CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Combined Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review

Date	Electronic stamp
From	Dmitri Iarikov, MD, PhD; Sumathi Nambiar, MD, MPH; John Farley, MD, MPH
Subject	Combined Cross-Discipline Team Leader, Division Director, and Deputy Office Director Summary Review
NDA #	210867
Applicant	Medicines Development for Global Health
Date of Submission	October 13, 2017
PDUFA Goal Date	June 13, 2018
Proprietary Name	Not proposed
Established or Proper Name	Moxidectin
Dosage Form	2 milligram (mg) oral tablet
Applicant Proposed Indication/Population	Treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older
Applicant Proposed Dosing Regimen	Single dose of 8 mg (four 2 mg tablets)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older
Recommended Dosing Regimen	Single dose of 8 mg (four 2 mg tablets)

Materials Reviewed/Consulted OND Action Package, including:	**Name of discipline reviewers**
Medical Officer Review	Hiwot Hiruy, MD, PhD
Statistical Review	Edward Bein, PhD
Pharmacology Toxicology Review	James Wild PhD
OPQ ATL Review	Dorota Matecka, PhD
Microbiology Review	Shukal Bala, PhD
Clinical Pharmacology Review	Yang He, PhD
OPDP	David Foss, PharmD, BCPS
OSI	John Lee, MD
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OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
ATL= Application Technical Lead
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The Applicant has provided substantial evidence of the safety and efficacy of moxidectin administered as a single 8 mg oral dose in the treatment of onchocerciasis, an infection caused by a nematode parasite *Onchocerca volvulus*. The efficacy of moxidectin was demonstrated in two adequate and well-controlled trials comparing moxidectin with ivermectin, the only FDA-approved treatment for onchocerciasis. In both trials, moxidectin was superior to ivermectin in decreasing the number *O. volvulus* microfilariae (a microscopic larval stage of the parasite) in the skin 12 months post-treatment. This was considered a meaningful measure of moxidectin efficacy with established clinical benefit because symptoms of onchocerciasis are caused by host inflammatory reactions to microfilariae in the infected tissues. Both trials also demonstrated that more moxidectin-treated patients had no microfilariae detected on skin examination 12 months post-treatment. This outcome is important because the absence of microfilariae in the skin may interrupt the transmission of the parasite and improve the control of onchocerciasis in endemic areas.

The rates of serious adverse events (SAEs) and deaths were balanced in moxidectin- and ivermectin-treated patients. The adverse events (AEs) reported in the moxidectin-treated patients were mostly related to symptoms and laboratory abnormalities caused by inflammatory reactions to dying microfilariae, known as Mazzotti reaction, which includes itching, rashes, muscle pains, fever, tender lymph nodes, hypotension, tachycardia, and eosinophilia. Mazzotti reaction was seen more frequently in the moxidectin- as compared to ivermectin-treated patients. A notable safety finding was a higher incidence of symptomatic orthostatic hypotension, defined as inability to stand without support after lying down for 5 minutes, in the moxidectin-treated patients.

Importantly, moxidectin is not active against adult *O. volvulus* worms which will continue to produce microfilariae after administration of moxidectin. Therefore, repeat dosing of moxidectin during the life-span of the parasite to control onchocerciasis will likely be needed. The Applicant agreed to a post-marketing commitment to conduct a prospective, randomized, ivermectin-controlled trial of repeated doses of moxidectin for control of onchocerciasis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Onchocerciasis is caused by *O. volvulus*, transmitted to humans by the black fly. Adult female worms reside in the subcutaneous nodules and produce microscopic larvae (microfilariae) that migrate through the skin and eye causing inflammatory reaction in these tissues. • Onchocerciasis affects 18 million people worldwide, mostly in sub-Saharan Africa, with a few additional foci in South America and the Middle East. • Onchocerciasis is the second-leading infectious cause of blindness after trachoma; 270,000 people are blind due to onchocerciasis. Another debilitating manifestation of onchocerciasis is severe itching and skin atrophy.	Onchocerciasis is a tropical infection that may lead to debilitating consequences with visual impairment being the most serious. Debilitating symptoms of onchocerciasis are caused by host inflammatory reactions to microfilariae in the infected tissues.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The only FDA-approved drug for the treatment of onchocerciasis is ivermectin. Ivermectin, which is considered the drug of choice for this disease, is active against microfilariae but does not kill adult *O. volvulus*. Subsequently, in endemic areas repeated, usually annual, administration of ivermectin is used over the life-span of the adult parasite, which may last up to 14 years. • Doxycycline may be used as an adjunct to ivermectin in non-endemic areas or in areas of low transmission. Doxycycline targets the endosymbiotic bacteria *Wolbachia* that are needed for survival and reproduction of adult *O. volvulus.* However, doxycycline is not used in areas of ongoing *O. volvulus* transmission because repeat 6-week treatment courses would be required.	Ivermectin is the only FDA-approved drug for the treatment of onchocerciasis. Additional treatment options are needed to expand treatment options for onchocerciasis.
Benefit	• Two adequate and well-controlled trials comparing moxidectin with ivermectin demonstrated superiority of moxidectin in decreasing the number of *O. volvulus* microfilariae in the skin. One trial was a randomized, double-blind trial that enrolled 1472 patients with onchocerciasis. Another trial was a smaller dose-ranging trial comparing 2 mg, 4 mg, and 8 mg single doses of moxidectin with ivermectin. The number of microfilariae in the skin was measured 12 months post-treatment and expressed as microfilarial skin density (microfilariae/mg skin). • Microfilarial skin density was considered a meaningful measure of moxidectin efficacy with established clinical benefit because symptoms of onchocerciasis are caused by inflammatory reaction to microfilariae in the infected tissues. • Both trials also demonstrated that more moxidectin-treated patients had no microfilariae detected on skin examination 12 months post-treatment. This efficacy outcome is important as in the absence of microfilariae in the skin, the parasite may not be taken up by the fly vector leading to interruption of the transmission of *O. volvulus* and improvement of the control of onchocerciasis in endemic areas.	Superiority of moxidectin over ivermectin, the standard of care of onchocerciasis, has been demonstrated in two adequate and well-controlled trials.
Risk and Risk Management	• The rates of SAEs and deaths were balanced in moxidectin- and ivermectin-treated patients. • Most common AEs noted in the moxidectin arm were related to Mazzotti reaction caused by inflammatory reactions to dying microfilariae. As compared to ivermectin, these AEs were seen at higher rates in moxidectin-treated patients and included, among others, itching, rashes, muscle pains, fever, tender lymph nodes, hypotension, and tachycardia. This information is provided in the Warning and Precautions section of the moxidectin label.	There are no safety issues requiring implementation of a Risk Evaluation and Mitigation Strategy (REMS) and routine postmarketing surveillance activities will suffice at this point. Labeling for the product adequately informs on the safety aspects of moxidectin use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Symptomatic orthostatic hypotension occurred more frequently in the moxidectin (5%) as compared to ivermectin (2%) treated patients. A warning recommending patients who feel dizzy or light-headed after taking moxidectin to lie down until the symptoms resolve is included in the moxidectin label. • Transient hyperbilirubinemia was more commonly observed after moxidectin as compared to ivermectin use. Elevations in bilirubin resolved without clinical sequelae and were not associated with concurrent elevation in transaminases in most patients. There is no clear explanation for these findings. Information on (b) (4) bilirubin elevation is provided in the Adverse Reactions section of the moxidectin label. • As moxidectin is not active against adult *O. volvulus,* a single treatment with moxidectin will not be curative and repeat administration of moxidectin may be expected. Given that only a single dose of moxidectin has been tested in clinical trials, the moxidectin label includes a limitation of use statement informing that the safety and efficacy of repeat administration of moxidectin have not been studied. The Applicant agreed to a postmarketing commitment (PMC) to conduct a prospective, randomized, ivermectin-controlled trial of repeated doses of moxidectin for control of onchocerciasis. • Moxidectin should not be used in patients co-infected with *Loa loa*, a nematode parasite transmitted in some geographical areas where onchocerciasis occurs, because it may result in fatal encephalopathy. The moxidectin label includes a warning recommending that individuals who may have been exposed to *L. loa* undergo diagnostic screening for loiasis prior to treatment with moxidectin.	Safety information on repeat administration of moxidectin will be collected in the study being conducted as a PMC.

2. Background

Moxidectin is a macrocyclic lactone of the milbemycin class derived from the actinomycete *Streptomyces cyanogriseus*. Moxidectin is used in veterinary medicine for treatment of various nematodes as well as larvae of parasitic flies. Moxidectin has not been approved for human use in any country. In this new drug application (NDA), the Applicant is seeking the indication of treatment of onchocerciasis in patients aged 12 years and older.

Onchocerciasis is caused by the filarial nematode *O. volvulus* which is transmitted to humans by black flies of the genus *Simulium*. During the bite the fly deposits infective larvae into the skin. The larvae develop into adult worms called macrofilariae. Adult females live in subcutaneous tissues where they form nodules while the males migrate between nodules to fertilize females, which then produce microfilariae, an early stage of the parasite. Microfilariae migrate through the skin, and after being ingested by the *Simulium* black fly during a blood meal mature to infective larvae, thereby completing the life cycle. The reproductive lifespan of *Onchocercae* is 9–11 years. Female worms measure about 50 cm in length and 0.4 mm in diameter and male worms are about 4 cm in length and 0.2 mm in diameter. Microfilariae measure about 0.3 mm by 0.009 mm and have a life span of about 1-2 years.

Clinical manifestations of the disease result from inflammatory reaction to microfilariae. Microfilariae migrate through the skin and eye and provoke minimal immune and inflammatory responses while alive; when they die, they cause inflammation in the surrounding tissues. In the eye, it results in keratitis, uveitis, optic atrophy, and chorioretinitis. Skin infection causes generalized itching, skin atrophy, and depigmentation.

Onchocerciasis afflicts approximately 18 million people of whom 99% live in rural areas of sub-Saharan Africa; onchocerciasis also occurs in Yemen, Mexico, Guatemala, Ecuador, Colombia, Venezuela, and Brazil. Over 6.5 million infected with onchocerciasis suffer from severe itching and dermatitis and 270,000 are blind, which makes the disease second only to trachoma as an infectious cause of blindness.

Onchocerciasis is diagnosed by skin biopsy when small (around 2 mm) skin snips are taken and incubated in normal saline at room temperature for 24 hours to allow the microfilariae to emerge and be identified microscopically.

The only approved drug for treatment of onchocerciasis is ivermectin, another macrocyclic lactone. Ivermectin is active against microfilariae but not against adult *Onchocercae*. Subsequently, treatment is usually repeated to reduce microfilarial burden as well as transmission of onchocerciasis. The most commonly used dose interval in treatment programs is 12 months.

In addition to ivermectin, doxycycline has been used in the treatment of onchocerciasis. Doxycycline causes death of the adult worms by targeting the endosymbiotic bacteria *Wolbachia* that are needed for survival and reproduction of *O. volvulus*. A 6-week course is

commonly used. Doxycycline, however, is not used in areas of ongoing *O. volvulus* transmission because repeated treatment courses would be required.

Moxidectin acts on microfilariae and is not directly active against adult worms. It is hypothesized that moxidectin inhibits microfilarial motility and pharyngeal pumping, functions required for survival of micro- but not macrofilariae. It appears, however, that moxidectin affects macrofilarial fertility thereby indirectly reducing microfilarial burden. Moxidectin should not be used in patients co-infected with *L. loa*, a nematode parasite transmitted in some geographical areas where onchocerciasis occurs, because it may result in fatal encephalopathy.

The development of moxidectin for treatment of onchocerciasis was initiated in 1999 by Wyeth Research in collaboration with the World Health Organization/Special Programme for Research and Training in Tropical Diseases (WHO/TDR). In September 2010, moxidectin for the treatment of onchocerciasis was designated an orphan drug. In 2011, WHO/TDR assumed sole sponsorship of moxidectin; in June 2014, Medicines Development for Global Health (MDGH) assumed sponsorship from WHO/TDR. Investigational new drug (IND) application for moxidectin was filed in November 2016. NDA for moxidectin was submitted on October 13, 2017.

The moxidectin clinical program includes six phase1 studies in 260 adult healthy volunteers of whom 244 received moxidectin, a phase 2 trial in patients with onchocerciasis where 127 adult patients received moxidectin and 45 patients received ivermectin, and a phase 3 trial in patients aged ≥ 12 years where 978 patients received moxidectin and 494 received ivermectin.

3. Product Quality

Dorota Matecka, PhD, is the Application Technical Lead (ATL) for this NDA.

Drug Substance
The chemistry manufacturing and controls (CMC) information for moxidectin drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4) The DMF was reviewed and found to be acceptable. Available stability data support a retest period of (b) (4) months for moxidectin drug substance stored at (b) (4)

Drug Product
The drug product, moxidectin tablet, is an immediate release, uncoated, white to pale yellow, oval shaped tablet debossed with 'AKKA' on one side. Each tablet contains 2 mg of (b) (4) moxidectin and the following inactive ingredients: anhydrous lactose, sodium croscarmellose, microcrystalline cellulose, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate, all of which meet compendial standards.

The commercial drug product packaging container closure system consists of a 120-cc white polyethylene bottle with (b) (4) closure, induction seal liner, (b) (4) pharmaceutical coil (b) (4) and a 1 gram silica gel (desiccant sachet). Each bottle contains

500 tablets. The proposed container closure system was found to be safe and suitable for the proposed drug product. Provided stability data support the proposed expiry dating of 12 months for moxidectin tablets to be stored below 30°C (86°F).

The biopharmaceutics review found the proposed dissolution method and acceptance criterion acceptable. The review of the application and inspectional documents for all manufacturing sites listed in this NDA determined that there are no manufacturing or testing facility risks that prevent approval of this application.

The Office of Pharmaceutical Quality (OPQ) recommends approval of NDA 210867. No CMC-related Post-Marketing Commitments (PMCs) are proposed. We agree with the OPQ review team's assessment.

4. Nonclinical Pharmacology/Toxicology

James Wild, PhD, is the pharmacology/toxicology reviewer for this NDA.

The primary moxidectin-related toxicity in test animals is dose-dependent transient central nervous system (CNS) toxicity. The toxicity occurred with single and repeated doses in mice, rats, and dogs and manifested by piloerection, reduced arousal, tremors, abnormal gait, irregular or slowed breathing, and impaired righting reflex in rodents, and lacrimation, languid appearance, tremors, salivation and slight ataxia in dogs. The effects were transient and not accompanied by correlating histopathology after repeated moxidectin dosing suggesting that permanent structural or functional sequelae are not expected.

CNS-related clinical signs were observed at moxidectin doses 6-10-fold higher than the 8 mg dose in humans based on body surface area comparison. The reviewer notes that the safety of the recommended clinical dose of moxidectin for CNS toxicity is supported by data in clinical trials where CNS-related adverse events other than headache have not been reported.

Moxidectin was assessed in long-term studies with durations of 1-month (all species), 3 months (rats and dogs), and 1-year (dogs). Decreased food consumption and decrease in body weights were the main toxicities observed. Of note, animals resumed normal eating patterns and gained weight upon dosing cessation.

In a full battery of *in vitro* and *in vivo* genotoxicity studies, moxidectin was negative for mutagenicity and clastogenesis. Moxidectin was also tested in 2-year carcinogenicity studies in mice and rats, and a preliminary review of these studies suggests that moxidectin did not stimulate tumor formation. A comprehensive review of the carcinogenicity studies awaits electronic submission of revised tumor-tabulation tables necessary for a new statistical analysis.

In a male and female fertility study in rats, moxidectin did not impair any fertility or pregnancy indices. Moxidectin administered orally to pregnant rats during the period of organogenesis (Gestation Days (GD) 6 to 15), was not associated with significant embryo-fetal developmental effects at doses of approximately 15 times the recommended human dose based

on body surface area. When moxidectin was dosed orally to pregnant rabbits during the period of organogenesis (GD 7 - 19), no embryo-fetal developmental effects were observed at oral doses of moxidectin up to 24 times the recommended human dose based on body surface area.

Range-finding and definitive pre-postnatal studies with moxidectin were conducted approximately 30 years ago. The results of these studies indicate that moxidectin at a dose approximately equivalent to the recommended clinical dose based on body surface area comparison did not inhibit survival or fertility or reduce body weights in the parental generation or in first and second generation offspring. However, beginning at a slightly higher dose, approximately 1.3 times the recommended clinical dose, the survival and body weights of first generation offspring were decreased during the lactation period, and at a dose approximately equivalent to 13 times the recommended clinical dose, fetal viability at birth was decreased. The results of the current pre-postnatal studies are considered sufficient to support approval of NDA 210867. However, in these studies, physical development and neurological function were not assessed in the first-generation offspring as recommended in the ICH S5a Guidance. A new pre-postnatal study which will include the assessments missing in the previously conducted studies will be conducted as a postmarketing requirement (PMR). Until the final study report for the new study has been evaluated, Section 8.1 of the moxidectin label will state: "offspring were only assessed for survival, body weights, and fertility; developmental milestones were not assessed in this study."

Dr. Wild recommends approval of this NDA and we agree with his assessment.

5. Clinical Pharmacology

Yang He, PhD, is the clinical pharmacology reviewer for this NDA.

Maximum plasma concentration (C_{max}) of moxidectin is reached within approximately 4-5 hours after oral administration. A standard high fat meal (900 calories) increases moxidectin C_{max} and the area under the concentration-time curve (AUC) by 34% and 39%, respectively, as compared to fasted conditions. This increased absorption with a high fat meal did not result in exposures that are concerning from a safety perspective. In patients with onchocerciasis and healthy volunteers, the mean apparent volume of distribution of moxidectin ranges from 2000 to 3000 L. In the healthy female volunteers, the percentage of the 8 mg moxidectin dose excreted into the breast milk over 28 days was approximately 0.70% (approximately 0.06 mg).

The mean terminal half-life following the 8 mg moxidectin dose is approximately 23 days in patients with onchocerciasis and approximately 20 to 47 days in healthy volunteers. Moxidectin is minimally metabolized by cytochrome P450 (CYP). There is no evidence for non-CYP-mediated metabolism of moxidectin, including glucuronidation. Renal elimination of intact drug is negligible. Following a single 8 mg oral dose of moxidectin, 2% of the dose is eliminated unchanged in feces within the first 72 hours.

Moxidectin is not a substrate of CYP450 enzymes, uridine 5'-diphosphoglucuronosyltransferases, the drug transporter P-glycoprotein, and is not an inhibitor

of CYP450 in vitro. It induced CYP3A4 in vitro but there was no in vivo drug-drug interaction between moxidectin and the CYP3A4 substrate, midazolam, in healthy subjects.

No clinically significant differences in the pharmacokinetics of moxidectin were observed based on age (18 to 60 years), sex, or weight. Based on a population pharmacokinetic analysis and negligible renal elimination of moxidectin, no dose adjustment is necessary in patients with creatinine clearance ≥ 30 mL/min. The pharmacokinetics of moxidectin in patients with CrCL < 30 mL/min or with end-stage renal disease is unknown. The pharmacokinetics of moxidectin in patients with hepatic impairment is also unknown.

In a thorough QT study, a dose of 36 mg (4.5 times the recommended dose), moxidectin did not prolong the QT interval to any clinically relevant extent.

The Office of Clinical Pharmacology review team recommends approval of this NDA from a clinical pharmacology perspective. We agree with their assessment.

6. Clinical Microbiology

Shukal Bala, PhD, is the clinical microbiology reviewer for this NDA.

The exact mechanism of action of moxidectin against *O. volvulus* is not known. Studies with other nematodes suggest that moxidectin binds to glutamate-gated chloride channels (GluCl), gamma-aminobutyric acid (GABA) receptors and/or ATP binding cassette (ABC) transporters. This leads to increased permeability, influx of chloride ions, hyperpolarization and muscle paralysis. Additionally, there is a reduction in motility of all stages of the parasite, excretion of immunomodulatory proteins, and the fertility of both male and female adult worms.

Moxidectin is active against the microfilariae of *O. volvulus* and is not effective in killing the adult worms. However, it inhibits intra-uterine embryogenesis and release of microfilariae from the adult worms. No studies have reported the activity of moxidectin against the infective larvae of the *Onchocerca* species in experimentally infected rodents.

Studies *in vitro* and infected animals suggest a potential for development of resistance to moxidectin and cross-resistance with other macrocyclic lactones, such as ivermectin. The mechanism of resistance may be multifactorial including alteration in the target GluCl, GABA receptors and/or ABC transporters. The clinical relevance of these findings is not known.

The parasitological assessments in the moxidectin phase 2 and 3 clinical trials included measurement of microfilariae density in the skin and eye. Skin microfilariae were counted directly in the wells of the microtiter plates containing skin snips after overnight incubation in an isotonic solution. The entire well was examined using an inverted microscope. Ocular microfilariae count was performed by an ophthalmologist using a slit lamp. Appropriate training and quality control measures were implemented. Section 7 of the Clinical Microbiology review provides more detail regarding parasitological assessments in the moxidectin efficacy studies.

Dr. Bala recommends approval of this NDA from a clinical microbiology perspective and we agree with her recommendation.

7. Clinical/Statistical- Efficacy

Hiwot Hiruy, MD, PhD, is the clinical reviewer, and Edward Bein, PhD, is the statistical reviewer for this NDA.

The efficacy of moxidectin in the treatment of onchocerciasis is supported by data from two randomized, double-blind trials comparing a single dose of moxidectin with ivermectin. Both trials were conducted in sub-Saharan Africa. Efficacy assessment was based on measurements of skin microfilarial density (the number of microfilariae per milligram of skin (mf/mg)) calculated as the mean of 4 skin snips sampled at 4 body sites (right and left iliac crests, right and left calves) per person per time point.

The question of the acceptability of skin microfilarial density as the primary efficacy endpoint was specifically examined during the review. Based on the current knowledge of the pathophysiology of onchocerciasis, the prior experience of using this endpoint in the ivermectin trials, as well as discussions with an expert in the field who was consulted as a special government employee during the review of the NDA , skin microfilarial density was considered an acceptable endpoint to measure improvement or resolution of onchocerciasis and assess clinical benefit of moxidectin because symptoms of onchocerciasis are caused by inflammatory reaction to microfilariae in the infected tissues.

The initial trial was a phase 2 dose-ranging trial (NCT 00300768) comparing 2 mg (n = 44), 4 mg (n = 45), and 8 mg (n = 38) single doses of moxidectin with ivermectin 150 mcg/kg (n=45). The trial was conducted from 2006 to 2009 in Ghana in adults aged ≥ 18 to ≤ 60 years. Reduction in skin microfilarial density from baseline was measured at 1, 6, 12, and 18 months post-treatment. Following the first month of treatment, skin microfilarial densities were significantly lower in the moxidectin- as compared to ivermectin-treated patients at any dose except for moxidectin 2 mg at month 18. At month 12, the comparison in the change in skin microfilarial density showed superiority of the proposed moxidectin 8 mg dose over ivermectin with $p < 0.001$. A trend towards improved efficacy of moxidectin 8 mg as compared to moxidectin 2 mg or 4 mg was also observed.

The second trial (NCT 00790998) compared single doses of moxidectin 8 mg and ivermectin 150 mcg/kg. This Phase 3 trial was conducted from 2009 to 2012 at 4 clinical sites, one in Ghana, two in the Democratic Republic of Congo (DRC) and one in Liberia. The trial enrolled 1472 patients randomized in a 2:1 ratio to moxidectin (n=978) and ivermectin (n=494). The patients were to be ≥ 12 years of age, weigh ≥ 30 kg and had ≥ 10 mf/mg skin microfilarial density.

Efficacy assessments were to be performed at months 1, 6, 12 and 18 (the protocol was later amended to remove the 18-month assessment). The primary endpoint was the skin microfilarial density at 12 months after the administration of study drug.

Baseline demographic characteristics in the trial were overall comparable. Mean (± SD) age was 42.5 (± 16.3) years, height 1.59 (± 0.09) meters, weight 51.6 (± 8.2) kg; 36.1% were female and 100% were black. Mean (± SD) pretreatment skin microfilarial density was 39.5 (± 30.7), 69.6% had ≥ 20 microfilariae/mg skin and 39.7% had at least one ocular microfilaria.

For the primary efficacy endpoint of skin microfilarial density at 12 months post-treatment, moxidectin was significantly superior to ivermectin; on average 8 fewer microfilariae per mg skin were detected after the use of moxidectin as compared to ivermectin with a 95% confidence interval of -9.11, -6.98 and p<0.0001, Table 1. The superiority for the skin microfilarial density endpoint was also demonstrated at 1 and 6 months post-treatment, p<0.0001.

Moxidectin was also superior to ivermectin for the endpoint of the percentage of patients with undetectable microfilariae at months 1, 6, and 12, p<0.0001 at each time point. For instance, at 12 months 40.4% more patients had undetectable microfilariae after the use of moxidectin as compared to ivermectin with a 95% confidence interval of 36.7-44.1, Table 1.

Table 1: Mean Microfilarial Density and Percentage of Undetectable Microfilariae in Skin of *O. volvulus* Patients at Months 1, 6, and 12 in Phase 3 Trial

Endpoint	Moxidectin N=977	Ivermectin N=495	Difference (95% Confidence Interval)
1 month			
Mean Microfilarial Density [a]	0.10	2.30	-2.20 (-2.83, -1.58) p < 0.0001
% Undetectable Microfilariae [b]	83.4%	42.9%	40.5% (35.7, 45.3) p < 0.0001
6 months			
Mean Microfilarial Density	0.14	3.71	-3.57 (-4.11, -3.03) p < 0.0001
% Undetectable Microfilariae	91.0%	11.5%	79.6% (76.3, 82.9) p < 0.0001
12 months			
Mean Microfilarial Density	1.79	9.83	-8.04 (-9.11, -6.98) p < 0.0001
% Undetectable Microfilariae	45.9%	5.4%	40.4% (36.7, 44.1) p < 0.0001

[a] Microfilarial density is microfilariae count/mg skin. Mean microfilarial density in skin is the average microfilarial density over skin snips from four sites.
[b] Proportion of subjects undetectable (defined as a mean skin microfilariae density of zero across all 4 skin snips).
Source: FDA Statistical Review, adapted from Tables 6 and 7

The FDA statistical reviewer also conducted "worst case scenario" sensitivity analyses where missing endpoint values in the moxidectin arm were substituted with the participant's baseline value, indicative of treatment failure, whereas missing endpoint values in the ivermectin arm

were substituted with zero, indicative of complete treatment success. These sensitivity analyses yielded statistically significant results in favor of moxidectin over ivermectin, p<0.0001, Table 2.

Table 2: Mean Microfilarial Density and Percentage of Undetectable Microfilariae in Skin of *O. volvulus* Patients at Months 1, 6, and 12 in Phase 3 Trial, "Worst Case" Analysis [a]

Endpoint	Moxidectin N=977	Ivermectin N=495	Difference (95% Confidence Interval)
1 month			
Mean Microfilarial Density [b] "Worst Case" Analysis	0.31	2.29	-1.98 (-2.64, -1.32) p < 0.0001
% Undetectable Microfilariae [c] "Worst Case" Analysis	83.0%	43.2%	39.8% (35.0, 44.7) p < 0.0001
6 months			
Mean Microfilarial Density "Worst Case"	0.55	3.70	-3.15 (-3.76, -2.54) p < 0.0001
% Undetectable Microfilariae "Worst Case" Analysis	89.8%	11.6%	78.2% (74.8, 81.5) p < 0.0001
12 months			
Mean Microfilarial Density "Worst Case" Analysis	2.56	9.58	-7.02 (-8.12, -5.91) p < 0.0001
% Undetectable Microfilariae "Worst Case" Analysis	44.5%	7.8%	36.8% (33.0, 40.6) p < 0.0001

[a] Missing endpoint values in the moxidectin arm are filled in with the participant's baseline value whereas missing endpoint values in the ivermectin arm are were filled with zero.
[b] Microfilarial density is microfilariae count/mg skin. Mean microfilarial density in skin is the average microfilarial density over skin snips from four sites.
[c] Proportion of subjects undetectable (defined as a mean skin microfilariae density of zero across all 4 skin snips).
Source: FDA Statistical Review, adapted from Tables 6 and 7

The reduction in ocular microfilariae was also evaluated. This analysis was conducted in patients with the sum of microfilariae in the anterior chambers of both eyes > 10 at baseline. At month 12 post-treatment, both moxidectin and ivermectin reduced ocular microfilariae count by 98% with no statistical difference between treatment arms.

Dr. Bein concludes that moxidectin was significantly superior to ivermectin in both clinical trials and recommends approval of moxidectin for the treatment of onchocerciasis. Dr. Hiruy also concludes that the Applicant provided substantial evidence of the efficacy of moxidectin for the treatment of onchocerciasis. We agree with their assessment.

8. Safety

Hiwot Hiruy, MD, PhD, is the clinical reviewer for this NDA.

A total of 1349 subjects received a single dose of moxidectin during the moxidectin development program, including 244 healthy volunteers who received moxidectin at doses ranging from 3 mg to 36 mg in pharmacokinetics (n=5) and a thorough QT study, and 1105 patients with onchocerciasis in the phase 2 (n=127) and the phase 3 trial (n=978). A total of 1016 patients (38 in phase 2 and 978 in phase 3) received the proposed 8 mg dose of moxidectin.

In the phase 1 studies there were no deaths or SAE. The most commonly reported AEs included headache, rhinitis, flu syndrome, and nausea with no apparent relation to the dose administered and the rates were similar to placebo. It should be noted that Mazzotti reaction did not occur in phase 1 studies as these studies enrolled healthy volunteers.

Due to different safety assessment schedules in the phase 2 and phase 3 trials, the trials were analyzed separately. In the phase 2 trial one death was reported. A patient in the moxidectin 2 mg arm died of snake bite on day 310 post-treatment. The were no discontinuations due toAEs in the trial. There were 8 patients who experienced at least one SAE, 5 in the moxidectin 2 mg, 1 in the moxidectin 4 mg, and 2 in the moxidectin 8 mg arm. No patients in the ivermectin arm had SAEs. None of the SAEs in the moxidectin arms was deemed related to study drug; most of the SAEs were related to infections such as malaria, typhoid fever, and pneumonia. No correlation between the rate of SAEs and the dose of moxidectin was noted.

Treatment emergent adverse events (TEAEs) were observed in 43/44 patients in the moxidectin 2 mg arm, 45/45 patients in the moxidectin 4 mg arm, 37/38 patients in the moxidectin 8 mg arm, and 45/45 patients in the ivermectin arm. AEs related to Mazzotti reaction such as pruritus, postural orthostatic tachycardia syndrome and orthostatic hypotension occurred at higher rates in patients treated with any dose of moxidectin as compared to ivermectin. In moxidectin-treated patients, the rates of TEAEs increased with the dose of the drug. Table 3 presents selected TEAEs in the phase 2 trial (of note, laboratory abnormalities were not reported as AEs in the phase 2 trial).

Table 3: Selected Treatment Emergent Adverse Events in the Phase 2 Trial

Adverse Event	Moxidectin			Ivermectin N=45 n (%)
	2 mg N=44 n (%)	4 mg N=45 n (%)	8 mg N=38 n (%)	
Pruritus/generalized pruritus	23 (52)	36 (80)	33 (878)	29 (64)
Rash	18 (41)	24 (53)	24 (63)	19 (42)
Postural orthostatic tachycardia Syndrome	21(48)	14 (31)	24 (63)	16 (36)
Orthostatic hypotension	8 (18)	13 (29)	23 (60)	12 (27)
Lymphadenitis/lymph node pain	9 (20)	16 (36)	20 (53)	10 (22)

Source: FDA Clinical Review, adapted from Table 27

The safety analyses in this NDA are primarily based on the phase 3 trial where 978 patients treated with the proposed moxidectin dose of 8 mg were compared with 494 patients treated with ivermectin. Patients were assessed for safety daily for 4 days, at days 6 and 14 and at

months 1, 3, 6, 12 and 18 after study drug administration (the protocol was later amended to remove the 18-month assessment).

Dr. Hiruy defined TEAEs as AEs reported during 12 months post-treatment whereas the Applicant's definition included events reported during 180 days post-treatment. Given that moxidectin is a lipophilic drug and may be present in tissues beyond 180 days, in Dr. Hiruy notes that believed a longer period for TEAEs assessments is warranted.

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. Ten deaths occurred during the 12-month follow-up period and 4 more deaths occurred by month 18. Dr. Hiruy noted that the deaths appeared to be related to co-morbidities and concurrent infections rather than to study drug. No patients withdrew from the trial due to AEs related to study drug.

SAEs occurred in 6.1% of patients in the moxidectin and in 5.9% of patients in the ivermectin arm. Approximately 4% of the SAEs were related to infections, mostly to malaria. No SAEs were deemed to be related to study drug.

Most common TEAEs in the Phase 3 trial were related to Mazzotti reaction and these TEAEs, except for eosinophilia, occurred at higher rates in the moxidectin arm. Table 4 presents most common TEAEs reported in the trial

Table 4: Selected Treatment Emergent Adverse Events in the Phase 3 Trial

Adverse Event	**Moxidectin N=978 n (%)**	**Ivermectin N=494 n (%)**
Eosinophilia	721 (74)	390 (79)
Pruritus	640 (65)	268 (54)
Musculoskeletal pain	623 (64)	257 (52)
Headache	566 (58)	267 (54)
Lymphocytopenia	470 (48)	245 (44)
Tachycardia	382 (39)	148(30)
Rash	358 (37)	103 (21)
Hypotension including	289 (30)	125 (25)
Orthostatic hypotension	212 (22)	81 (16)
Pyrexia/Chills	268 (27)	68 (18)
Lymph node pain	129 (13)	28 (6)

Source: FDA Clinical Review, adapted from Table 30

Ocular AEs were reported at similar rates in both treatment arms including eye pain in 8% and 6%, eye pruritus in 7% and 5%, visual impairment in 3% and 2%, eyelid edema in 2% and 1%, ocular discomfort in 2% and 2%, ocular and conjunctival hyperemia in 2% and 1% and increased lacrimation in 1% and 2% in the moxidectin and ivermectin arms, respectively.

Forty-seven (5%) patients in the moxidectin arm as compared to 8 (2%) patients in the ivermectin arm developed symptomatic orthostatic hypotension. Blood pressure readings were

taken after lying for ≥ 5 min as well as standing for 2 minutes. The decreases in blood pressure most commonly occurred during first 2 days post-treatment, were transient, and managed by resumption of recumbency.

Twenty-seven (2.8%) patients in the moxidectin arm as compared to 3 (0.6%) patients in the ivermectin arm experienced elevation in bilirubin above the upper limit of normal. Out of 27 patients, 24 had isolated hyperbilirubinemia without concurrent elevation in transaminases and 14 had a single bilirubin elevation during the study. Bilirubin elevations occurred at various timepoints; in 17 patients they were reported by month 3 visit. Fifteen patients had at least 1 point drop in hemoglobin level at the time of hyperbilirubinemia. One patient was diagnosed with malaria at the time of bilirubin elevation. Elevations in bilirubin resolved without clinical sequelae. No explanation for these findings is apparent. Notably, the assessment of hyperbilirubinemia was limited because only total, rather than fractionated bilirubin values were reported.

Nine (1%) patients in the moxidectin and 2 (0.4%) patients in the ivermectin arm had elevation in ALT of more than 5 times upper limit of normal; ten (1%) patients in the moxidectin and 3 (0.6%) patients in the ivermectin arm had elevation in AST to more than 5 times upper limit of normal. Transaminase elevations either resolved or improved in the majority of patients over the follow-up period.

Otherwise, there were no notable differences in hematological and biochemistry laboratory findings in the Phase 3 trial.

In the Phase 3 trial the safety of moxidectin in 53 pediatric patients aged 12 to 17 years and 83 patients older than 65 years was similar to that observed in the remainder of the trial population.

We agree with Dr. Hiruy's assessment that the Applicant has provided sufficient evidence of safety of a single 8 mg dose of moxidectin in the treatment of onchocerciasis in patients aged 12 years and older. The Prescribing Information will include Warnings regarding the risks of Mazzotti reaction, symptomatic orthostatic hypotension, encephalopathy in patients co-infected with *Loa loa*, and worsening of onchodermatitis in patients with hyper-reactive onchodermatitis. This information will also be included in the Patient Counseling Information section of the label.

9. Advisory Committee Meeting

Thee NDA was not discussed at an advisory committee meeting as there were no specific issues requiring input from the committee.

10. Pediatrics

The Applicant is exempt from the requirements described under the Pediatric Research Equity Act because moxidectin has an orphan drug designation for the treatment of onchocerciasis.

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safety and efficacy of moxidectin were evaluated in the phase 3 trial in 53 pediatric patients aged 12 to 17 years.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits

John Lee, MD is the OSI reviewer for this NDA. A clinical investigator and the World Health Organization Special Program for Research and Training in Tropical Diseases (WHO-TDR) which provided continued program support as a contract research organization (CRO) to the Applicant, were inspected. The clinical investigator was selected for inspection because he was the principal investigator for the Phase 2 trial and the principal investigator for one of the four clinical sites in the Phase 3 trial. Inspection feasibility was also considered due to travel restriction to other African sites.

Dr. Lee notes that for both inspections, the establishment inspection report (EIR) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. If new significant findings are discovered at completion of the EIR, an addendum will be provided. The preliminary classification of the inspection outcome is Voluntary Action Indicated (VAI) for the investigator and No Action Indicated (NAI) for the CRO. Evidence of serious deficiencies indicative of unreliable study data was not observed and study conduct otherwise appeared Good Clinical Practice compliant. All audited NDA data were verifiable against source records and case report forms and are considered acceptable to support the NDA.

12. Labeling

Recommendations from reviewers from OPDP and DMEPA were incorporated into labeling. No proprietary name was proposed in the NDA.

A warning informing health care providers on the possibility of orthostatic hypotension after the administration of moxidectin and recommending to advise patients who feel dizzy or light-headed after taking moxidectin to lie down until the symptoms resolve is included in the moxidectin label.

The label also includes a warning recommending that individuals who have had exposure to *L. loa*-endemic areas undergo diagnostic screening for loiasis prior to treatment with moxidectin due to risk of encephalopathy, and a warning regarding the risk of worsening of onchodermatitis in patients with hyper-reactive onchodermatitis.

In addition, the label includes a limitation of use statement informing that moxidectin does not kill adult *O. volvulus* parasites and that the safety and efficacy of repeat administration of moxidectin in patients with *O. volvulus* have not been studied.

13. Postmarketing Recommendations

Joyce Weaver, PharmD, the Division of Risk Management (DRISK) reviewer notes that a REMS is not necessary to ensure that the benefits of moxidectin outweigh its risks. Labeling, routine pharmacovigilance, and postmarketing requirements and commitments are considered adequate to address the safety issues at this time.

The Applicant has agreed to the following postmarketing requirement:

3367-1: Conduct a standard GLP pre-postnatal toxicity study in the rat with orally administered moxidectin that includes maternal evaluations and assessment of physical development, neurological function, maturation, and fertility in first-generation offspring.

Final Protocol Submission: 06/2019
Study Completion: 11/2019
Final Report Submission: 08/2020

The Applicant has also agreed to the following postmarketing commitment:

3367-2: Conduct a prospective, randomized, ivermectin-controlled trial of repeated doses of 8 mg moxidectin for control of onchocerciasis.

Final Protocol Submission: 02/2019
Trial Completion: 08/2023
Final Report Submission: 03/2024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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06/13/2018

SUMATHI NAMBIAR
06/13/2018

JOHN J FARLEY
06/13/2018