 (0.6%)

Patient Request	4 (0.4%)	2 (0.4%)
Investigator Request	1 (0.1%)	0

*Completion of the study means patients were followed up to at least 12 months; some patients enrolled prior to amendment 3 completed the 18-month follow-up.

NOTE: The number of patients that received study drug for each arm was used as a denominator for percentage calculation

Brief narrative of the patient withdrawn by investigator's request is as follows:

Patient (b) (6) This 70-year-old male patient received moxidectin 8 mg. His medical history included ongoing episodes of upper abdominal pain and peptic ulcer disease. At approximately day 317, he had SAE of life-threatening anemia, which resolved after blood transfusion. On day 415, he was admitted with frequent urination, distended abdomen, abdominal pain, constipation, cough, and wasting. His physical exam revealed distended abdomen, bulging flanks, fluid thrill and shifting dullness, epigastric tenderness, palpable liver and pitting pedal edema. He admitted to ingesting herbal medication and was noted to have hepatic failure and cirrhosis. Of note, his liver function tests were within the normal limit throughout the 6-month post-treatment period. He had blood transfusion and removal of 2 liters of ascitic fluid. The patient was discharged from the hospital after his request. On day 470, the investigator withdrew the patient from the study due to "herbal intoxication" and the patient was subsequently reported to have died on day 479.

Reviewer Comment: Close to 98% of participants in each arm completed the trial. There does not appear to be a major imbalance in patient disposition between the moxidectin and ivermectin arm. There were slightly more patient deaths in moxidectin arm as compared to ivermectin. Review of these deaths did not appear to be related to moxidectin.

As can be inferred from patient (b) (6) *narrative, the cause of his liver failure appears unrelated to moxidectin as he had normal liver function tests for visits up to month 6; the patient also reported ingestion of herbal medicines, which may be the more likely culprit for his liver failure and subsequent death.*

8.4.4. Significant Adverse Events

Please refer to the laboratory section for analysis of hematological AEs by study arm.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Phase 1 Studies
The safety findings from five of the six Phase 1 studies is summarized in **Table 24**.

Table 24: Summary of Safety Events in Phase 1 Studies

Study Number	3110A1-100 EU	3110A1-101-EU	3110A1-1002-EU	3110A1-1004-EU	3110A1-1005-EU
Study short title	Single ascending dose study	Relative bioavailability study	Milk excretion study	Drug interaction study**	Food Effect study
Dose (formulation)#	3, 9, 18, 36 mg (liquid)	10 mg (tablet and liquid)	8 mg (tablet)	8 mg (tablet)	8 mg (tablet)
Duration of follow up	80 days	180 days	90 days	93 days	90 days
Number of subjects	31 (moxidectin) 7 (placebo)	29 (tablet) 29 (liquid)	12	39	54
Subjects with SAEs	0	0	0	0	0
Subjects with TEAEs (%)	26 84%	36 62%	9 75%	17 43%	29 54%
TEAEs occurring in ≥10% of subjects across all treatment groups, if applicable (% of subjects)	Headache 35% Infection 29% Pharyngitis 16% Leukopenia 13% Dizziness 13% Somnolence 10% ALT increase 10% AST increase 10% Pain 10% Rhinitis 10% Cough increased 10%	Flu syndrome 19% Headache 16% Infection 10%	Headache 33% Nausea 33% Rhinitis 17% Viral pharyngitis 17% Viral URTI 17%	None	Headache 24% Rhinitis 15%
Subjects with TEAEs investigator considered as drug related* (%)	21 68%	0 0%	0 0%	6 15%	11 20%
TEAEs investigator considered drug related* occurring in ≥5% of subjects	Headache 16% Leukopenia 10% AST increase 10% ALT increase 10% Dizziness 10% Diarrhea 6% GGT increase 6% Nausea 6% Anorexia 6% Somnolence 6% Amblyopia 6% Pyuria 6%				

#All doses administered as single dose
*includes TEAEs with relationship to study drug the investigator considered unknown across all treatment groups, if applicable.
** Included midazolam administration 2 days before as well as 7 days and 89 days after administration of moxidectin. TEAEs listed include all TEAEs reported after the administration of moxidectin. TEAEs considered drug related by investigator listed are independent of whether drug relationship to moxidectin or midazolam.
AST: aspartate Aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; URTI: Upper respiratory tract infection; AP: alkaline phosphatase; LDH: lactate dehydrogenase
Source: Modified from Sponsor's Table 1 of ONCBL60801 Study Protocol

Phase 2 Trial

TEAEs were observed in 43/44, 45/45, 37/38 patients in the moxidectin 2mg, 4mg and 8 mg treatment groups, respectively; all 45 patients in the ivermectin treatment group reported a TEAE. Table 25 and Table 26 summarize the TEAEs that occurred in >10% of the 8mog Moxidectin arm over the first 6 months of the trial.

Table 25: Treatment Emergent Adverse Events that Occurred in >10% of Patients in Moxidectin 8 mg Arm in the Phase 2 Trial by MedDRA System Organ Class (SOC)

	Moxidectin			Ivermectin N=45
	2mg N=44	4mg N=45	8mg N=38	
Patients with at least 1 TEAE	43 (97.7)	45 (100)	37 (97.4)	45 (100)
Skin & subcutaneous tissue disorders	33 (75)	39 (86.7)	35 (92.1)	32 (71.1)
General disorders & administration site conditions	31 (70.5)	35 (77.8)	32 (84.2)	31 (68.9)
Infection & infestation	17 (38.6)	22 (48.9)	29 (73.6)	23 (51.1)
Cardiac disorders	23 (52.3)	17 (37.8)	26 (68.4)	20 (44.4)
Nervous system disorders	29 (65.9)	31 (68.9)	26 (68.4)	26 (57.8)
Musculoskeletal and connective tissue disorders	27 (61.4)	28 (62.2)	25 (65.8)	26 (57.8)
Investigations	17 (38.6)	19 (42.2)	16 (42.1)	16 (35.6)
Gastrointestinal	16 (36.4)	16 (35.6)	10 (26.3)	15 (33.3)
Vascular disorders	11 (25)	20 (44.4)	24 (63.2)	13 (28.9)
Blood and lymphatic system disorders	11 (25)	11 (24.4)	15 (39.5)	10 (22.2)
Respiratory, thoracic & mediastinal disorders	12 (27.3)	8 (17.8)	11 (28.9)	10 (22.2)
Eye disorders	10 (22.7)	13 (28.9)	9 (23.7)	10 (22.2)
Injury, poisoning & procedural complication	6 (13.6)	4 (8.9)	4 (10.5)	6 (13.3)
Immune system disorders	7 (15.9)	4 (8.9)	4 (10.5)	3 (6.7)

Source: Modified from the sponsor's Table 10-1 in the Phase 2 Study Report

Table 26: Treatment Emergent Adverse Events that Occurred in >10% of Patients in Moxidectin 8 mg Arm in the Phase 2 Trial by MedDRA Preferred Terms

MedDRA Preferred Term	Moxidectin			Ivermectin N=45
	2 mg N=44	4 mg N=45	8 mg N=38	
Pruritus/generalized pruritus	23 (52.3)	36 (80)	33 (86.8)	29 (64.5)
Rash	18 (40.9)	24 (53.3)	24 (63.2)	19 (42.2)
Postural orthostatic tachycardia Syndrome	21 (47.7)	14 (31.1)	24 (63.2)	16 (35.6)
Orthostatic hypotension	8 (18.2)	13 (28.9)	23 (60.5)	12 (26.7)
Malaria	7 (15.9)	9 (20.0)	21 (55.3)	10 (22.2)
Headache	19 (43.2)	23 (51.1)	23 (60.5)	22 (48.9)
Lymphadenitis/lymph node	9 (20.5)	16 (35.6)	20 (52.6)	10 (22.2)

MedDRA Preferred Term	Moxidectin			Ivermectin N=45
	2 mg N=44	4 mg N=45	8 mg N=38	
Pain				
Pain	12 (27.3)	20 (44.4)	19 (50.0)	15 (33.3)
Edema peripheral	13 (29.5)	5 (11.1)	16 (42.1)	9 (20.0)
Pyrexia/Chills	23 (52.3)	25 (55.6)	16(42.1)	19 (42.2)
Heart rate increased	17 (38.6)	19 (42.2)	16 (42.1)	16 (35.6)
Non-cardiac chest pain	7 (15.9)	4 (8.9)	12 (31.6)	6 (13.3)
Arthralgia	13 (29.5)	13 (28.9)	11 (28.9)	11 (24.4)
Cough	7 (15.9)	7 (15.6)	7 (18.4)	6 (13.3)
Hypotension	9 (20.5)	11 (24.4)	7 (18.4)	6 (13.3)
Eye pruritus/Ocular discomfort	6 (13.6)	9 (20)	6 (15.8)	8(17.8)
Myalgia	1 (2.3)	3 (6.7)	6 (15.8)	5 (11.1)
Pain in extremity	9 (20.5)	10 (22.2)	6 (15.8)	10 (22.2)
Dizziness/Postural dizziness	12 (27.3)	10 (22.2)	6 (15.8)	7 (15.6)
Furuncle	4 (9.1)	3 (6.7)	5 (13.2)	5 (11.1)
Back pain	0	5 (11.1)	5 (13.2)	5 (11.1)
Abdominal pain	7 (15.9)	6 (13.3)	5 (13.2)	5 (11.1)
Localized edema	1 (2.3)	4 (8.9)	5 (13.2)	1 (2.2)
Schistosomiasis	1 (2.3)	1 (2.2)	4 (10.5)	2 (4.4)
Tachycardia	7 (15.9)	3 (6.7)	4 (10.5)	5 (11.1)

Source: Modified from the sponsor's Table 10-1 in the Phase 2 Study Report

Reviewer Comment: Symptoms of Mazzotti reaction (headache, lymph node pain, peripheral edema, pyrexia, tachycardia, musculoskeletal pain, postural dizziness) predominated in the observed TEAEs. These are expected AEs for microfilaricidal drugs, and focused review of these signs/symptoms are presented for the larger Phase 3 trial in section 8.5.1.

Phase 3 Trial

Of the 1472 patients that make up the safety population, 1470 patients were reported to have at least one TEAE; all patients in the moxidectin arm (n=978) and 492 of the 494 patients in the ivermectin arm had a TEAE by month 12 visit.

Table 27 and Table 29 summarize the reported TEAEs by MedDRA SOC and PT classification, respectively.

Table 27: Treatment Emergent Adverse Events in the Phase 3 Trial by System Organ Class

SOC	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Patients with at least 1 TEAE by month 12 visit	978 (100)	492 (99.6)
Blood and lymphatic system disorders	857 (87.6)	431 (87.2)
Skin & subcutaneous tissue disorders	761 (77.8)	320 (64.8)
General disorders & administration site conditions	680 (69.5)	317 (64.2)
Nervous system disorders	652 (66.7)	321 (65)
Musculoskeletal and connective tissue disorders	608 (62.2)	311 (63)
Investigations	599 (61.2)	297 (60.1)
Infection & infestation	575 (58.8)	287 (58.1)
Gastrointestinal	496 (50.7)	278 (56.3)
Vascular disorders	317 (32.4)	136 (27.5)
Metabolism & nutrition disorder	267 (27.3)	144 (29.1)
Renal and urinary disorders	254 (26)	150 (30.4)
Eye disorders	230 (23.5)	101 (20.4)
Respiratory, thoracic & mediastinal disorders	227 (23.2)	121 (24.5)
Injury, poisoning & procedural complication	107 (10.9)	48 (9.7)
Ear and labyrinth disorders	91 (9.3)	56 (11.3)
Reproductive system & breast disorders	61 (6.2)	24 (4.9)
Psychiatric disorders	25 (2.6)	8 (1.6)
Hepatobiliary disorders	23 (2.4)	2 (0.4)
Neoplasms (benign, malignant and unspecified)	3 (0.3)	1 (0.2)
Immune system disorders	1 (0.1)	0

Reviewer Comment: SOCs with higher incidence of adverse events in the moxidectin arm as compared to ivermectin arm include skin and subcutaneous tissue disorders (13% higher), general disorders and administration sites (5.3% higher), vascular disorders (4.5% higher) eye disorders (3.1% higher) and hepatobiliary disorders (2% higher). Most of these higher AE incidences are related to Mazzotti reaction (please refer to section 8.5.1). Of note, 23 of the 25

hepatobiliary TEAEs occurred in patients in the moxidectin arm. These events were further evaluated and discussed below.

In Table 27, the number of patients with TEAEs in the hepatobiliary disease SOC were small in both groups; however, there were more patients in moxidectin arm that experienced hepatobiliary AEs. Of the 25 patients that experienced TEAS in the hepatobiliary SOC, 23 of the 25 were in the moxidectin arm. The reported hepatobiliary AEs for the moxidectin arm include hyperbilirubinemia (n=19), hepatomegaly (n=2), drug-induced (herbal) liver injury (n=1), hepatic cirrhosis and liver failure (n=1), chronic active hepatitis (n=1), and liver tenderness (n=1). Of the 19 patients with hyperbilirubinemia, two had additional liver disease reported: Patient (b) (6) had drug-induced (herbal medicine) liver disease, hepatic cirrhosis, and hyperbilirubinemia at Month 12. Another patient (b) (6) had chronic active hepatitis and hyperbilirubinemia. These two patients are further discussed in section 8.4.6 under the assessment of liver function heading. The two patients in the ivermectin arm had hyperbilirubinemia.

The laboratory dataset was reviewed to determine the number of patients with >2X upper limit of normal (ULN) bilirubin level; there were 14 patients in the moxidectin arm and 2 patients in the ivermectin arm. Eight patients in the moxidectin arm and 1 patient in the ivermectin arm with >2XULN bilirubin were not reported as having hyperbilirubinemia as TEAE in the AE dataset.

To parse out treatment emergent AEs from prior medical conditions, the medical history dataset was evaluated and there were 39 patients (n= 28 in the moxidectin arm, n=11 in the ivermectin arm) with reported hepatobiliary disease in their medical history. **Table 28** summarizes these patients and the reported hepatobiliary conditions at baseline.

Table 28: Hepatobiliary Disease Conditions Reported at Baseline for Phase 3 Patients

	Moxidectin N=978 N, %	Ivermectin N=494 N, %
Hyperbilirubinemia*	17 (1.7)	2 (0.4)
Jaundice	8 (0.8)	5 (1)
Hypertransaminasemia*	3 (0.3)	4 (0.8)
Liver tenderness	1 (0.1)	0

*One patient had both hyperbilirubinemia and hypertransaminasemia

Of note, of the 19 patients with hyperbilirubinemia reported as TEAE in the AE dataset, only 1 patient (b) (6) had reported hyperbilirubinemia in his medical history; the remaining 18 did not have reported history of hyperbilirubinemia at baseline.

Between the AE dataset and the lab dataset, there were 27 patients in the moxidectin arm (2.8%) and 3 patients in the ivermectin arm (0.6%) with hyperbilirubinemia. Review of these

patients revealed the following:

- 17/27 had first reported bilirubin elevation by month 3 visit
- 14/27 had single measurement of high bilirubin without any additional abnormal bilirubin levels during the study
- 24/27 had isolated hyperbilirubinemia without concurrent elevation in transaminases
- 15/27 had at least 1 point drop in hemoglobin level at the time of bilirubin elevation

*Reviewer Comment: Even after accounting for the 2:1 randomization, there appears to be a slight excess of patients with elevated bilirubin level in the moxidectin arm (n=27) as compared to ivermectin (n=3). There is no clear mechanism for explaining these single measurement bilirubin elevations. Some of our working hypotheses were a concurrent illness such as malaria. Another possibility is underlying genetic predisposition to hemolysis such as G6PD deficiency. Even though the Phase 3 trial did not evaluate for underlying G6PD deficiency, the Phase 2 data (refer to **Table 6**) showed that 10-28% of the Phase 2 participants had some defect in G6PD. As stated above, most of these elevations resolved after the single incident, and did not have concurrent transaminitis. Of note, ivermectin's post-marketing experience, as noted in its label, has shown that it causes liver enzyme elevation and hyperbilirubinemia. Since moxidectin and ivermectin belong to the macrocyclic lactone class of anti-helminth, the contribution of moxidectin to these hyperbilirubinemia events cannot be excluded.*

Table 29: Treatment Emergent Adverse Events Reported in >10% of Moxidectin-Treated Patients in Phase 3 Trial

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Eosinophilia	721 (73.7)	390 (78.9)
Pruritus	640 (65.4)	268 (54.3)
Musculoskeletal pain[#, a]	623 (63.7)	257 (52)
Myalgia	248 (25.4)	120 (24.3)
Arthralgia	177 (18.1)	86 (17.4)
Pain	232 (23.7)	122 (24.7)
Back pain	229 (23.4)	125 (25.3)
Musculoskeletal pain	34 (3.5)	15 (3)
Headache	566 (57.9)	267 (54)
Lymphocytopenia	470 (48)	245 (43.5)
Tachycardia (all terms)[#,b]	382 (39.4)	148(30)
Orthostatic tachycardia[#, c]	333 (34)	130 (26.3)
Non-orthostatic tachycardia[#, d]	179 (18.3)	57 (11.5)
Rash[#, e]	358 (36.6)	103 (20.9)
Rash and papular rash	246 (25.2)	75 (15.2)

Urticaria	112 (11.5)	28 (5.7)
Abdominal pain[#, f]	305 (31.2)	173 (35)
Hypotension (all terms)[#, g]	289 (29.6)	125 (25.3)
Orthostatic hypotension[#, h]	212 (21.7)	81 (16.4)
Symptomatic orthostatic hypotension[i]	47 (4.8)	8 (1.6)
Hypotension[#, j]	135 (13.8)	59 (11.9)
Malaria/*Plasmodium falciparum* infection	279 (28.5)	131 (26.5)
Pyrexia/Chills	268 (27.4)	68 (18)
Leukocytosis	240 (24.5)	125 (25.3)
Influenza like illness	226 (23.1)	102 (20.6)
Neutropenia	207 (21.2)	(117 (23.6)
Cough	168 (17.2)	88 (17.8)
Lymph node pain	129 (13.2)	28 (5.7)
Dizziness	121 (12.4)	44 (8.9)
Diarrhea/Gastroenteritis/Enteritis	144 (14.7)	84 (17)
Hyponatremia	112 (11.5)	65 (13.2)
Peripheral swelling	107 (10.9)	30 (6.1)

#MedDRA grouped term
[a] Includes preferred terms “myalgia”, “arthralgia”, “musculoskeletal pain”, “pain” and “back pain”
[b] Includes preferred terms “orthostatic heart rate increased”, “postural orthostatic tachycardia syndrome”, “heart rate increased” and “sinus tachycardia”
[c] Includes preferred terms “orthostatic heart rate increased” and “postural orthostatic tachycardia syndrome”
[d] Includes preferred terms “heart rate increased”, “tachycardia”, and “sinus tachycardia”
[e] Includes preferred terms “rash,” “papular rash” and “urticaria”
[f] Includes preferred terms “abdominal pain”, “abdominal pain upper” and “abdominal pain lower”
[g] Includes preferred terms “orthostatic hypotension”, “blood pressure orthostatic decreased”, “blood pressure decreased”, “mean arterial pressure decreased”, “hypotension”
[h] Includes preferred terms “orthostatic hypotension”, and “blood pressure orthostatic decreased”
i refers to subset of patients with orthostatic hypotension who were unable to stand without support after being supine for 5 minutes
[j] Includes preferred terms “mean arterial pressure decreased”, “hypotension”, “blood pressure decreased”
[*]Patients required support to stand after remaining supine for 5 minutes

Reviewer Comment: The observed TEAEs in both trial arms are predominantly due to Mazzotti reaction. There is a trend of higher proportion of patients in the moxidectin arm experiencing these TEAEs as compared to ivermectin. From the mechanism of action of the two drugs, more microfilariae killing in the moxidectin arm may have resulted in higher immune response, leading to the higher TEAEs noted in the moxidectin arm. Of note, 4.8% and 1.6% patients experienced symptomatic orthostatic hypotension in the moxidectin and ivermectin arm, respectively. These findings are further discussed in section 8.4.7.

8.4.6. **Laboratory Findings**

The ADLB dataset for the Phase 2 and Phase 3 trials were reviewed. Because the data from the

Phase 2 trial accounted only for less than 4% of the patients that received the 8 mg dose, the Phase 3 data were reviewed in more detail and are presented below.

The Phase 3 trial safety laboratory investigations included complete blood counts with white blood cell differential and platelets, liver tests panel, serum electrolytes, and urinalysis with microscopic analysis. Blood and urine samples for these studies were collected at the screening visit, and at days 6, 14, month 1, month 3 and month 6 visits. In addition, evaluation for lymphatic filariasis (LF) was done at screening, month 1, 6, 12 and 18 visits. Please refer to **Table 8** for additional detail.

Assessment of Liver Tests in the Phase 3 Trial

Overall, there were 44 patients (n=30 in the moxidectin arm, n=14 in the ivermectin arm) with transaminase elevation to more than 3-times the upper limit of normal (3X ULN). Table 30, Table 31 and Table 32 present the number of patients that had post-baseline elevations in transaminases and total bilirubin.

Table 30: Phase 3 Patients with Post-Baseline Elevation in Alanine Aminotransferase (ALT)

	Moxidectin N=978				**Ivermectin N=494**	
	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)	BL >2X ULN ≤3X ULN n, (%)	BL >3X ULN ≤5X ULN n, (%)	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)
Post-BL >ULN ≤2X ULN	181 (18.5)	0 (0)	0 (0)	0 (0)	85 (17.2)	0 (0)
Post-BL >2X ULN ≤3X ULN	25 (2.6)	14 (1.4)	0 (0)	0 (0)	12 (2.4)	6 (1.2)
Post-BL >3X ULN ≤5X ULN	7 (0.7)	2 (0.2)	0 (0)	0 (0)	3 (0.6)	3 (0.6)
Post-BL >5X ULN ≤10X ULN	3 (0.3)	0 (0)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0)
Post-BL >10X ULN ≤15X ULN	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)
Post-BL >20X ULN	1 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)
Total	217 (22.2)	16 (1.6)	1 (0.1)	2 (0.2)	102 (20.6)	9 (1.8)

BL: Baseline; ULN: upper limit of normal (>40 IU/mL)

Table 31: Phase 3 Patients with Post-Baseline Elevation in Aspartate Aminotransferase (AST)

	Moxidectin N=978			Ivermectin N=494		
	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)	BL >2X ULN ≤3X ULN n, (%)	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)	BL >2X ULN ≤3X ULN n, (%)
Post-BL >ULN ≤2X ULN	188 (19.2)	0 (0)	0 (0)	99 (20)	0 (0)	0 (0)
Post-BL >2X ULN ≤3X ULN	20 (2.0)	13 (1.3)	0 (0)	7 (1.4)	5 (1)	0 (0)
Post-BL >3X ULN ≤5X ULN	6 (0.6)	7 (0.7)	4 (0.4)	6 (1.2)	1 (0.2)	1 (0.2)
Post-BL >5X ULN ≤10X ULN	3 (0.3)	3 (0.3)	0 (0)	2 (0.4)	1 (0.2)	0 (0)
Post-BL >10X ULN ≤15X ULN	0 (0)	2 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)
Post-BL >15X ULN ≤20X ULN	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Post-BL >20X ULN	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Total	218 (22.3)	26 (2.7)	4 (0.4)	114 (23.1)	7 (1.4)	1 (0.2)

BL: Baseline; ULN: upper limit of normal (>40 IU/mL)

Table 32: Phase 3 Patients with Post-Baseline Elevation in Total Bilirubin

	Moxidectin N=978		Ivermectin N=494	
	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)
Post-BL >ULN ≤2X ULN	91 (9.3)	0 (0)	47 (9.5)	0 (0)
Post-BL	2 (0.2)	8 (0.8)	0 (0)	2 (0.4)

	Moxidectin N=978		Ivermectin N=494	
	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)	BL Normal n, (%)	BL >ULN ≤2X ULN n, (%)
>2X ULN ≤3X ULN				
Post-BL >3X ULN ≤5X ULN	2 (0.2)	0 (0)	0 (0)	0 (0)
Post-BL >5X ULN ≤10X ULN	1 (0.1)	0 (0)	0 (0)	0 (0)
Post-BL >20X ULN	1 (0.1)	0 (0)	0 (0)	0 (0)
Total	97 (9.9)	8 (0.8)	47 (9.5)	2 (0.4)

BL: Baseline; ULN: upper limit of normal (>18µmol/L)

There were 15 patients in the moxidectin arm (1.5%) and 3 patients (0.6%) in the ivermectin arm with post-baseline elevation of transaminases by more than 5X ULN. Three of 15 patients in the moxidectin arm had some elevation in their transaminases at the screening visit. **Table 33** provides more detail on patients in the moxidectin arm that had >5X ULN post-baseline transaminase elevation.

Table 33: Phase 3 Patients with >5-times Upper Limit of Normal Elevation in Liver Enzymes

Unique Patient ID Number	BL ALT IU/mL	BL AST IU/mL	Elevated transaminase IU/mL		Visit	Concurrent Abnormal Liver Tests
			ALT	AST		
Moxidectin						
(b) (6)	20.5	31.8	66.5	221	M 6	
	29	44	203.7	440.8	M 3	
	22	**23.8**	**1268**	**631**	**D 6**	
	24.3	42.5	179.5	375.4	M 6	
	26.4	31.7	258.9	205	M 3	
	25.1	48.3	64.9	212	M 6	
	60.2	70.8	136.9	420	M 6	
	15	21	267	333	M 6	GGT 4.7XULN
	96	70	264	175	M 3	Bili and GGT <2XULN
	184	**74**	**833 (20X**	**1533 (38X**	**D 6**	**Bili 4XULN**

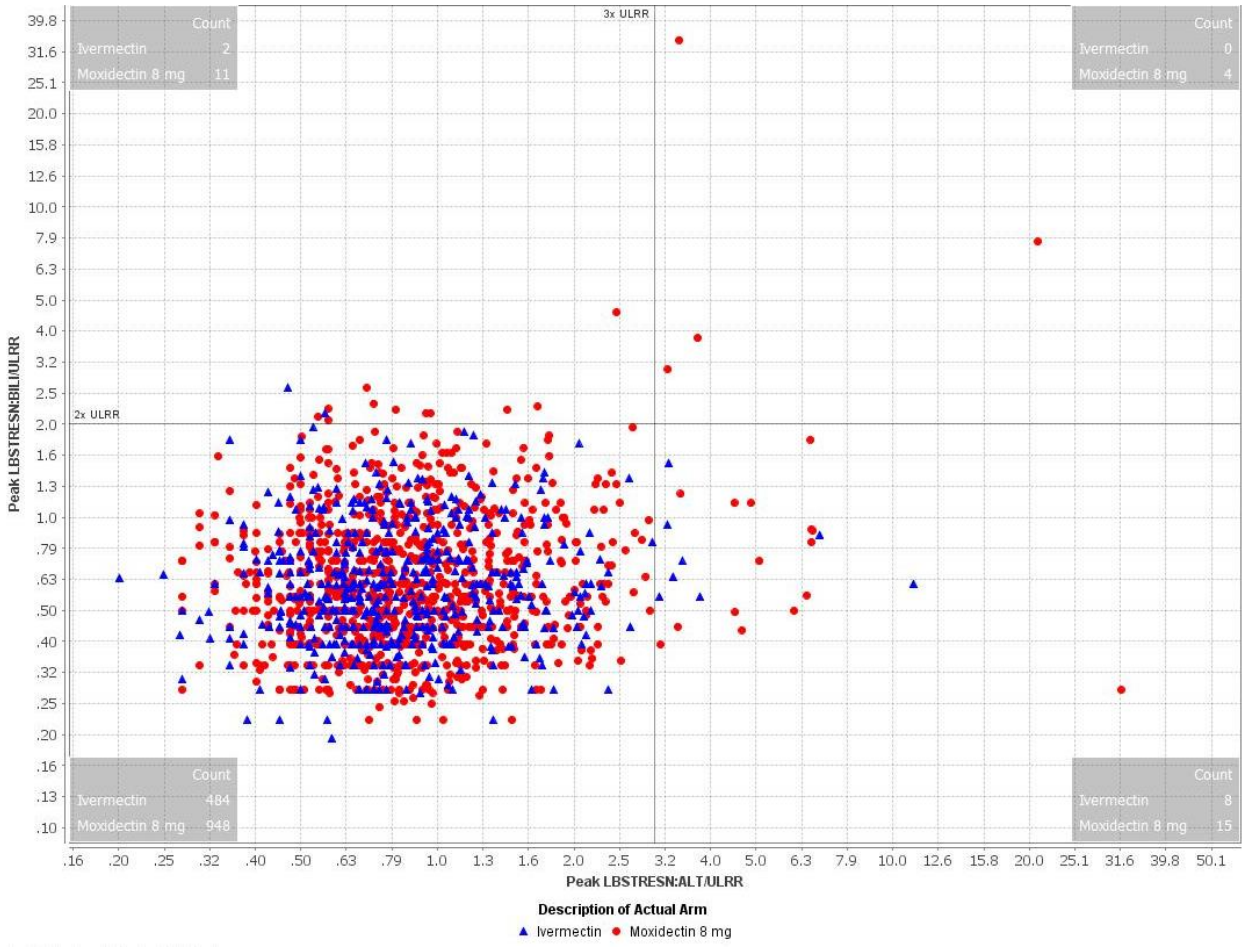
			ULN)	**ULN)**		
(b) (6)	40	41	195	233	M 3	
	169	106	243	159	M 1	
Ivermectin						
(b) (6)	18.4	23.2	443.3	342.9	M3	
	30.8	27	276.9	302.7	D14	
	42	57.6	131.4	362.6	M 6	

BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: gamma glutamyl Transferase; M: month; D: Day; Bili: Bilirubin; ULN: upper limit of normal (ULN for AST and ALT=40IU/ml; GGT=50 IU/mL, Bili=18µmol/L)

Reviewer Comment: Of the 15 patients with 5X ULN post-baseline transaminase elevation, patients (b) (6) *and* (b) (6) *are of particular interest due to the degree of elevation of transaminases and proximity of the elevation to administration of moxidectin (day 6 post moxidectin). Narratives of selected patients with post-baseline liver tests abnormalities are provided below.*

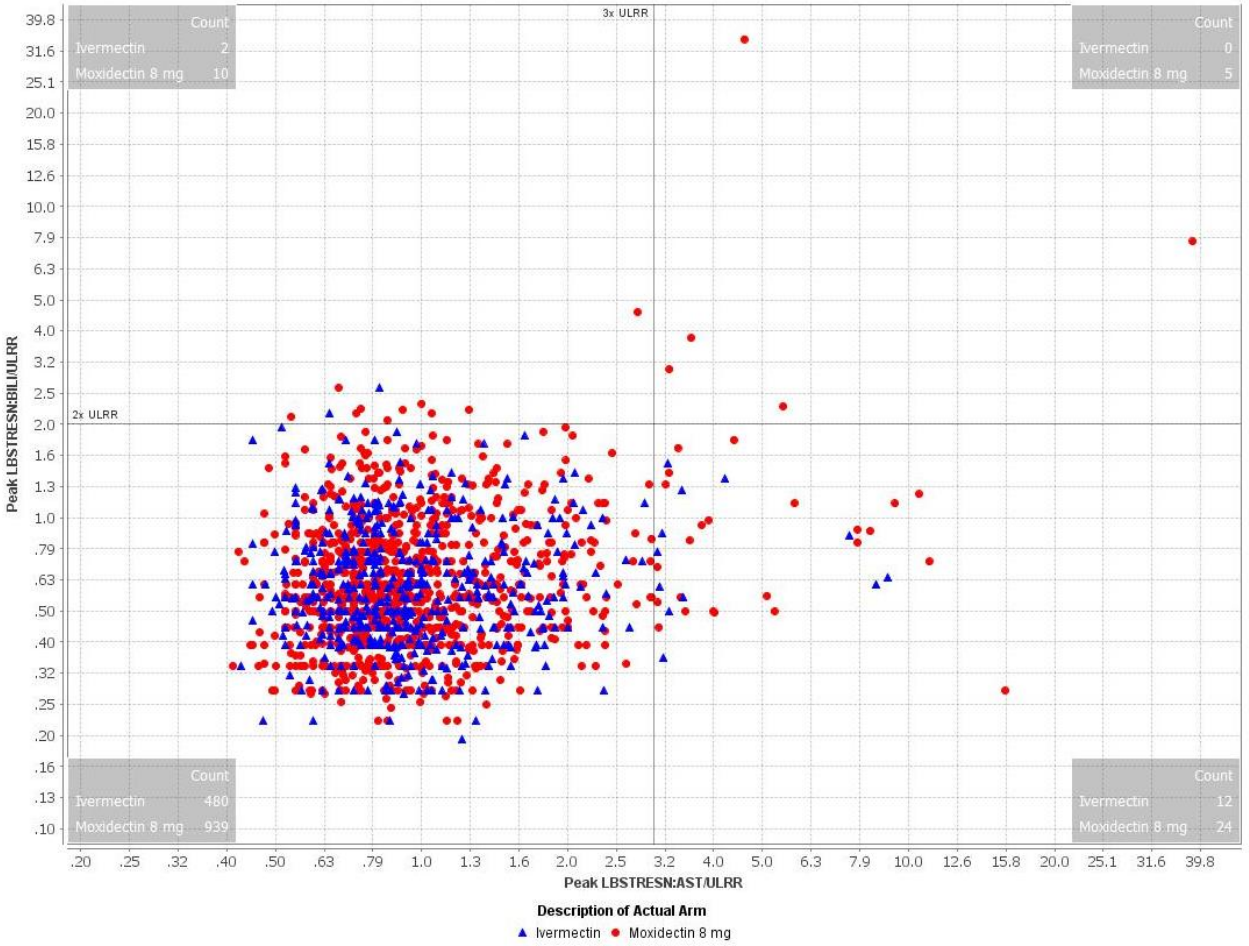
Additional evaluations of liver tests to identify potential patients that fulfill the biochemical criteria of Hy's law, with 2X ULN increase in bilirubin and 3X ULN increase in transaminases, at any time during the trial follow up period were conducted. Figure 5 and Figure **6** present plots without excluding patients with elevated alkaline phosphatase.

Figure 5: Peak ALT/ULN vs. Peak Total Bilirubin/ULN Plot in the Phase 3 Trial



ALT: Alanine aminotransferase; ULN: upper limit of normal (ULN ALT=40 IU/ml; ULN Bilirubin = 18 µmol/L)

Figure 6: Peak AST/ULN vs. Peak Total Bilirubin/ULN Plot in the Phase 3 Trial



AST: Aspartate aminotransferase; ULN: upper limit of normal (ULN AST=40 IU/ml; ULN Bilirubin = 18 µmol/L)

Review of the above figures shows there were no patients that fulfilled Hy's law biochemical criteria in the ivermectin arm. In the moxidectin arm, there were 4 patients (patients (b) (6) (b) (6) who met Hy's law criteria for ALT and AST, and one additional patient (b) (6) who met Hy's law criterion for AST only. After excluding patients with alkaline phosphatase levels 2 times upper limit of normal, 2 patients (b) (6) fulfilled Hy's criteria for both ALT and AST. Patient (b) (6) met Hy's law criterion for AST. Narratives for these patients are presented below:

Patient (b) (4) This was a 37-year-old male who had asymptomatic transient increases in ALT and AST at Day 6. The patient experienced signs and symptoms of Mazzotti reaction (lymphadenopathy, headache, rash, peripheral edema, chills) on study days 1-3 and eosinophilia on day 14. His concomitant medications included paracetamol

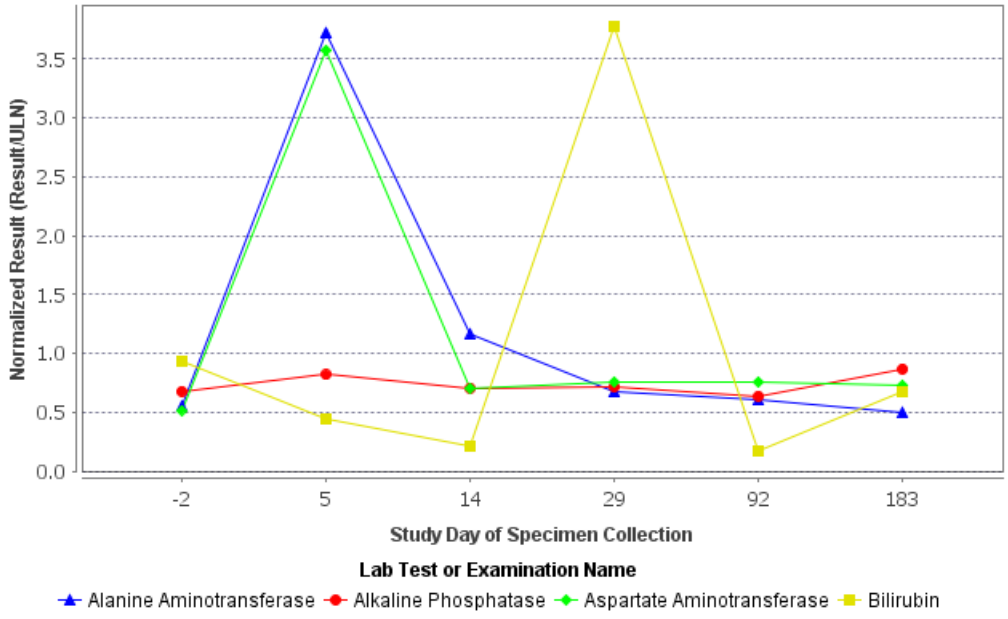
(acetaminophen) for headache from Day 2 to 13, and mebendazole for hookworm infection (Day 14 to 17). The increases in ALT (3.7 x ULN) and AST (3.6 x ULN) on Day 6 were asymptomatic and were deemed to be part of the Mazzotti reaction by the investigator. ALT and AST were within normal range by month 1 visit. Of note, the patient had an isolated elevation in bilirubin at month 1, which returned to normal by Month 3. **Table 34** and Figure 7 summarize the patient's liver enzyme trends.

Table 34: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Alb (g/L)	TBili (µmol/L)
Screening	*22*	*21*	*85*	*42*	*17*
D6	149	143	104	37	8
D14	46	28	89	38	4
M1	27	30	91	42	68
M3	24	31	81	42	3
M6	20	29	109	39	12

Source: Modified from the sponsor's Table 60 in the integrated summary of safety report
ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for alb=32 g/L

Figure 7: Graphical Presentation of Laboratory Values for Patient (b) (6)



Reviewer Comment: Review of patient (b) (6) *liver enzymes show that he did not have concurrent elevation in transaminases and bilirubin. ALT and AST elevations are reported as part of Mazzotti reaction in the literature, and are presumed to be the case in this patient. The*

isolated bilirubin elevation occurred at month 1 and bilirubin went back to normal by month 3. There is no clear explanation for the single elevation of bilirubin.

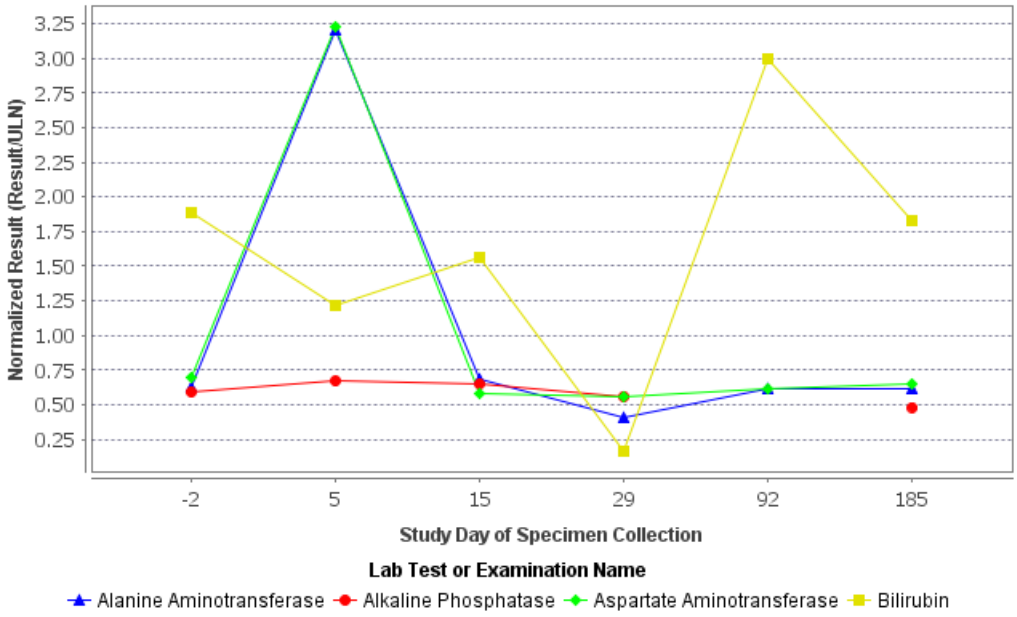
Patient (b) (6) This was a 24-year-old male with a history of pruritus, ocular pain, and polyneuritis. He had normal transaminases at screening visit and developed elevation in transaminases (> 3X ULN for AST and ALT) on study day 6. He also had concurrent mild elevation in total bilirubin, though he had baseline elevation in bilirubin. During the first five study days, he was also noted to have Mazzotti reaction with decreased mean arterial pressure, pruritus, headache, orthostatic tachycardia, and myalgia. Concomitant medications included paracetamol (days 2-4), promethazine (days 2 and 3), tropicamide (day 3), phenylephrine hydrochloride (day 3), and ibuprofen (day 4). Transaminase elevations resolved by day 14. Separately, on study day 92, he was reported to have isolated hyperbilirubinemia with total bilirubin 3X ULN. **Table 35** and Figure 8 summarize the liver enzyme trends for patient (b) (6).

Table 35: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Alb (g/L)	TBili (µmol/L)
BL	25	28	74	46	34
D6	128	129	85	45	22
D14	27	23	82	42	28
M1	16	22	70	43	3
M3	24	24	ND	43	54
M6	24	26	61	43	33

BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin; ND: Not done
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for alb=32 g/L
Note: Lab values were rounded to the nearest integer.

Figure 8: Graphical Presentation of Laboratory Values for Patient (b) (6)



Reviewer Comment: Review of patient (b) (6) *liver enzymes show that he had mild concurrent elevation of bilirubin along with elevation in transaminases on day 6; however, the bilirubin elevation was present at baseline and was less than 2xULN. He did not fulfill the Hy's biochemical criteria. As noted earlier, elevation of ALT and AST are part of Mazzotti reaction which is presumed to be the cause of transaminase elevation in this patient. A significant isolated bilirubin elevation (3X ULN) occurred at month 3 and went down to <2XULN at month 6. There is no clear explanation for the single elevation of bilirubin, and there were no additional bilirubin levels to evaluate if the bilirubin elevation resolved completely.*

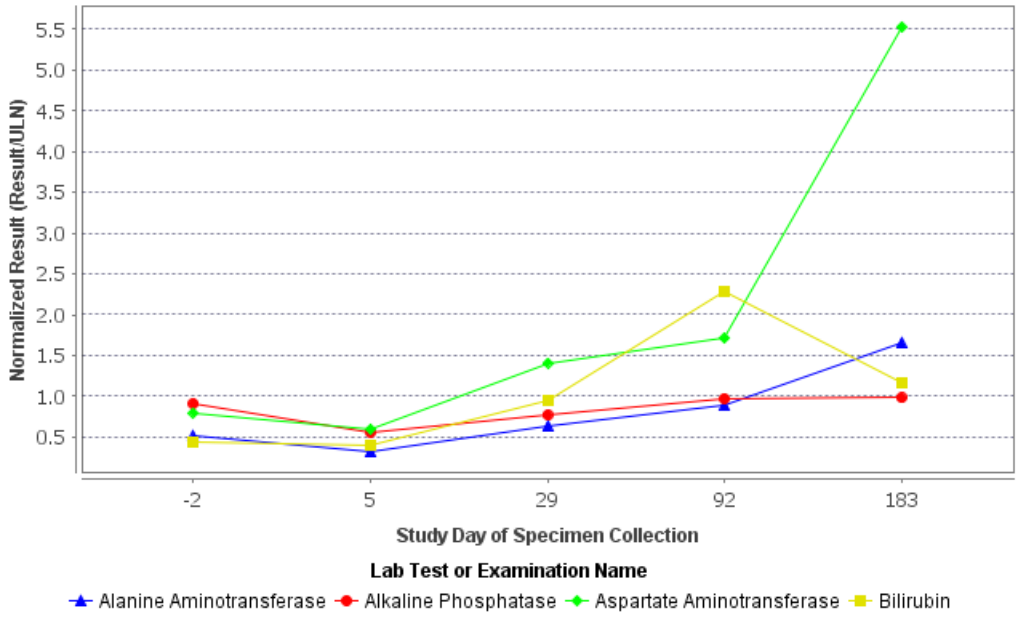
Patient (b) (6) This was a 55-year-old male with a history of gastritis, schistosomiasis, thrombocytosis, hookworm infection, chronic enteritis, and abdominal pain. He had enteritis prior to study start (Day -5 to -4) and a grade 1 lower abdominal pain on Day 3. His concomitant medications included amoxicillin, papaverin, ibuprofen and metronidazole. A mild increase in AST was noted on Day 29 and attributed to the Mazzotti reaction by the investigator. However, the patient had additional elevation in AST on Day 92 (1.7X ULN) and month 6 visit (5.5X ULN). At month 6, he had elevation in ALT (1.7X ULN), and marked increase in GGT (>11 XULN), with concurrent Grade 1 abdominal pain on Day 177, and hematochezia on Day 178. The investigator recorded no causal relationship to the study drug for these AEs. No subsequent laboratory investigations for AST or ALT were recorded, but GGT was down to <2X ULN by month 12.

Table 36: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Alb (g/L)	TBili (µmol/)
BL	*21*	*32*	*115*	*27*	*8*
D6	13	24	70	25	7
M1	26	56	97	29	17
M3	36	68	122	26	41
M6	67	221	123	30	21

Source: Sponsor's Table 61 from the integrated summary of safety report
BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for Alb=32 g/L
Note: Lab values were rounded to the nearest integer

Figure 9: Graphical Presentation of Laboratory Values for Patient (b) (6)



Reviewer Comment: There is no clear explanation to the patient's elevation in AST. Given the rising trend in AST occurred after moxidectin administration, moxidectin's contribution cannot be ruled out.

Four additional narratives are presented for moxidectin patients: Patient (b) (6) had

10X ULN post-baseline transaminase elevations on day 6 (refer to **Table 33**). Patients (b) (6) and (b) (6) experienced >3X ULN post-baseline elevation in total bilirubin during the study.

Patient (b) (6): The patient was a 54-year-old female whose medical history included episodes of nausea, heartburn, and lumbar pain. She did not report any other hepatobiliary events in her medical history. She experienced Mazzotti reactions including pruritus and increased respiratory rate during study days 1 and 2. She was also diagnosed with malaria on study day 4. On day 6, she had marked elevation of her transaminases with 30X ULN ALT, >15X ULN AST and >5X ULN GGT, as shown in the table below. The investigator flagged these increases as part of Mazzotti reaction. Her concurrent medications included artesunate-amodiaquine (Days 4 to 6), paracetamol (days 4-6), ciprofloxacin (Days 5 to 9) and chlorpheniramine (Days 1 to 5). The patient's liver enzyme values returned to the normal range by day 14.

Table 37: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	GGT (IU/L)	ALP(IU/L)	LDH (IU/L)	TBili (µmol/L)
BL	*22*	*24*	*14*	*63*	*195*	*4*
D6	1268	632	275	133	865	5
D14	39	19	86	73	260	3
M1	18	26	44	68	264	4
M3	16	19	14	61	167	5
M6	24	21	15	59	146	5

Source: Sponsor's Table 52 in the Integrated Summary of Safety report
BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for alb=32 g/L
Note: Lab values were rounded to the nearest integer

Reviewer Comment: The patient had a marked elevation in ALT and AST on day 6. These increases were temporally related to moxidectin; however, the patient was also diagnosed with malaria on day 4, and started on artesunate-amodiaquine. It is difficult to parse out the contribution of the concurrent malaria, concomitant medication known to cause transaminitis (amodiaquine), concurrent Mazzotti reaction vs. moxidectin to the observed marked transaminitis. Note that the patient did not have elevation in bilirubin. Her liver enzymes were within normal limits by day 14.

Patient (b) (6)**:** This was an 18-year-old male with past medical history of headache, dysuria, and itching. His screening visit physical examination and labs were notable for hepatomegaly and mild elevated liver enzymes with AST >1.8X ULN, ALT >4X ULN, and GGT >3X ULN. Chronic active hepatitis was reported as serious adverse event on day 5 of the study. There were no reported concomitant medications. On day 6, he had further elevation of liver enzymes with

ALT >20X ULN, AST >38X ULN, GGT >6X ULN, and total bilirubin >4X ULN with no significant clinical symptoms. On day 14, there was some improvement in liver tests, but at month 1 visit transaminases remained elevated (ALT>10X ULN; AST>20X ULN; GGT >2X ULN) and were accompanied by marked hyperbilirubinemia (>7X ULN). A hepatitis antibody screen was conducted on day 24 and was reported as confirming pre-existing hepatitis B virus infection. However, the kit used could not differentiate between IgM and IgG immunoglobulin. Further testing 5 months post moxidectin administration revealed HBsAg positive, HBsAb negative, HBcAb IgG positive, HBcAb IgM negative. The investigator considered this patient as having viral hepatitis, which started before treatment with moxidectin. The patient completed the 18-month follow up and was reported as "recovered" from the SAE. The investigator and the sponsor assessed the liver test abnormalities as not related to the study drug.

Table 38 summarizes the laboratory trends for patient (b) (6)

Table 38: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Alb (g/L)	TBili (µmol/L)
BL	*184*	*74*	*48*	*41*	*15*
D6	833	1533	96	33	79
D14	192	458	97	35	35
M1	411	910	86	33	139
M3	109	120	72	38	12
M6	203	181	72	37	13
M12	198	154	53	38	10
M18	71	80	46	37	5

Source: Sponsor's Table 51 in the integrated summary of safety report
BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for Alb=32 g/L
Note: Lab values were rounded to the nearest integer

Reviewer Comment: Based on the screening exam that showed hepatomegaly and elevation of transaminases, subsequent positive hepatitis B surface antigen testing and accompanying hepatitis B antibody pattern, the patient had hepatitis B. It is notable that his transaminases were markedly risen from the baseline mild elevation with moxidectin treatment. It appears that his baseline liver inflammation was exacerbated by treatment with moxidectin. Once again, it is difficult to parse out the contribution of the moxidectin directly vs. ensuing Mazzotti reaction vs. ongoing hepatitis B infection to the observed marked elevation.

Patient (b) (6) This was a 20-year-old male with past medical history of itching and abdominal pain. At the screening visit, his physical examination revealed body weight of 39.6 kg, excoriation of the skin and variable tachycardia. Laboratory testing showed hypernatremia and

low creatinine and urea levels. He had Mazzotti reaction in the first few days after treatment with fever, headache, and postural and supine tachycardia. In addition, he had concurrent malaria diagnosed on day 3. At month 12 visit, the patient had new elevation in liver enzymes and severe hyperbilirubinemia with >34X ULN; there were moderate elevation in AST and ALT (3-4X ULN). At the same visit, an AE of "liver intoxication due to consumption of unknown traditional drugs" was reported and presumably, the patient was icteric as treatment with Vitamin B complex for icterus was implemented. No further laboratory results were available. The investigator considered the event unrelated to the study drug and the patient did not withdraw from the study.

Table 39: Liver Enzyme Trends for Patient (b) (6)

Visit	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Albumin (g/L)	TBili (µmol/L)
BL	*41*	*28*	*216*	*42*	*5*
D6	27	23	157	39	3
D14	25	23	157	39	3
M1	31	26	215	41	5
M3	46	32	242	39	7
M6	32	33	258	45	4
M12	136	184	295	35	621.5

Source: Sponsor's Table 55 in the integrated summary of safety report
BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L
Lower limit of normal (LLN) value for Alb=32 g/L
Note: Lab values were rounded to the nearest integer

Reviewer Comment: This patient's elevation in liver enzymes and bilirubin are not temporally related to moxidectin. The patient had a clear alternative explanation for his liver enzyme and bilirubin abnormalities.

Patient (b) (6) The patient was a 31-year-old male with past medical history of intermittent fever, headache, and lower abdominal pain. In the first week after treatment, he had symptoms of Mazzotti reaction including pruritus and orthostatic tachycardia. On day 6, a 2-fold elevation in transaminases and more than a 9-fold increase in bilirubin were noted as shown in Table 40. The marked hyperbilirubinemia was reported as asymptomatic. He also had more than a 3-fold increase from his baseline normal creatinine of 99 to 368.3 µmol/L. He had no reported concomitant medications for the first 2 weeks post moxidectin. Other than orthostatic tachycardia, there was no report of hypotension.

By Day 14, the serum creatinine and bilirubin level were down to normal range. Except for trace urine albumin at month 1, the patient had negative urine albumin at baseline, day 6, day 14 month 3 and 6 visits.

Table 40: Laboratory Trends for Patient (b) (6)

Visit	Creat (µmol/L)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	ALB (g/L)	T.Bili (µmol/L)
BL	99	39	38	82.4	44	9
D6	368	99	111	241	39	82
D14	95	60	41	95	42	7
M1	90	64	66	228	44	10.7
M3	88	57	41	78	42	5
M6	72	31	29	72	42	4

Source: Modified from sponsor's Table 55 in the integrated summary of safety report
BL: Baseline; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; TBili: Total bilirubin; Alb: albumin; Creat=Serum creatinine
Upper limit of normal (ULN) values: ALT and AST=40 IU/L; ALP=126 IU/L; Bili=18 µmol/L; Creat=135 µmol/L
Lower limit of normal (LLN) value for Alb=32 g/L
Note: Lab values were rounded to the nearest integer

Reviewer Comment: The mild elevation in ALT and AST are as expected in Mazzotti reaction. However, the marked increase in total bilirubin and significant rise in creatinine are not typical findings for Mazzotti reaction. The significant rise in creatinine is temporally related to moxidectin so its contribution to the observed abnormality cannot be ruled out.

Assessment of Kidney Function in Phase 3 Trial

Figure 10 shows the comparison of the mean percent change from baseline creatinine between the two study arms for each study visit.

Figure 10: Percent Change from Baseline Serum Creatinine in the Phase 3 Trial

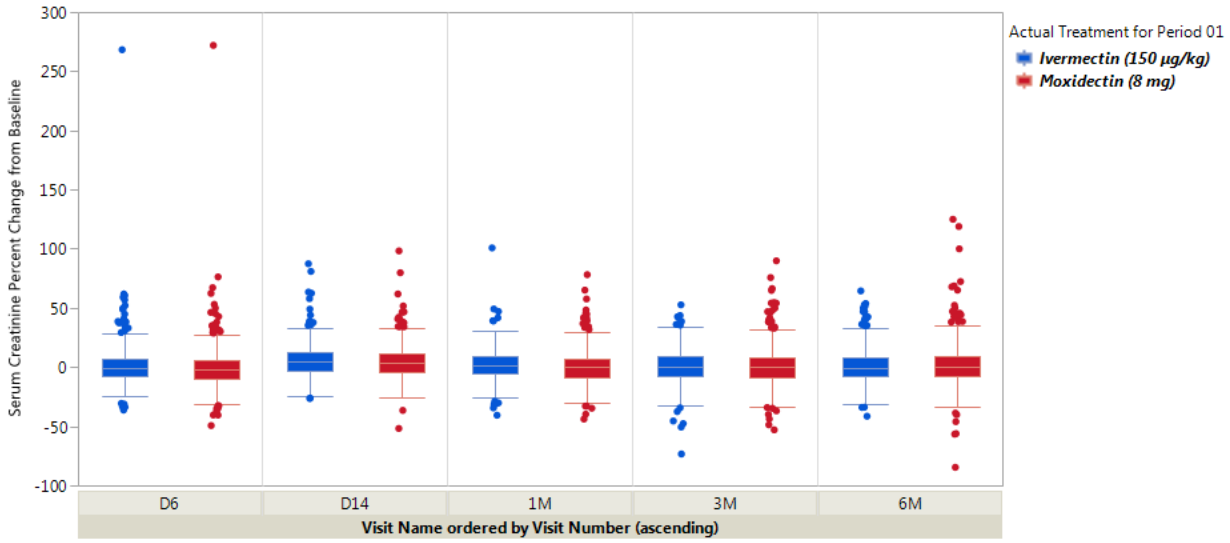


Table 41 shows the number of patients with >1.5-fold increase from baseline serum creatinine for study visits up to month 6.

Table 41: Phase 3 Patients with >1.5x Increase from Baseline Serum Creatinine

Visit	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Patients with 1.5X increase in serum creatinine by month 6 visit	22 (2.2)	17 (3.4)
Day 6	5 (0.5)	6 (1.2)
Day 14	4 (0.4)	5 (1.0)
Month 1	3 (0.3)	1 (0.2)
Month 3	7 (0.7)	1 (0.2)
Month 6	5 (0.5)	6 (1.2)

Review of moxidectin patients with 1.5-fold increase from baseline creatinine on day 6 revealed that 4 of these patients (patient (b) (6)) had serum creatinine values within the upper limit of normal. All 4 patients also had creatinine levels back to baseline by day 14. One patient, patient (b) (6) had a 3.7-fold elevation in serum creatinine on day 6 (271% change from baseline noted in Figure 10). Patient (b) (6) also had concurrent 9-fold elevation in bilirubin and 2-fold increase in transaminases. A short narrative for this patient is provided in the assessment of liver function tests section above along with the summary of trends of the patient's laboratory results in **Table 40**.

Reviewer Comment: Overall, there does not appear to be notable changes in kidney function after a single dose of moxidectin when compared with ivermectin.

In regards to patient (b) (6)*, based on the clinical sign/symptoms and laboratory abnormalities, as well as temporal association with administration of moxidectin, he appears to have Mazzotti reaction at time of his serum creatinine elevation. Although liver function abnormalities are part of Mazzotti reaction, marked elevation in serum creatinine is not reported as part of Mazzotti reaction. One hypothesis that explains the observed elevation may be ensuing intense inflammatory response resulting in acute kidney injury. Of note, both the creatinine and bilirubin levels were back to normal range on day 14.*

Assessment of Hematologic Labs

Changes in white blood cell, neutrophil, lymphocyte, platelets, and especially eosinophil count are expected with Mazzotti reaction. Median and ranges of the observed values for each test are summarized by study visit in **Table 42** below.

Table 42: Summary of Hematologic Labs in the Phase 3 Trial by Study Visit

	Arm	BL Med (25^{th}, 75^{th})	D6 Med (25^{th}, 75^{th})	D14 Med (25^{th}, 75^{th})	M1 Med (25^{th}, 75^{th}	M3 Med (25^{th}, 75^{th})	M6 Med (25^{th}, 75^{th})
WBC (10^9/L)	Mox	6.9 (5.7-8.6)	7.6 (6.1-9.3)	9.3 (7-12.7)	7.3 (6-9)	5.8 (4.9-7)	5.7 (4.8-6.8)
	Iver	7 (5.7, 8.7)	7.4 (6-9.1)	9 (6.9-12.1)	8.1 (6.6-10.6)	6.2 (5.1-7.4)	6.1 (5.1-7.4)
Eos (10^9/L)	Mox	0.85 (0.45-1.5)	1.1 (0.63-1.7)	2.2 (1.2-3.8)	1.7 (1-2.6)	0.5 (0.31-0.87)	0.46 (0.25-0.78)
	Iver	0.78 (0.41-1.4)	0.96 (0.64-1.6)	2 (1.1-3.7)	2.2 (1.3-3.6)	0.76 (0.43-1.3)	0.65 (0.36-1.2)
Lymph (10^9/L)	Mox	2.4 (1.9-3.2)	1.8 (1.4-2.4)	2.5 (1.9-3.1)	1.4 (0.57-2.6)	2.4 (1.8-3)	2.2 (1.7-2.8)
	Iver	2.4 (1.9-3.1)	1.9 (1.5-2.5)	2.4 (1.8-3.2)	1.6 (0.6-2.6)	2.4 (1.9-3)	2.3 (1.8-2.8)
Neut (10^9/L)	Mox	2.7 (2-3.5)	3.7 (2.8-4.9)	3.1 (2-4.9)	2.1 (1.5-2.9)	2.1 (1.6-2.8)	2.2 (1.7-2.9)
	Iver	2.7 (2-3.7)	3.5 (2.6-4.7)	3.3 (1.9-4.9)	2.2 (1.6-3.1)	2.1 (1.6-2.8)	2.3 (1.7-3.1)
Hgb (g/dL)	Mox	14.3 (13.1-15.6)	13.9 (12.6-15.2)	14 (12.8-15.3)	13.7 (12.6-14.8)	14 (12.9-15.3)	14.2 (12.9-15.4)
	Iver	14.4 (13-15.6)	14.1 (12.8-15.5)	14.3 (12.8-15.5)	13.8 (12.5-14.8)	14 (12.8-15.1)	14 (12.9-15.2)

Mox: Moxidectin; Iver: Ivermectin; Med: median; 25th and 75th indicate the 25th and 75th quartiles; WBC: White Blood Cell; Eos: Eosinophil; Lymph: Lymphocyte; Neut: Neutrophil; Hgb: Hemoglobin

Summary of extreme hematologic abnormalities is presented in **Table 43**.

Table 43: Extreme Hematologic Laboratory Findings in the Phase 3 Trial

	Moxidectin (n = 978) n (%)	**Ivermectin (n = 494) n (%)**
Severe eosinophilia (> 5 x10^9/L)	173 (18)	111 (23)
Grade 3 lymphocytopenia (< 0.5 x10^9/L)	220 (23)	98 (20)
Grade 4 neutropenia (< 0.5 x10^9/L)	65 (7)	46 (9)
Eosinopenia (<0.045 x10^9/L)	51 (5)	21 (4)

NOTE: Grading used for lymphocyte and neutrophil count was based on the NCI CTCAE grading; there are no NCI CTCAE grading for eosinophil count so common clinical cut-offs were used.

Reviewer Comment: There were slightly more patient in the moxidectin arm with grade 3 lymphocytopenia, but overall, there was no major imbalance in the hematologic abnormalities seen between the two arms.

Since eosinophilia is a hallmark of filarial diseases, trend and magnitude of eosinophilia over the 6 month study period was evaluated; the results are summarized in **Table 44** and Figure 11.

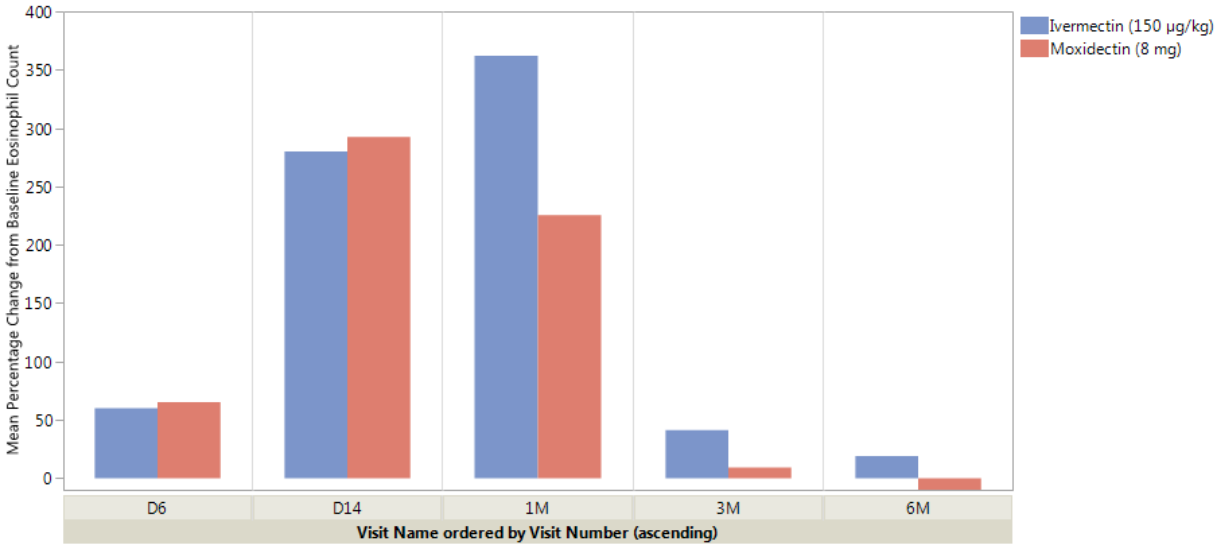
Table 44: Eosinophil Count in the Phase 3 Trial by Study Visit

	BL	D6	D14	M1	M3	M6
Moxidectin	N=977 n, %	N=961 n, %	N=873 n, %	N=953 n, %	N=966 n, %	N=949 n, %
All patients with eosinophil count ≥0.5x10^9/L	697 (71.3)	807 (84)	810 (92.8)	880 (92.3)	492 (50.9)	443 (46.7)
≥0.5 to <1.5 x10^9/L	455 (46.6)	512 (53.3)	234 (26.8)	331 (34.7)	421 (43.6)	370 (39)
≥ 1.5 to <5 x10^9/L	237 (24.3)	280 (29.1)	439 (50.3)	509 (53.4)	70 (7.2)	72 (7.6)
≥5 x10^9/L	5 (0.5)	15 (1.6)	137 (15.7)	40 (4.2)	1 (0.1)	1 (0.1)
Missing	1 (0.1)	7 (0.7)	101 (11.6)	19 (2)	1 (0.1)	13 (1.4)
Ivermectin	N=494 n, %	N=485 n, %	N=456 n, %	N=473 n, %	N=485 n, %	N=488 n, %
All patients with eosinophil count ≥0.5x10^9/L	342 (69.2)	399 (82.3)	421 (92.3)	444 (93.9)	337 (69.5)	296 (60.7)
≥0.5 to <1.5 x10^9/L	229 (67)	265 (54.6)	128 (28.1)	126 (26.6)	248 (51.1)	219 (44.9)

	BL	D6	D14	M1	M3	M6
Moxidectin	N=977 n, %	N=961 n, %	N=873 n, %	N=953 n, %	N=966 n, %	N=949 n, %
≥1.5 to <5 x10^9/L	111 (22.5)	131 (27)	230 (50.4)	254 (53.7)	86 (17.7)	76 (15.6)
≥5 x10^9/L	2 (0.4)	3 (0.6)	63 (13.1)	64 (13.5)	3 (0.6)	1 (0.2)
Missing	0(0)	3 (0.6)	38 (9)	19 (4)	2 (0.4)	2 (0.4)

NOTE: Number of patients with available test result for each study visit for moxidectin or ivermectin study arm was used as denominator

Figure 11: Phase 3 Mean Percent Change in Eosinophil Count from Baseline by Study Visit



Reviewer Comment: More than two-thirds of patients in each study arm had some degree of eosinophilia at baseline. After treatment, the number of patients and degree of eosinophilia peaked around day 14 for the moxidectin arm and month 1 for the ivermectin arm. Number and degree of eosinophilia continues to fall over the rest of the study, more quickly in the moxidectin arm. This trend of faster lowering of eosinophilia in the moxidectin arm may related to higher moxidectin's efficacy over ivermectin in reducing microfilarial burden.

8.4.7. Vital Signs

The ADVS dataset was evaluated for changes in vital signs. Changes in body temperature, heart rate, and blood pressure are part of the clinical signs of Mazzotti reaction. The following tables

summarize the changes in body temperature, heart rate, and blood pressure reported in the Phase 3 trial.

Changes in Body Temperature

Since Mazzotti reaction is mainly described within two weeks after drug administration, the number of patients with temperature over 39°c in the first 14 days post administration of study drugs was reviewed, and the result showed that 19 patients (1.9%) in the moxidectin arm vs. 4 patients in ivermectin (0.8%) had body temperature >39°c. Temporal occurrence of fever is presented in **Table 45**.

Table 45: Phase 3 Patients with Body Temperature above 39°C by Study Visit

Study Visit	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Day 1	3 (0.3)	0 (0)
Day 2	11 (1.1)	1 (0.2)
Day 3	3 (0.3)	1 (0.2)
Day4	1 (0.1)	1 (0.2)
Day 6	0 (0)	0 (0)
Day 14	1 (0.1)	1 (0.2)

Orthostatic Changes in Heart Rate

Orthostatic tachycardia was defined as an increase in heart rate by 20 bpm from supine to standing. **Table 46** summarizes proportion of patients with orthostatic tachycardia for the study visits up to month 1 visit.

Table 46: Phase 3 Patients with Orthostatic Changes in Heart Rate by Study Visit

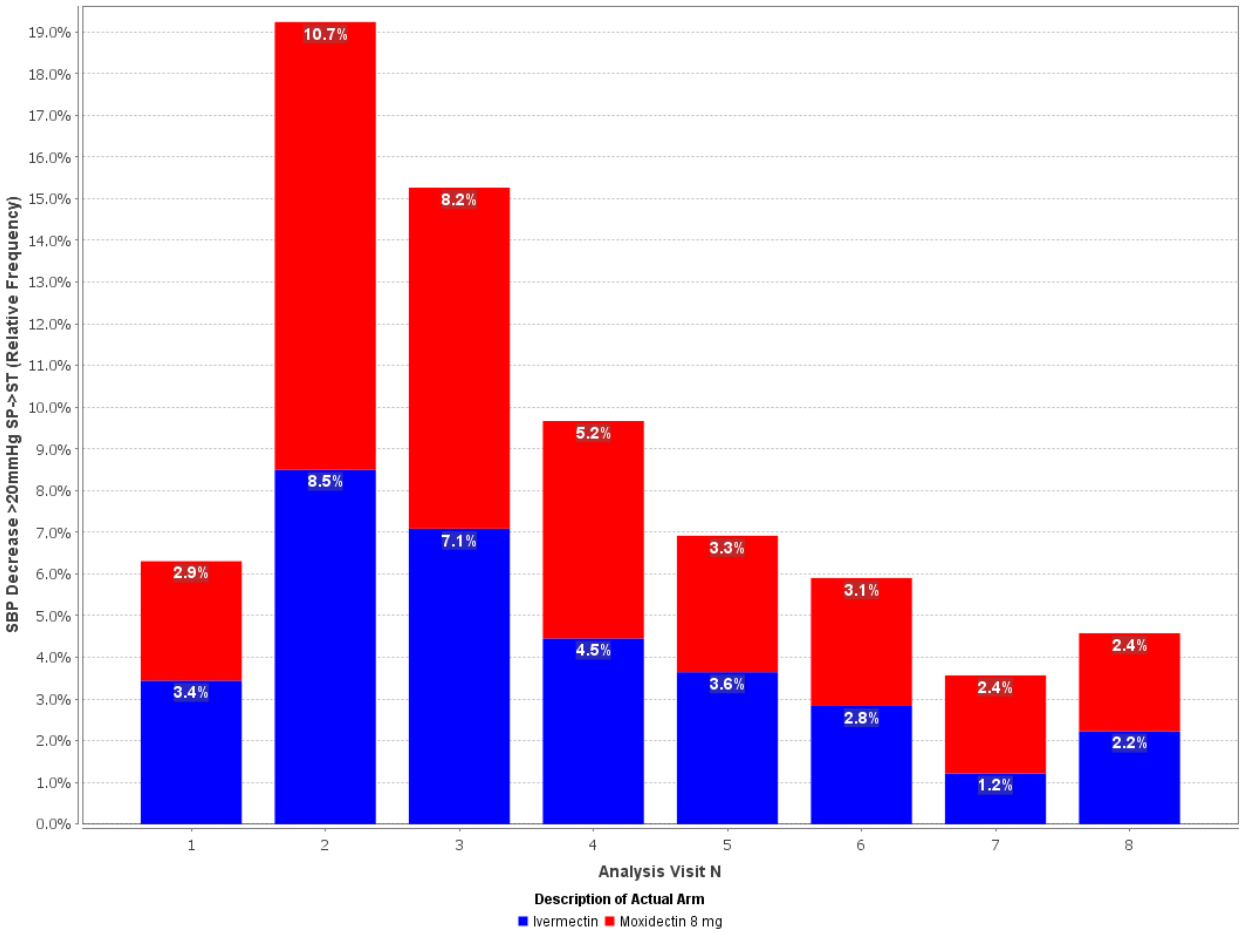
Study day (Visit Number)	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Screening (1)	49 (5)	23 (4.7)
Day 1 (2)	164 (16.8)	67 (13.6)
Day 2 (3)	213 (21.8)	93 (18.8)
Day 3 (4)	112 (11.5)	64 (13)
Day4 (5)	95 (9.7)	47 (9.5)
Day 6 (6)	66 (6.8)	35 (7.1)
Day 14 (7)	67 (6.9)	40 (8.1)
Month 1 (8)	43 (4.4)	27 (5.5)

Orthostatic Changes in Blood Pressure

Decrease of >20mmHg in systolic (SBP) or decrease of >10mmHg in diastolic blood pressure (DBP) measures obtained supine to standing were considered orthostatic blood pressure changes.

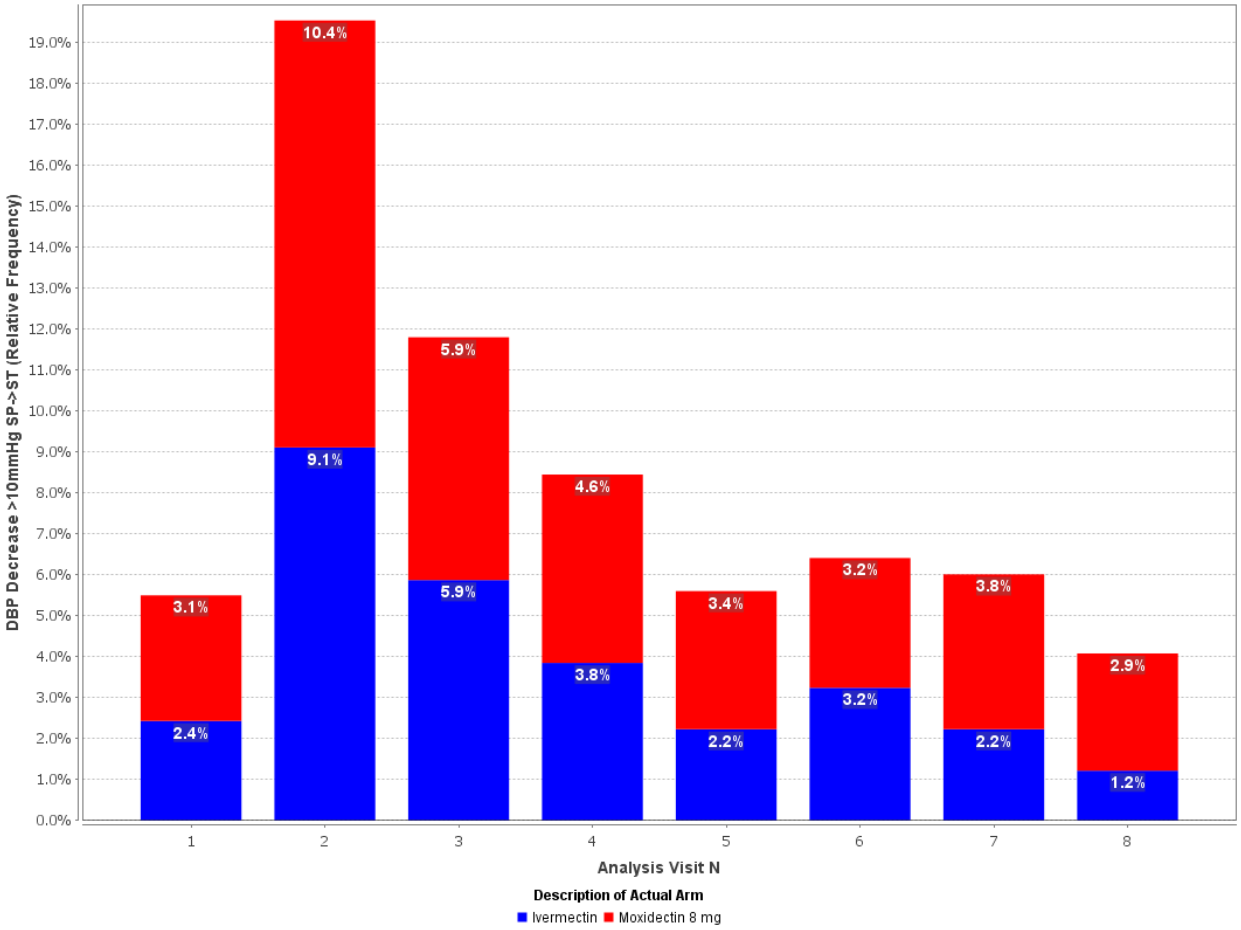
Figure 12 and Figure 13 summarize the proportion of patients with these changes in SBP and DBP, respectively, by study visit.

Figure 12: Proportion of Phase 3 Patients with a 20 mmHg Decrease in Systolic Blood Pressure When Measured Supine to Standing by Study Visit



NOTE: Study visits: 1=Screening; 2=day1; 3=day 2; 4=day 3; 5=day4; 6=day6; 7=day14; 8=month 1; SBP=Systolic blood pressure; SP=Supine; ST=Standing

Figure 13: Proportion of Phase 3 Patients with a 10mmHg Decrease in Diastolic Blood Pressure When Measured Supine to Standing by Study Visit



NOTE: Study visits: 1=Screening; 2=day1; 3=day 2; 4=day 3; 5=day4; 6=day6; 7=day14; 8=month 1; DBP=Diastolic blood pressure; SP=Supine; ST=Standing

Of note, 55 patients were identified as having symptomatic orthostatic hypotension, which was defined as inability to stand without support or dizziness for 2 minutes after 5 minutes in supine position. Forty-seven of these patients (4.8%) were in the moxidectin arm, while the remaining 8 patients were in the ivermectin arm (1.6%).

To understand the magnitude of the orthostatic hypotension, review of patients that required hydration (IV or oral) was carried out. Four patients (0.4%) in the moxidectin and 7 patients (0.8%) in ivermectin arm received some hydration. Two of the four patients in the moxidectin arm received oral hydration on day 2 and 12, respectively; the other two patients in moxidectin arm received IV hydration for intercurrent illnesses (malaria, peritonitis) 2 months after study drug administration.

Review of possible trauma that may have arisen from orthostatic changes/dizziness was also undertaken. There were 10 patients in the moxidectin arm (n=8 laceration, n=2 fractures) and 4 patients in the ivermectin arm (n=4 laceration) with fall/injury in the first month of the study.

Reviewer Comment: Overall, as expected, patients in both study arms experienced vital sign changes. There were more patients in moxidectin arm that experienced fever and orthostatic hypotension as compared to ivermectin. There were 19 patients (1.9%) vs. 4 patients in ivermectin (0.8%) that experienced fever (>39°c). There were also more patients with symptomatic orthostatic hypotension in the moxidectin arm as compared to ivermectin. Most patients experienced orthostatic hypotension on days 1 and 2 post administration of moxidectin. It appears that majority of these symptomatic patients resolved with lying down, and did not require hydration, and as the sponsor stated, none required additional pharmacological support. Clinicians that will use moxidectin should be made aware of the potential for orthostatic hypotension in the first few days after treatment with moxidectin so they can make patients aware and counsel them to lie down if they experience dizziness.

Electrocardiograms (ECGs)

All of the clinical studies (6 Phase 1 studies, one Phase 2 and one Phase 3 trial) included ECGs as part of the evaluation. The Phase 1 studies included at least 2 post-moxidectin administration ECGs. One of the Phase 1 studies, study 1008, was a 12-week concentration-QT study and findings of this study will be discussed in some detail in section 8.4.9.

Phase 1 Studies

An exploratory pharmacokinetic/pharmacodynamics analysis was performed in Study 1005 to explore the relationship between moxidectin pharmacokinetics and potential changes in corrected QT interval. ECGs were done pre-dose, and 1, 2, 4, 6, 8, 12, 24, and 48-hours post moxidectin dose. Statistical analysis of the ECG QTc interval using population specific Q wave-T wave correction (QTcN) and Q wave-T wave correction using Frederica's correction (QTcF) showed no time point having a statistically significant increase in QTc, nor an upper bound greater than 10 msec change for either analysis. Of note, in the Phase 1 studies, there were no deaths, SAEs or premature discontinuations due to AEs.

Phase 2 and 3 Trials

In the Phase 2 trial, ECGs were performed at screening, and on study day 1, 2, 3 and 8 post moxidectin administration. Table 47 summarizes the number of patients with potential clinically significant ECG changes.

There were two events of syncope reported. One patient (b) (6) is a 33-year-old male who received 4mg moxidectin and reported syncope on day 440. The other patient (b) (6) was a 26-year-old male who received 2mg moxidectin and reported syncope on day 15. Both patients' QTcF and QTcN were normal on day 1, 2,3, and 8 with no change from baseline.

Table 47: Patients in Phase 2 Study with Potentially Clinically Significant ECG Changes

Evaluation	Treatment				Total n=172 n (%)
	Mox 2 mg n=44 n (%)	Mox 4 mg n=45 n (%)	Mox 8 mg n=38 n (%)	Iver 150 µg/kg n	
Any Change from normal to abnormal	14 (31.8)	7 (15.6)	4 (10.5)	6 (13.3)	37 (21.5)
PR interval Increase of ≥ 10 % and > 200 msec	3 (6.8)	3 (6.7)	2 (5.3)	1 (2.2)	9 (5.2)
QTc interval Increase of ≥ 10 % and > 450 msec	0	1 (2.2)	1 (2.6)	0	2 (1.2)

Source: Table 72 of the Sponsor's Integrated Summary of Safety Report.

In the Phase 3 trial, patients had an ECG at screening, and on day 2 of the study. Summary of changes from baseline QTc for the Phase 3 trial participants are summarized in Table **48**.

Table 48: Potentially Clinically Significant QT-interval Changes from Baseline in Phase 3 Trial

	Post-baseline ECG	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Baseline QTc <450 msec	QTc ≥450-480 msec	8 (0.8)	1 (0.2)
	QTc ≥481-500 msec	1 (0.1)	0 (0)
	QTc ≥501 msec or >60 msec change from BL	9 (0.9)	2 (0.4)
Baseline QTc ≥450-480 msec	QTc ≥481-500 msec	6 (0.6)	2 (0.4)

QTc: QT interval with Frederica's correction; ms: milliseconds

There were 8 patients (n=6 in moxidectin, n=2 ivermectin arm) with baseline QTc between 450-480 msec, and two patients (both in ivermectin arm) with baseline QTc of >480 msec; none of these patients had increase in QTc from their baseline.

Of note, in the Phase 3 trial during the 12-month follow-up, there were 3 TEAEs meeting the ICH E14 guidance for potential cardiovascular AEs of interest including 2 patients who reported loss of consciousness (patient (b) (6) on day 25 and patient (b) (6) on day 111) and one patient

experienced sudden death (patient (b) (6) on study day 291. None of MedDRA preferred terms such a s torsade de pointes, ventricular tachycardia, ventricular fibrillation, ventricular flutter or seizure were reported.

Reviewer Comment: Overall, the non-clinical and clinical studies did not reveal concerning findings and changes in ECG with administration of moxidectin. However, due to the long half-life of the drug, the agency requested a dedicated QT study and results of this study (Study 1008) are presented in section 8.4.8.

8.4.8. QT Study

Study MDGH-MOX-1008, referred to as study 1008 from here on, is a randomized, double-blind placebo-controlled concentration-QT study that evaluated the potential effect of a single oral dose of moxidectin on QT interval in healthy adult male patients over a dose range of 4 to 36 mg. The study had six treatment arms with 10 participants in each arm for a total of 50 patients exposed to moxidectin (4, 8, 16, 24, and 36 mg) and 10 patients to placebo. The average age of the participants was 32 years (± 8.2 SD). The racial makeup of the patients was as follows: 48.3% (29/60) black or African American, 45% (27/60) white, and 6%(4/60) reported as other.

Of note, the study did not include a positive control; however, per ICH E14, the requirement for inclusion of a positive control can be waived if the study includes doses resulting in exposures that are 2-fold higher than the worst-case scenario. The highest dose in study 1008, 36 mg, resulted in a Cmax that is over 4-fold higher than the Cmax for the recommended therapeutic dose of 8 mg. This is higher than the regulatory requirement of 2-fold higher exposure, even in the worst-case scenario of administering 8 mg moxidectin with food, which would increase concentration of moxidectin by 30%. Figure 14, Figure 15 and Figure 16 summarize the concentration-time plot for moxidectin, and changes in heart rate and QT interval post administration of moxidectin, respectively.

Figure 14: Concentration-Time Profile of Moxidectin in the Concentration-QT Study 1008

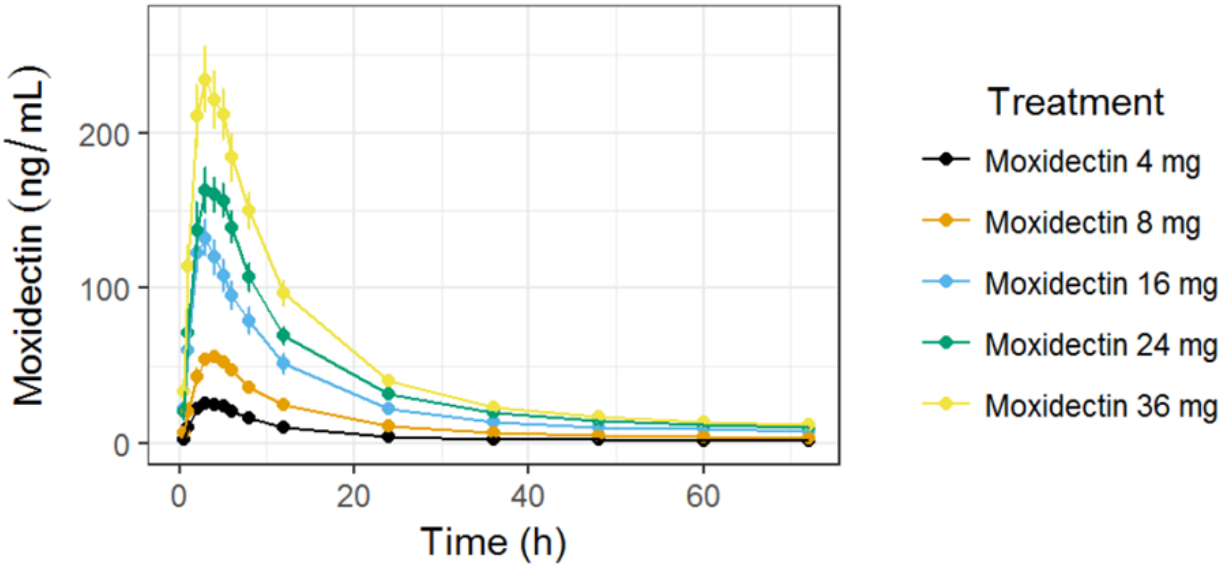


Figure 15: Changes in Heart Rate by Time from Administration of Moxidectin in the Concentration-QT Study 1008

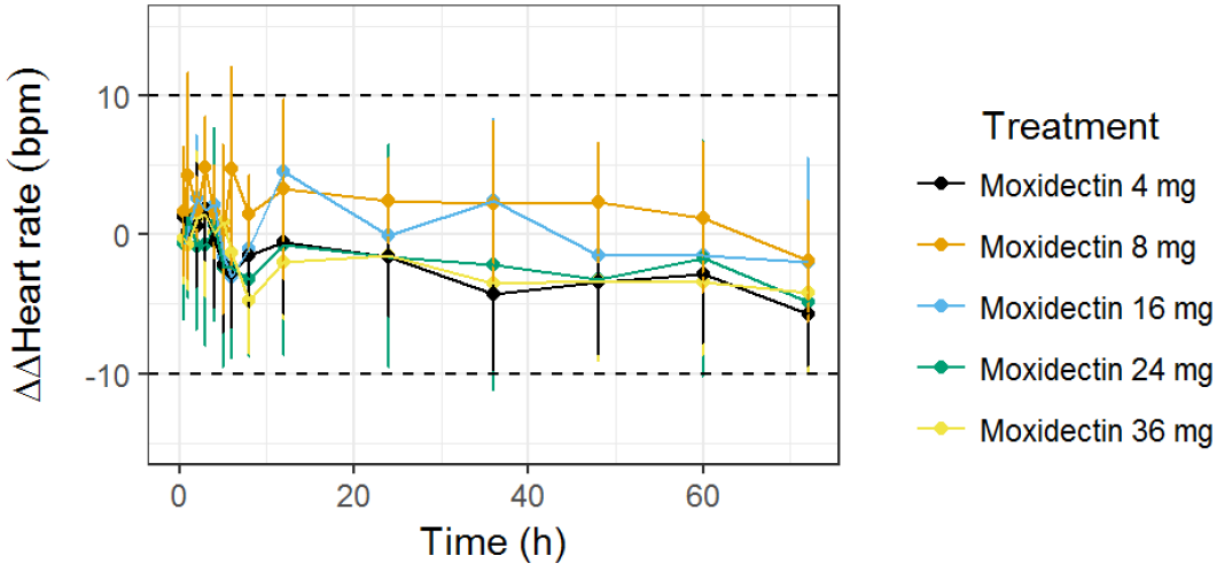
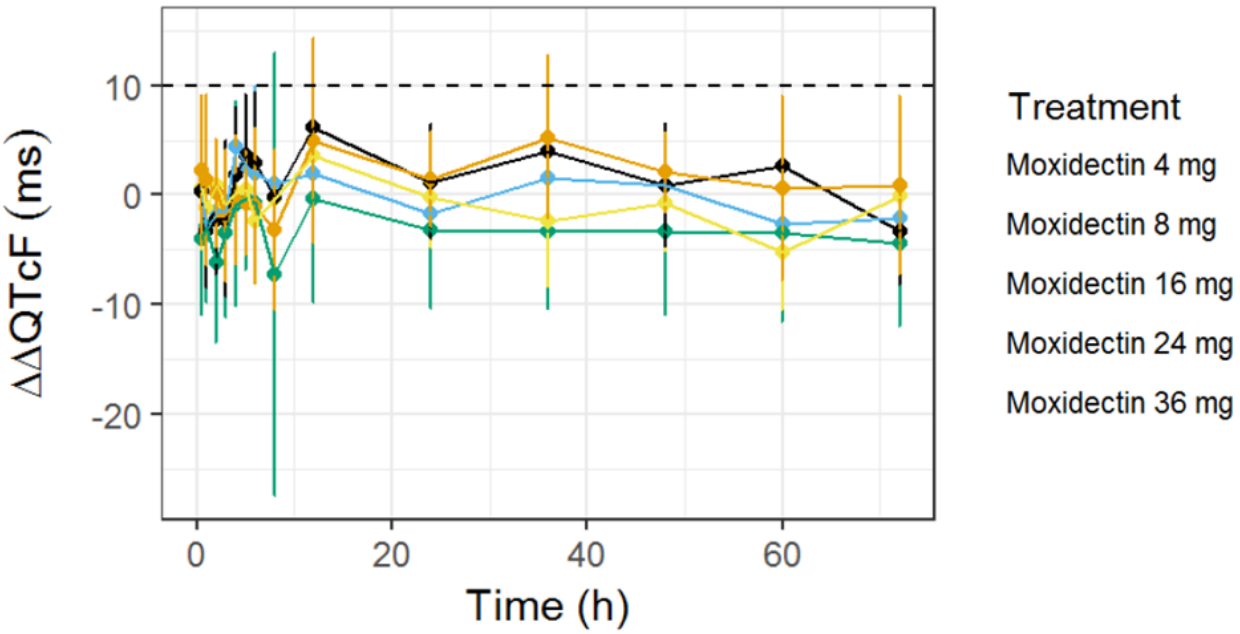


Figure 16: Changes in QT-interval by Time from Administration of Moxidectin in the Concentration-QT Study 1008



The interdisciplinary review team for QT studies (IRT-QT) reviewed the full data from Study 1008. Their review concluded that the study did not show a relationship between moxidectin concentration and QTc with a two-sided upper 90% confidence interval below 10 milliseconds. None of the events identified to be of clinical importance per ICH E14 guideline, including, syncope, seizure, significant ventricular arrhythmias, and sudden cardiac death, occurred in the study. Please refer to the IRT-QT consultation report by Dr. Lars Johannesen for details of the result of study 1008.

The QT-IRT team recommended the following language to summarize the findings of the study under the Cardiac electrophysiology (section 12.2) of the label:
"At a dose (b) (4) times the (b) (4) approved recommended dose, MOXIDECTIN does not prolong the QT to any clinically relevant extent."

Reviewer Comment: The absence of relationship between moxidectin concentration and changes in QT-interval in this study, along with the negative pre-clinical studies (in-vitro hERG study, and studies in beagle dogs) as well as the absence of significant QT-changes in the Phase 2 and Phase 3 trials provide evidence that moxidectin may have low potential to cause QT-interval prolongation.

8.4.9. Immunogenicity

This section is not applicable to this NDA.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Mazzotti Reaction

Since moxidectin is a microfilaricidal drug, Mazzotti reaction was considered an adverse event of special interest. As previously described in section 2.2, Mazzotti reaction is an immune reaction to dying microfilariae and encompasses physical, sign/symptoms, laboratory, and vital signs changes.

Mazzotti reaction usually occurs in the first few days to weeks after therapy; hence, all AEs that occurred during the 14-days following treatment were evaluated. Of the 1472 study participants, 1443 experienced a TEAE than can be classified as Mazzotti reaction over the 14-days post treatment; 970/978 (99.2%) patients in the moxidectin arm and 473/494 (95.6%) patients in the ivermectin arm.

Table 49, **Table 50**, and **Table 51** depict the physical, laboratory and vital signs of Mazzotti reaction that occurred in the 14-days post treatment with the study drug.

Table 49: Physical Signs and Symptoms of Mazzotti Reaction Experienced by >5% Moxidectin-Treated Patients in Phase 3 Trial over 14-days Post Study Drug Administration

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Pruritus	610 (62.4)	254 (51.4)
Musculoskeletal pain	494 (50.5)	255 (51.6)
Pain	200 (20.4)	104 (21.1)
Myalgia	179 (18.3)	87 (17.6)
Back pain	157 (16.1)	86 (17.4)
Arthralgia	96 (9.8)	52 (10.5)
Headache	449 (45.9)	193 (39.1)
Rash*	335 (34.3))	92 (18.6)
Rash, pruritic, and papular rash	227 (23.2)	68 (13.8)
Urticaria	110 (11.2)	24 (4.9)
Pyrexia/Chills	207 (21.2)	49 (9.9)
Peripheral swelling**	142 (14.5)	47 (9.6)
Lymph node pain	126 (12.9)	28 (5.7)
Dizziness	103 (10.5)	35 (7.1)
Lymphadenopathy	92 (9.4)	38 (7.7)
Facial swelling#	90 (9.2)	42 (8.5)

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Lymphadenitis	75 (7.7)	20 (4)
Influenza like illness	73 (7.5)	29 (5.9)
Lymphoedema	65 (6.6)	31 (6.3)

*Includes "Rash," "papular rash," and "urticaria"
**Includes "peripheral swelling" and "oedema peripheral"
#Includes "Swelling face" and "Face oedema"

Table 50: Vital Sign Changes of Mazzotti Reaction in the Phase 3 Trial over 14-days Post Study Drug Administration

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Pyrexia	174 (17.8)	34 (6.9)
Orthostatic tachycardia*	364 (37.2)	139 (28.1)
Orthostatic hypotension	202 (20.7)	74 (15)
Heart rate increased	128 (13.1)	42 (8.5)
Hypotension	120 (12.3)	47 (9.5)

*Includes "orthostatic heart rate response increased" and "postural orthostatic tachycardia syndrome"

Table 51: Laboratory Abnormalities of Mazzotti Reaction Experienced by >5% of Moxidectin-Treated Phase 3 Patients over 14-days Post Study Drug Administration

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Eosinophilia	623 (63.7)	312 (63.2)
Leukocytosis	219 (22.4)	103 (20.9)
Blood lactate dehydrogenase increased	160 (16.4)	89 (18)
Alanine aminotransferase increased	64 (6.5)	34 (6.9)
Thrombocytosis and platelet count increased	65 (6.6)	24 (4.9)
Gamma-glutamyltransferase increased	57 (5.8)	17 (3.4)
Aspartate aminotransferase increased	56 (5.7)	36 (7.3)
Lymphopenia	53 (5.4)	18 (3.6)

Reviewer Comment: Overall, there appears to be a trend of the increase in the rate of the physical sign/symptoms and changes in vital signs associated with Mazzotti reactions in the moxidectin as compared to ivermectin arm. Laboratory findings were comparable between the two arms except for GGT elevation, which appears to be more frequent in the moxidectin arm. The observed trends of higher rates of Mazzotti reaction in the moxidectin arm may be due to increased killing of microfilariae by moxidectin, resulting in increased inflammatory response.

Ocular Mazzotti Reactions

Overall, 188 patients (n=137 moxidectin, n=51 ivermectin) experienced signs/symptoms attributable to ocular Mazzotti reactions over 14 days post administration of study drugs. Ninety-two patients (n=63 moxidectin, n=29 ivermectin) did not have baseline ocular microfilariae. The ocular signs/symptoms that occurred in >2 moxidectin-treated patients over the 14-days are shown in **Table 52**.

Table 52: Ocular Mazzotti Reaction Experience in >2 Moxidectin-Treated Patients in the Phase 3 Trial During 14 Days Post-Administration of Study Drug

MedDRA Preferred Term	Moxidectin N=978 n (%)	Ivermectin N=494 n (%)
Eye pruritus	45 (4.6)	13 (2.6)
Eye pain	41 (4.2)	11 (2.2)
Eyelid edema	19 (1.9)	5 (1)
Ocular/conjunctival hyperemia	16 (1.6)	2 (0.4)
Foreign body/abnormal sensation in the eyes and ocular discomfort	11(1.1)	5 (1)
Vision blurred	6 (0.6)	4 (0.8)
Lacrimation increased	5 (0.5)	7 (1.4)
Conjunctivitis allergic	3 (0.3)	4 (0.8)
Visual impairment	3 (0.3)	1 (0.2)

Reviewer Comment: Slightly more patients in the moxidectin arm experienced eye pruritus, pain, eyelid edema, and hyperemia. It is notable that some of the patients that experienced ocular sign/symptoms did not have baseline ocular microfilariae. It may be that these patients had a low number of ocular microfilariae that were reported as none or it could be that the symptoms were due to post-treatment microfilariemia and subsequent eye involvement.

8.5.2. Subgroup Analysis by Body Mass Index (BMI)

As previously noted, moxidectin is a lipophilic drug, so review of adverse events by BMI was considered for subgroup analysis. However, since TEAEs occurred in almost all participants of the Phase 3 trial, analysis of the rates of TEAEs by BMI may not be informative and was not conducted. Instead, incidence of SAEs and deaths were looked at by baseline BMI.

Table 53: Phase 3 Serious Adverse Events and Deaths by Body Mass Index

	BMI <18.5 N=345 (M=233, I=112)	**BMI ≥18.5-25 N=1054 (M=694, I=360)**	**BMI ≥25 N=73 (M=51, I=22)**
SAE			
Moxidectin	16/233 (6.9)	39/694 (5.6)	5/51 (9.8)
Ivermectin	9/112 (8)	17/360 (4.7)	3/22 (13.6)
Death			
Moxidectin	2/233 (0.9)	6/694 (0.9)	0
Ivermectin	0/112 (0)	2/360 (0.6)	0

NOTE: The number of patients in each subcategory of BMI in each arm were used as denominators; M=moxidectin; I=Ivermectin

Reviewer Comment: It appeared that there was a higher percentage of SAEs in the BMI≥25 subgroup; however, a detailed look at the reported SAEs showed that 4 out of the 5 SAEs were malaria, unrelated to the study drugs. With such a small incidence of events, it is difficult to make conclusions about the effect of BMI on the incidence of SAEs.

8.5.3. Subgroup Analysis by Baseline Mean *O. volvulus* Microfilariae Density

Since all patients in the moxidectin arm and 99.5% of patients in the ivermectin arm had TEAEs, this subgroup analysis was not performed for TEAEs. **Table 54** shows the SAEs and deaths in the Phase 3 trial by baseline skin microfilariae count.

Table 54: Phase 3 Serious Adverse Events and Deaths by Baseline Microfilariae Count

Baseline *O. volvulus* microfilariae density (mf/mg of skin)	**<20**	**≥20 to <50**	**≥50 to <80**	**≥80**
SAE				
Moxidectin	14/296 (4.7)	38/444 (8.6)	7/157 (4.5)	1/80 (1.2)
Ivermectin	10/151 (6.6)	13/185 (7)	5/106 (4.7)	1/52 (1.9)
Death				

Baseline *O. volvulus* microfilariae density (mf/mg of skin)	<20	≥20 to <50	≥50 to <80	≥80
Moxidectin	1/296 (0.3)	7/444 (1.6)	0	0
Ivermectin	0	2/185 (1.1)	0	0

Reviewer Comment: It appears that patients with baseline skin microfilariae count between ≥20 to <50 mf/mg had the highest rate of SAE; again, this interpretation of the data is limited by a significant number of SAEs that appear unrelated to study drug (e.g. malaria).

8.5.4. Subgroup Analysis for Nervous System Adverse Events

Moxidectin binds to GABA receptors of helminths. Although the human GABA-receptors are protected by the blood-brain barrier, we looked at the incidence of nervous system adverse events. Summary of these events is presented in **Table 55**.

Table 55: Nervous System-related Adverse Events in the Phase 3 Trial

	Moxidectin N=978 n, %	Ivermectin N=494 n, %
Nervous system TEAEs	652 (66.7)	321 (65)
SAE	4 (0.4)	2 (0.4)
Death	1 (0.1)	1 (0.2)

The SAEs in the moxidectin arm were: loss of consciousness (n=1 on study day 25, n=1 on study day 111), left hemiplegia (n=1 on day 126) and headache (n=1 on day 286). The two SAEs in the ivermectin arm were post-traumatic neuralgia (n=1 on day 319) and diabetic ketoacidotic hyperglycemic coma and meningismus (n=1 on day 76).

Reviewer Comment: Of the 5507 nervous system related adverse events reported, majority were headache (n=3881), dizziness (n=561) and paresthesia (n=483). As shown in Table 29, 58% of moxidectin and 54 % ivermectin patients reported headache, and headache is part of Mazzotti reaction. Looking at the temporal relationship of the SAEs with the administration of moxidectin, only one of the four SAEs, loss of consciousness that occurred on day 25, appears possibly related to moxidectin.

8.5.5. Phase 3 Subgroup Analysis by baseline hepatobiliary disease

The rates of SAEs and deaths were evaluated among patients with baseline history of liver disease and/or baseline transaminases of >3X ULN. This analysis did not reveal any excess

serious adverse event in those with baseline liver abnormalities. Of note, this analysis was limited by the small number of SAEs observed in each treatment arm.

8.5.6. Phase 3 Subgroup Analysis by Baseline Renal Impairment

The creatinine clearance in the Phase 3 patients, as estimated by the Cockcroft-Gault equation, ranged from 47 to 89 mL/min. Since >99% of study participants in either arm experienced TEAE, there was no difference in the overall rate of TEAEs by creatinine clearance. The rates of SAEs and deaths among patients with baseline history of kidney disease and/or baseline creatinine clearance of<60ml/min did not reveal any excess serious adverse events and deaths in those with baseline kidney abnormalities; of note, this analysis was limited by the small number of SAEs and deaths observed in each treatment arm.

8.6. Safety Analyses by Demographic Subgroups

Subgroup analysis by race was not performed as the Phase 2 and Phase 3 trials took place in West Africa. In addition, subgroup analysis for TEAEs by demographic groups was not done as close to 100% of patient experienced TEAEs.

Table 56 and **Table 57** below present the SAEs and death by sex and age for the Phase 3 trial. Please not that these analyses are limited due to few SAEs and deaths that occurred in the trial.

Table 56: Serious Adverse Events and Deaths in the Phase 3 Trial by Sex

	Female Proportion (%)	Male Proportion, (%)
SAE		
Moxidectin	21/352 (6)	39/626 (6.2)
Ivermectin	17/179 (9.5)	12/313 (3.8)
Death		
Moxidectin	1/352 (0.3)	7/626 (1.1)
Ivermectin	2/179 (1.1)	0 (0)

SAE: All patients with at least one serious AE during the 12-month study period
Death: All patients who died during the 12-month study period

Reviewer Comment: Table 58 shows that there was no imbalance in SAEs between male and female patients; however, there was more death in males (1%) as compared to females (0.3%).

Table 57: Serious Adverse Events and Deaths in the Phase 3 Trial by Age Subgroup

	<18 years Proportion, (%)	≥18 to<30 years Proportion, (%)	≥30 to 65 years Proportion, (%)	≥ 65 years Proportion, (%)
SAE				
Moxidectin	0/53 (0)	9/228 (3.9)	42/614 (6.8)	9/83 (10.8)
Ivermectin	1/24 (4.2)	3/102 (2.9)	14/318 (4.4)	11/50 (22)
Death				
Moxidectin	0/53 (0)	0/228 (0)	7/614 (1.1)	1/83 (1.2)
Ivermectin	0/24 (0)	0/102 (0)	2/318 (0.6)	0/50 (0)

SAE: All patients with at least one serious AE during the 12-month study period
Death: All patients who died during the 12-month study period

Reviewer Comment: There were higher percentage of patients with SAEs in the ≥ 65 years age category; review of the SAEs show that a number of the reported SAEs (n=3 malaria, n=2 cellulitis, n=hepatic failure and cirrhosis after ingestion of herbal medicine) did not appear to be related to moxidectin. All the deaths occurred in patients >30 years of age.

8.7. Specific Safety Studies/Clinical Trials

This section is not applicable to this NDA.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

All the clinical studies of moxidectin used a single dose regimen. Over the 12-month follow-up period for Phase 3, there were 4 patients with adverse events of neoplasm/tumor (n=3 in moxidectin arm, n=1 ivermectin). Two moxidectin patients had skin papilloma and one had a mole on the left buttock. The ivermectin patient had a lipoma.

8.8.2. Human Reproduction and Pregnancy

Pregnant women were excluded from the moxidectin clinical trials. Patients who became pregnant after receiving the study drug were followed and information on the outcome of each pregnancy was collected. In total, there were 12 pregnancies during the Phase 2 and 3 trials (n=3 in Phase 2, n=9 in Phase 3). Of these, 8 occurred in moxidectin-treated patients, and 4 occurred in ivermectin-treated patients.

In the Phase 2 trial, three pregnancies occurred in patients treated with moxidectin, one each in the 2 mg, 4 mg, and 8 mg treatment arms. One pregnancy (moxidectin 2 mg) resulted in a healthy birth and two resulted in spontaneous abortions.

The following are brief narratives for the two spontaneous abortions:

- Patient (b) (6) received moxidectin 4 mg and conceived around Day 310 post dose. Spontaneous abortion occurred on Day 410.

- Patient (b) (6) received moxidectin 8 mg. After a negative pregnancy test at screening, this patient was administered depot medroxyprogesterone acetate on Day 11. A positive pregnancy test was recorded on Day 29 after the patient was 3 weeks with amenorrhea. Spontaneous abortion occurred on Day 34.

In the Phase 3 trial, three of the nine pregnancies occurred following maternal exposure to study drug, two in the moxidectin and one in the ivermectin arm (positive pregnancy test at Month 1 post dose). The two female patients in the moxidectin arm were not pregnant at the time of dosing and delivered at approximately 11 and 14 months post-dose administration. Three of the 6 pregnancies that resulted after paternal exposure were in the moxidectin arm. All pregnancies resulted in live births with no signs of birth defect or congenital abnormalities. Infant follow-ups between 11 months and 3 years post-birth showed normal development in all cases.

One Phase 1 study, Study 1002, evaluated breast milk excretion in lactating, non-breastfeeding women over 28 days. This study was a single center, open-label, non-randomized study. Twelve lactating women received a single 8 mg dose of moxidectin. The percentage of the 8 mg moxidectin dose excreted into the breast milk of healthy volunteers over 28 days was approximately 0.7 (±0.3) % of the 8mg dose. The mean absolute infant dose, assuming all the breast-milk collected was consumed, was 0.056 (±0.024) mg (8.73 ±3.17% of the maternal dose).

Reviewer Comment: Two of the tree pregnancies in the Phase 2 trial ended with spontaneous abortion. Temporally, the spontaneous abortion that occurred on day 410 post dose does not appear to be related to moxidectin, while the second spontaneous abortion that occurred on day 34 post dose occurred within the half-life of moxidectin; hence, it is not possible to rule out causality. The larger Phase 3 trial did not reveal any adverse association between moxidectin exposure and pregnancy outcome as all 5 pregnancies in the moxidectin arm resulted in live birth without congenital abnormalities. From study 1002, moxidectin appears to be minimally excreted in breast milk.

8.8.3. Pediatrics and Assessment of Effects on Growth

Seventy-seven adolescents (≥12 to 18 years) were included in the Phase 3 trial; fifty-three of

these patients were treated with moxidectin. From the safety and efficacy results, there does not appear to be any difference between the safety and efficacy of moxidectin in the adolescents as compared to adults; however, this interpretation should be made with caution as there were a small number of adolescents in the Phase 3 trial.

Moxidectin has a waiver from pediatric studies due to its orphan drug designation. (b) (4) [redacted].

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no overdose experiences with moxidectin in humans. Of note, the concentration QT study, study 1008, evaluated doses up to 36 mg. In that study, there were no increased adverse events in the higher dose (16 mg, 24 mg and 36 mg) groups as compared to the 4 mg and 8 mg dose cohorts. Of note, the adverse events seen with moxidectin are related to Mazzotti reaction, the immune response to dying microfilariae. Hence, tolerability of doses of up to 36 mg by healthy adults cannot be extrapolated to patients with onchocerciasis.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with moxidectin as it is a new molecular entity and has not been previously used in humans.

8.9.2. Expectations on Safety in the Postmarket Setting

All of the clinical studies of moxidectin evaluated a single administration of the drug. Hence, there is a paucity of safety data regarding repeat doses of moxidectin; if moxidectin were to be used in the same manner as ivermectin in semi-annual or annual mass drug administration for elimination of onchocerciasis, potential adverse effects of repeat doses are not known. Post-marketing study of repeated moxidectin dosing may be important in elucidating any safety issues associated with repeated dosing.

8.10. Integrated Assessment of Safety

In the Phase 2 and 3 trials, there were no major imbalances in serious adverse events and

deaths between moxidectin-treated and ivermectin-treated patients. Most of the TEAEs noted in the moxidectin-treated patients were related to Mazzotti reaction, immune response elicited by dying microfilariae. These reactions encompassed, among other symptoms, itching, rashes, muscle pains, fever, tender lymph nodes, hypotension, tachycardia, and eosinophilia. There were higher incidences of these reactions in the moxidectin- as compared to ivermectin-treated patients.

Of note, there was a higher incidence of symptomatic orthostatic hypotension, inability to stand without support after lying down for 5 minutes, in the moxidectin arm (4.8%) as compared to the ivermectin arm (1.6%). These adverse events were mainly seen in the first few days after moxidectin. Only two patients in the moxidectin arm required oral hydration and none of the patients required pharmacologic intervention. Most patients' symptoms of dizziness were ameliorated by recumbency.

There was also higher incidence of single measurement hyperbilirubinemia without concurrent elevation in transaminases in the moxidectin-treated patients (2.8%) when compared to ivermectin (0.6%). There was no clear mechanism for these single measurement hyperbilirubinemia. Since most occurred within the 3-month period after moxidectin, it is possible that it may be related to moxidectin administration.

Moxidectin, like ivermectin, is a microfilaricidal drug and does not kill the adult worm; hence, a single treatment with moxidectin will not be curative. Only a single dose of moxidectin was evaluated in the clinical studies. Hence, if moxidectin were to be used in similar fashion as ivermectin, including repeated mass drug administrations to reduce/eliminate onchocerciasis, the safety of repeat courses of moxidectin is not known. It may be important to assess the safety of repeat courses of moxidectin in the post-marketing setting.

In summary, moxidectin appears to have higher efficacy against *O. volvulus* as compared to ivermectin with no major safety concerns. It may provide an important addition to the onchocerciasis treatment armamentarium.

9. Advisory Committee Meeting and Other External Consultations

There was no Advisory Committee (AC) for this application. However, a special government employee (SGE) consult was sought from a physician with parasitology expertise. The two main questions presented to the SGE were the clinical relevance of the skin microfilariae density, the primary endpoint for both the Phase 2 and Phase 3 trial and the need for a repeat dose study of moxidectin. Please refer to section 6.1 for the discussion about the clinical relevance of the

primary endpoint of reduction in skin microfilariae.

The development program for moxidectin thus far only evaluated safety and efficacy of a single 8 mg dose. Given the microfilaricidal mechanism of action of moxidectin, a single dose will not be curative. If moxidectin were to be used in mass administration programs for eradication of onchocerciasis, multiple doses may be administered at some time interval. At this time, there is a paucity of safety and efficacy data for multiple dose of moxidectin. The SGE concurred with the agency's assessment that a repeat dose study of 8 mg moxidectin will be of utmost importance to fill in the current gap in assessing its "real world" safety and efficacy profile of moxidectin.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

APPEARS THIS WAY ON ORIGINAL

Based on the results of the safety review, the following two additions are recommended for the label:

1. Addition of warning regarding symptomatic orthostatic hypotension informing clinicians that dizziness and symptomatic orthostatic hypotension was reported at higher rate in the moxidectin arm as compared to ivermectin. This knowledge may enable clinicians educate their patients regarding these symptoms, when they occur and what they need to do ameliorate the symptoms.
2. Addition of information on a transient hyperbilirubinemia without concurrent transaminase elevation to the adverse reactions section. Although the mechanism for these elevations and their clinical significance is not clear, they were seen at higher proportion in the moxidectin arm as compared to the ivermectin arm and clinicians should be aware of these findings.

10.2. Nonprescription Drug Labeling

This section is not applicable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, there are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

12. Postmarketing Requirements and Commitments

As stated in section 9, there is a paucity of data regarding repeat dosing of moxidectin. To bridge the knowledge gap, the sponsor will be asked to conduct a prospective, randomized, ivermectin-controlled trial of repeated doses (b) (4) of 8mg moxidectin for control of onchocerciasis.

13. Appendices

13.1. References

Refer to footnotes in sections 2.1 and 2.2.

13.2. Financial Disclosure

Please refer to sections 6.2.2 and 6.3.2.

Covered Clinical Study (Name and/or Number): Phase 2 Trial (NCT00300768); Phase 3 Trial (NCT00790998)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

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/s/

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05/08/2018

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05/08/2018