CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210867Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	May 31, 2018
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Kristine Park, Ph.D., Regulatory Project Manager Hiwot Hiruwy, M.D., Ph.D., Medical Officer Dmitri Iarikov, M.D., Ph.D., Clinical Team Leader Sumati Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 210867
Applicant	Medicines Development for Global Health (MDGH)
Drug	Moxidectin (trade name pending)
NME	Yes
Review Status	Priority
Proposed Indication	Treatment of ochocerciasis due to Onchocerca volvulus
Consultation Date	December 15, 2017
CIS Goal Date	June 1, 2018
Action Goal Date	June 13, 2018
PDUFA Due Date	June 13, 2018

I. OVERALL ASSESSMENT OF FINDINGS

Studies 3110A1-200-GH and 3110A1-3000-AF/ONCBL60801 were audited at good clinical practice (**GCP**) inspections of a clinical investigator (**CI**) and a contract research organization (**CRO**). 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.

Both inspections revealed significant GCP deficiencies, typically (apparently) deficiencies in recordkeeping (Form FDA 483 issued at CI inspection, not issued at CRO inspection). Evidence of serious deficiencies indicative of unreliable study data was not observed and study conduct otherwise appeared GCP-compliant. All audited NDA data were verifiable against source records and CRFs and are considered acceptable for review.

II. BACKGROUND

Medicines Development for Global Health (**MDGH**) proposes moxidectin for the treatment of onchocerciasis (river blindness), a parasitic disease endemic to remote areas in sub-Saharan Africa, Arabian Peninsula, and limited regions in the Americas where infrastructure and health care is severely restricted. Moxidectin is a semisynthetic broad-spectrum veterinary drug used globally to control nematodes and arthropods in livestock (currently not approved for human use).

MDGH (Melbourne, Australia) assumed sponsorship of developing moxidectin for human use in 2014. World Health Organization Special Program for Research and Training in Tropical Diseases (**WHO-TDR**) provided continued program support as a contract research organization (**CRO**) to MDGH. Studies 3110A1-200-GH (Phase II) and 3110A1-3000-AF/ONCBL60801 (Phase III) were identified for on-site audit at GCP inspections of WHO-TDR and one CI site.

Study 3110A-200-GH

A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind, Safety, Tolerability, Pharmacokinetic, and Efficacy Study of Orally Administered Moxidectin in Subjects with Onchocerca volvulus Infection

This randomized, double-blind, active-controlled Phase 2 study was conducted over three years (2006-9) in 172 subjects with Onchocercus volvulus (**O. volvulus**) infection at a single CI site in Hohoe, Ghana. Onchocerciasis Chemotherapy Research Center (**CRC**) established by WHO-TDR (with Ghanan Ministry of Health) served as the sole CI site. The primary study objective was to determine the safety and tolerability of oral moxidectin for onchocerciasis, based on laboratory testing and adverse events (**AEs**).

Subjects with O. volvulus infection but otherwise in good health were enrolled into 9 (3x3) cohorts, consisting of three moxidectin dose groups (randomization in equal ratio, 2/4/8 mg) for each of the following categories of total body microfilarial load (randomization in 1/1/2 ratio): (1) 1-9 microfilariae/mg skin; (2) 10-20 microfilariae/mg skin, with $\leq$ 10 microfilariae in both eyes combined; and (3) $\geq$ 21 microfilariae/mg skin, with or without ocular involvement.

- Efficacy was evaluated at Day 8 and at Months 1, 2, 3, 6, 12, and 18 (skin snip samples, microfilariae/mg skin).
- Detection of microfilaria migration into blood and/or urine was used as an indirect indicator of microfilaricidal activity. All subjects with skin microfilariae at Month 18 were treated with ivermectin.
- Worm viability and fertility were evaluated at Month 18 (all identified nodules excised for histopathologic evaluation).
- Chlorpheniramine (to reduce AEs to fluorescein) and paracetamol (for pain) were given as needed (prohibited: ivermectin, albendazole, or other anthelmintic agents).
- Two 150-mg doses of depo-medroxyprogesterone acetate (**DMPA**) was given to women of childbearing potential at Day 11 and at Month 2 (if not on parenteral contraceptive).

Study 3110A1-3000-AF / ONCBL60801

A Single Dose, Ivermectin-Controlled, Double Blind, Efficacy, Safety, and Tolerability Study of Orally Administered Moxidectin in Subjects Infected with Onchocerca volvulus

This randomized, double-blind, active-controlled Phase 3 study was conducted from 2009 to 2012 in 1472 subjects at 4 CI sites in Africa (Congo, Liberia, and Ghana). The primary study objective was to compare the safety, tolerability, and anti-parasitic efficacy of a single oral dose of moxidectin relative to ivermectin in treating human onchocerciasis.

- Subjects of age ≥ 12 years and weighing ≥ 30 kg with O. volvulus infection were randomized 2:1 to (8 mg) moxidectin or (150 µg/kg) ivermectin, stratified by skin microfilarial density (< or ≥ 20 microfilariae per mg skin) and sex.
- Efficacy was assessed at Months 1, 6, 12 (primary endpoint) and 18 using skin microfilarial density. Diethylcarbamazine, suramin, non-study ivermectin, albendazole, levamisole, or any investigational agent were prohibited (standard therapies permitted).

III. INSPECTION OUTCOMES

Inspected Entity		Study / Site / Enrollment	Dates	Outcome*
1	Nicholas Opoku Onchocerciasis CRC Hohoe, Ghana	3110A1-200-GH only study site, 172 subjects 3110A1-3000-AF/ONCBL60801 Site 04, 251 subjects	April 2 – 6 2018	VAI preliminary
2	WHO-TDR Avenue Appia 20 Geneva, Switzerland	3110A1-200-GH 3110A1-3000-AF/ONCBL60801 (4 sites)	April 9 – 13 2018	NAI preliminary

CI site selection: large subject enrollment in Study ONCBL6080, only site for Study 3110A1-200-GH, and inspection feasibility (travel restriction in other African sites)

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

* Note: For both inspections, the EIR has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. An addendum to this clinical inspection summary (**CIS**) will be forwarded to the review division if new significant findings are discovered at completion of EIR review; otherwise, OSI's written letter to the inspected entity (to be copied to DAIP) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

1. Nicholas Opoku, M.D. (Hohoe, Ghana)

Study 3110A1-200-GH: 345 subjects screened, 173 enrolled, 172 treated, and 166 completing study

Study 3110A1-3000-AF/ONCBL60801: 641 subjects screened, 251 enrolled, 241 treated, and 237 completing study

Case records were reviewed in detail for 9 subjects in Study 3110A1-200-GH and for 17 subjects in Study 3110A1-3000-AF, to include comparing (verifying) the major NDA data against the original source data in subject case history files: subject randomization, major efficacy endpoints (skin microfilariae counts, nodulectomy data), AEs, protocol deviations, and subject discontinuation. The general records audit for each study included: informed consent forms, laboratory reports, electrocardiogram reports, microfilaria counts (skin and anterior chamber of eye), drug accountability records, correspondence with the sponsor and the institutional review board (**IRB**), sponsor's site monitoring of study conduct, and documentation of staff training.

No significant deficiencies were observed for Study 3110A1-3000-AF/ONCBL60801 (none cited). A Form FDA 483 was issued for deficiency observations limited to Study 3110A1-200-GH (Phase 2 study):

- Records maintenance
  - Complete skin sampling records were not consistently available for all 9 cohorts. Ocular fundus photography and fluorescein angiography images were not available for review for Cohorts 3-9.
  - Electrocardiogram (**ECG**) records were often faded, making it difficult to identify (subject, date) or interpret the tracings with confidence. Hematology laboratory source data were not available for review.
  - Subject (b) (6) was immediately withdrawn after randomization (same day) with no explanatory documentation about subject eligibility or disposition of the study medication dispensed. For Subject (b) (6) who refused nodulectomy, the number of nodules excised was not recorded on the CRF (noted as 0 on source record).
  - White-out was consistently used to correct serum creatinine data on chemistry laboratory worksheets (inconsistent with GCP, considered data obliteration).
- Protocol deviations
  - Screening chemistry laboratory tests were performed late for Subjects (b) (6) (blood sample collected 3 hours after treatment, analyzed 22 days later). Serum bicarbonate was not determined for any subject.
  - Per-protocol administration of DMPA to women of childbearing potential was not documented for Subject (b) (6).
- Uncited verbal discussion
  - Site monitoring records were not available for review. One monitoring visit appeared to have been replaced with remote communication. Drug accountability records could not be adequately audited.

- Some subject eligibility records were not available on-site (located elsewhere) and could not be audited. Screen failures did not appear to have been consistently and rigorously documented.
- Parasitology training records were not available for review, including training for quality control (**QC**) of microfilariae counts (initial and recount after formalin fixation). Good laboratory practice (**GLP**) for microfilariae counting could not be audited.
- Protocol Amendment 6 was not implemented at this site. Protocol Amendment 5 was partially implemented without documentation of approval from the Ghana Food and Drug Board (**GFDB**). GFDB audited the site laboratory and discovered many deficiencies, including "tampering" with lab results, which eventually led to laboratory personnel training conducted by WHO.
- The informed consent form (**ICF**) version dated May 10, 2006 does not indicate review by Ethics Review Committee (**ERC**) or GFDB. ERC documents typically did not show what was reviewed or submitted to ERC for review (ICF versions or other documents).
- The study ophthalmologist appears to have backdated training records (signature date inconsistent with that noted on corresponding site monitoring report). The ophthalmologist did not consistently support the study (and many eye examinations not completed, reported as protocol deviations).
- Performance and interpretation of ECGs appeared to be inconsistent. Repeat ECGs were sometimes obtained in several months, with apparently new abnormalities but without noting clinical significance. ECGs not performed at subject screening were not reported as protocol deviations.
- The sponsor considered some AEs reported by the CI as not being reportable, did not report such events in the NDA, and apparently instructed the CI to no longer report such events (follow up pending for listing of events).

An evaluation of these inspectional observations is incomplete and their significance is unclear (follow up pending). The observations appear to include deficiencies in good recordkeeping practice (**GRP**) as part of GCP. Based on the limited information available to date, study conduct at this CI site otherwise appeared to have been conducted in accordance with GCP (to not warrant an OAI inspection outcome classification), including sponsor oversight of study conduct. Audited NDA data were acceptably verifiable against source records and CRFs.

2. **WHO-TDR** (Geneva, Switzerland)

Study 3110A1-200-GH, conducted in Ghana (only study site)
Study 3110A1-3000-AF/ONCBL60801, as conducted at Site 03 (Liberia)

The sponsor's study records indicated many challenges in implementing and maintaining GCP for all major areas of study conduct, apparently due to inadequate infrastructure, equipment (maintenance), and uninterrupted provision of study supplies, specifically:

- Inadequate staff recruitment, retention, training, competency evaluation, and documentation of competency for all study personnel, including staff performing parasitology evaluations, site coordinator, and site monitor

- General communication difficulties among study staff and site monitors (language barrier, literacy/fluency in English versus local languages) leading to many queries (by site monitors, often unresolved), protocol deviations (typically minor), and poor general recordkeeping (including documentation of drug disposition and accountability)
- Inadequate site monitoring, often missed or inadequately performed and/or documented, with many queries remaining unresolved (e.g., clinical significance and/or outcome of AEs or abnormal laboratory results)

Specific Examples

- Worksheets and reports for skin microfilariae counts, nodule histology, and other laboratory data (maintained at clinical sites) were not available for audit at this inspection of WHO-TDR. The routine use of standardized worksheets and source record forms could not be verified.
- Training on the study protocol and the applicable center operating procedures (**SOPs**) cold not be verified for some study personnel, including those who performed parasitology assessments. Training records were not available for review at WHO/TDR.
- Site initiation (e.g., finalization of manuals/operating procedures, task delegation/staff designation, and staff training) and on-going communication with the study site were inadequately documented for Site 03 in Study 3110A1-3000-AF (Liberia).
- WHO staff reviewed and corrected the site monitoring reports without consistently providing an audit trail and/or adequate documentation to support the correction.
- Site 03 in Study 3110A1-3000-AF (Liberia) was not physically visited for monitoring of on-going study conduct for 18 months during the sponsor transition, during which updates on study progress and query resolution were apparently obtained by remote communication.

Many of the observed deficiencies (uncited) appear to reflect inadequate recordkeeping. Evidence of serious deficiencies indicative of unreliable study data was not observed. The inspectional observations appear to be consistent with the sponsor's explanations submitted to the NDA in response to OSI information request (May 29, 2018). All audited NDA data were acceptably verifiable against source records and CRFs. For both studies audited at this CRO location (WHO-TDR), study conduct appeared adequately GCP-compliant for the NDA data to be considered acceptable for review.

{See appended electronic signature page}

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/s/

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05/31/2018

JANICE K POHLMAN
05/31/2018

KASSA AYALEW
06/01/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 3, 2018

To: Hiwot Hiruy, M.D.
Division of Anti-Infective Products (DAIP)

Kristine Park, Regulatory Project Manager, (DAIP)

Abimbola Adebowale, Associate Director for Labeling, (DAIP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Moxidectin Tablets

NDA: 210867

In response to DAIP's consult request dated January 2, 2018, OPDP has reviewed the proposed product labeling (PI) and container labeling for the original NDA submission for Moxidectin Tablets.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on March 21, 2018, and are provided below.

Container Labeling: OPDP has reviewed the attached proposed container received by electronic mail from DAIP on March 21, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
04/03/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 210867
Brand Name	
Generic Name	Moxidectin
Sponsor	Medicines Development for Global Health
Indication	Treatment of onchocerciasis due to (b) (4) Onchocerca volvulus.
Dosage Form	Oral
Drug Class	Endectocide
Therapeutic Dosing Regimen	Single 8 mg dose
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not identified
Submission Number and Date	SDN 001, 10/13/2017
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of moxidectin (4 to 36 mg) was detected in this QT study.

The effect of moxidectin has been evaluated in healthy adult male subject over a wide dose range (4 to 36 mg). This study did not include a positive control, however 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 exposure scenario (ICH E14 Q&A (R3) 5.1). The highest dose in this study (36 mg) resulted in a C_{max} that is ~4.4-fold higher than the C_{max} for the highest recommended therapeutic dose (8 mg single dose). Because the worst-case exposure scenario for moxidectin is when it is given with food, which had a negligible impact on C_{max}, the highest dose is considered adequate to support waiving the requirement for inclusion of a positive control (section 4.2.6.2).

Concentration-QTc analysis of the healthy volunteer study shows an absence of relationship between moxidectin concentration and QTc with a two-sided upper 90% confidence interval below 10 ms (section 5.3). These findings are further supported by preclinical data (hERG assay and dog study), absence of significant QTc outliers and few AEs of interest per ICH E14 in the clinical development program.

2 PROPOSED LABEL

Please note, that all labeling edits are suggestions only and we defer the final labeling to the review division.

Below are the proposed edits to the label proposed by the sponsor by section (gray heading). For each edit we are including the original proposal by the sponsor (top) followed by our proposed edits below (addition, ~~deletion~~) and rational for our edits are included to the right.

12.2 Cardiac Electrophysiology	
Sponsor: (b) (4)	We recommend using the language in the clinical pharmacology labeling guidance that is recommended for negative TQT studies. In addition, it is not clear why the sponsor is proposing to include language about (b) (4) Generally, we only include language about (b) (4) when warranted, (b) (4) We therefore suggest that the language about (b) (4) s removed as no changes were observed, (b) (4)
QT-IRT's proposed edits: (b) (4)	
At a dose 4.4 times the maximum approved recommended dose, MOXIDECTIN does not prolong the QT to any clinically relevant extent.	

3 BACKGROUND

3.1 PRODUCT INFORMATION

Moxidectin is a potent broad-spectrum endectocide. Moxidectin is a widely prescribed veterinary product. However, it has not been approved in the United States or any other country for human use.

3.2 MARKET APPROVAL STATUS

Moxidectin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Moxidectin was incubated in protein-free phosphate buffer with human embryonic kidney (HEK) 293 cells cloned with human ether-a-go-go (hERG) cDNA (RPT-73657). The highest concentration that could be tested (10 μM) was limited by the poor solubility of moxidectin in the assay medium and produced < 20% inhibition of the hERG ion channel current. Accordingly, the IC50 was greater than 10 μM (6.4 μg/mL).

To evaluate the potential cardiovascular effects of moxidectin, a single oral dose of 1.0 mg/kg moxidectin was given to beagle dogs (3/sex/group) (RPT-74070). Doses above 1 mg/kg were not evaluated because of transient adverse clinical signs observed in a 1-month dog study at 3 mg/kg.

There were no mortality or adverse clinical signs in the study.

Moxidectin at 1.0 mg/kg resulted in a small (-14% relative to baseline) but significant decrease in heart rate, but no consistent statistically significant changes in systolic, diastolic or mean arterial blood pressure, and no effects on electrocardiograms (ECGs), including the QTc interval. The NOAEL for this study can be considered 1.0 mg/kg.

Reviewer's Comment: The highest dose studied in the in vitro hERG study resulted in a reduction of the hERG current of <20%. However, because of solubility issues at 10 μM and a similar inhibition of hERG at 3 and 10 μM (~17%) the highest concentration without solubility issues is likely 3 μM. Because of the solubility issue and that protein binding is unknown (could not be determined), the highest concentration is estimated to be ~34x times higher than the therapeutic C_{max}. This is a conservative estimate (as it assumes 0% protein binding) and suggests a low potential for inhibition of hERG. In addition, no QTc prolongation were observed in the dog study.

3.4 CLINICAL EXPERIENCE

In the other five Phase I studies, there were no deaths, SAEs or premature is continuations due to AEs. There were also no clinically significant changes in vital signs or ECGs observed in these studies. PCI ECG changes were reported in Studies 101 and 1005. None were assessed of individual clinical importance. Additionally, an exploratory pharmacokinetic/pharmacodynamic analysis was performed in Study 1005 to explore the relationship between moxidectin pharmacokinetics and potential changes in corrected QT interval. In that study, statistical analysis of the ECG QTc interval using QTcN and QTcF showed neither a time point having a statistically significant increase in QTc, nor an upper bound greater than 10 msec for either analysis.

Based on ICH E14 Guidance, potential cardiovascular AEs of interest were defined as MedDRA preferred term AEs of Torsade de pointes, ventricular tachycardia, sudden death, syncope, ventricular fibrillation, ventricular flutter and seizure.

In Phase III, there were no TEAEs meeting these definitions, although an expanded review identified three moxidectin subjects who reported a loss of consciousness and one experienced sudden death (broad preferred terms under the standardized MedDRA query for Torsades de pointes/QT prolongation).

The profile of cardiac AEs encountered in the Phase II study is similar to that of the Phase III study and there were no AEs suggestive of delayed repolarization (Phase II CSR).

All AEs were reviewed for preferred terms that would be consistent with delayed repolarization. There were two events of syncope (Standardized MedDRA Query broad for Torsades de Pointes) in two subjects:

- Subject (b) (6) (moxidectin 4 mg): a 33 year old male who reported syncope on Day 440.
- Subject (b) (6) (moxidectin 2 mg): a 26 year old male who reported syncope on Day 15.

There were no AEs for the cardiac disorders system organ class reported by either subject. The subjects' QTcB, QTcF and QTcN were normal on Day 1, 2, 3, and 8 with no change from Baseline.

Reviewer's Comments: The sponsor identified potential AEs of interest on ICH E14 guidelines. This search revealed few AEs, which do not appear to be caused by moxidectin based on the timing of the AE relative to moxidectin dosing.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of moxidectin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 126876 on 03/21/2016. The sponsor's planned concentration-QT assessment approach appeared acceptable to FDA in the protocol review, however, it was noted in the protocol review that the sponsor had not provided sufficient support for the adequacy of the highest dose included and the sponsor was recommended to use the single-delta model for the primary analysis.

The sponsor submitted the study report MDGH-MOX-1008 for the study drug, including electronic datasets and waveforms to the ECG warehouse. The sponsor also submitted an addendum to the study report describing safety assessments up to week 12 as well as the results of analysis of moxidectin concentrations in urine, feces and moxidectin metabolites for the 8 mg group. The focus of this review is the primary study report.

4.2 QT STUDY

4.2.1 Title

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Potential Effect of a Single Oral Dose of Moxidectin on the Cardiac QT Interval of Healthy Volunteers

4.2.2 Protocol Number

MDGH-MOX-1008

4.2.3 Study Dates

Study Initiation Date: 23 January 2017

Study Completion Date: 14 March 2017

4.2.4 Objectives

Primary Objective: The primary objective of the study was to analyze the effect of a single oral dose of moxidectin on the QT interval associated with moxidectin plasma concentrations.

Secondary Objective: The secondary objective of the study was to assess the safety and pharmacokinetics (PK) of a single oral dose of moxidectin.

Exploratory Objectives: The exploratory objectives of the study were:

- To gain preliminary information in humans on the metabolism and excretion of moxidectin;
- To evaluate the baseline-corrected changes in other electrocardiogram (ECG) and cardiovascular parameters; and
- To evaluate the ECG morphologic changes related to cardiac repolarization (ST segment and T waves).

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, single-center, double-blind, placebo-controlled, parallel-group study.

4.2.5.2 Controls

The Sponsor used placebo controls.

4.2.5.3 Blinding

The placebo tablets were matched in appearance to the active study drug, and contained the same excipients as moxidectin tablets but did not contain moxidectin.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- Treatment 1: moxidectin 4 mg (n = 10)
- Treatment 2: moxidectin 8 mg (n = 10)
- Treatment 3: moxidectin 16 mg (n = 10)
- Treatment 4: moxidectin 24 mg (n = 10)
- Treatment 5: moxidectin 36 mg (n = 10)
- Treatment 6: matching placebo (n = 10)

4.2.6.2 Sponsor's Justification for Doses

The proposed human dose for the treatment of onchocerciasis is 8 mg. This study assessed moxidectin as a single oral dose at doses up to 36 mg in tablet form and in the fasted state. In addition to the non-clinical safety pharmacology and toxicology studies, which provided adequate safety margin multiples in reference to the 36-mg dose, moxidectin has previously been administered at doses up to 36 mg in healthy human subjects and was well tolerated. Specifically, in Protocol 3110A1-100-EU, there was no evidence of clinically relevant safety findings after administration of moxidectin (oral liquid). No clinically relevant abnormalities were observed in vital sign measurements, ECGs, or laboratory test results during the study. A slightly higher incidence of central nervous system AEs (somnolence and mild dizziness) was observed in the 36-mg fed and fasted treatment groups (moxidectin or placebo). As this was prior to study unblinding and the dose was well above the predicted therapeutic dose, the decision was made to end the study prior to enrollment of a planned 54-mg cohort. There was found to be no major difference in the pattern and severity of AEs and the AEs reported during the study were mild to moderate in intensity with the exception of 1 Grade 3 event (enteritis) in the 36-mg group, which was deemed unrelated to test article. There were no SAEs and no subjects discontinued the study due to an AE.

Increased exposure to moxidectin has been observed in liquid presentations compared with tablets and when moxidectin is given with food. Of the 10 subjects who received moxidectin as an oral solution at 36 mg in Protocol 3110A1-100-EU, the fasted mean (± SE) AUC from time 0 extrapolated to infinity (AUC0-inf) was 451 (±48.2) ng*days/mL compared with fed AUC0-inf of 624 (±41.6) ng*days/mL. Therefore, moxidectin administered in tablet form and in the fasted state should have ensured that exposure was less than or equal to existing clinical experience.

Reviewer's Comment: Acceptable. Because the study does not include a positive control, the highest dose studied must result in a C_{max} that is greater than 2-times the worst-case exposure scenario to support waiving the requirement for a positive control (ICH E14 Q&A (R3) 5.1). The highest dose included in this study is 36 mg, which resulted in a ~4.4-fold higher C_{max} compared to the maximum recommended dose (8 mg). Because moxidectin is administered as a single dose, not significantly metabolized and not a substrate of P-gp or BCRP, the 36 mg dose is expected to result in an exposure that exceeds 2-times the worst-case exposure scenario.

4.2.6.3 Instructions with Regard to Meals

On Day –1, subjects began fasting as instructed and water was taken ad libitum. On Day 1, study drug administration (moxidectin or placebo) occurred after an overnight fast of at least 10 hours. Study drug was administered with at least 240 mL of water. No food was allowed for 4 hours after dosing; however, water was taken ad libitum.

Reviewer's Comment: Acceptable. The effect of food on moxidectin PK is minimal (~39% increase in C_{max}).

4.2.6.4 ECG and PK Assessments

The ECG data were transmitted wirelessly to the Surveyor system, which extracted triplicate 10-second ECG recordings (approximately 1 minute apart) at the following time points:

- Baseline (before dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing

Blood samples were collected for PK assessments at:

- Baseline (0 hour; within 15 minutes before dosing) and at 0.5, 1, 2, 3, 4*, 5, 6, 8, 12*,24*, 36*, 48, 60*, and 72 hours after dosing, and on Days 8, 15, and 22

* Planned time points for analysis of moxidectin metabolite concentrations

Reviewer's Comment: Acceptable, the ECG/PK timing allows for capturing peak effects of moxidectin and delayed effects.

4.2.6.5 Baseline

The average of pre-dose QT/QTc values on Day 1 was used as baseline.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 60 healthy male subjects were planned and enrolled, and 55 subjects were continuing as of the date of database lock. The average age (SD) of the 60 subjects was 32.0 (8.2) years, ranging from 18 to 48 years. The majority of the subjects were either Black or African American (29/60, 48.3%) or White (27/60, 45.0%) in race, and Non-Hispanic or Latino (54/60, 90.0%) in ethnicity.

The ECG and safety populations included all 60 subjects who received as least 1 dose of the study drug and had at least 1 pair of pre-dose and post-dose QTc data. The PK and PK/PD populations included 50 subjects. No subjects were excluded from the ECG, PK, PD, and PK/PD populations.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The exposure-response analysis was used for primary analysis. The findings of the study can be found in section 4.2.8.4.2.

4.2.8.2.2 Assay Sensitivity

Not Applicable

4.2.8.2.3 Categorical Analysis

One QTcF value greater than 450 msec (473 msec at hour 1) was observed for the 24-mg treatment group on a single ECG (Subject (b) (6)). This subject's triplicate mean value was under 450 msec (440 msec). Two subjects in the 8-mg treatment group and 3 subjects in the 24-mg treatment group had a change in QTcF over baseline of more than 30 msec. There were no changes exceeding 60 msec. Outlier PR and QRS intervals and HR are summarized in Table 14.2.2.7. There were no outliers observed for PR and QRS. An HR below 50 bpm with at least a 25% decrease from Baseline was observed in 1 subject in the 36-mg treatment group at hours 2 and 3. No other low HR outliers were observed. A HR above 100 bpm with at least a 25% increase over Baseline was observed in 1 subject in the 8-mg treatment group at hour 1.

4.2.8.3 Safety Analysis

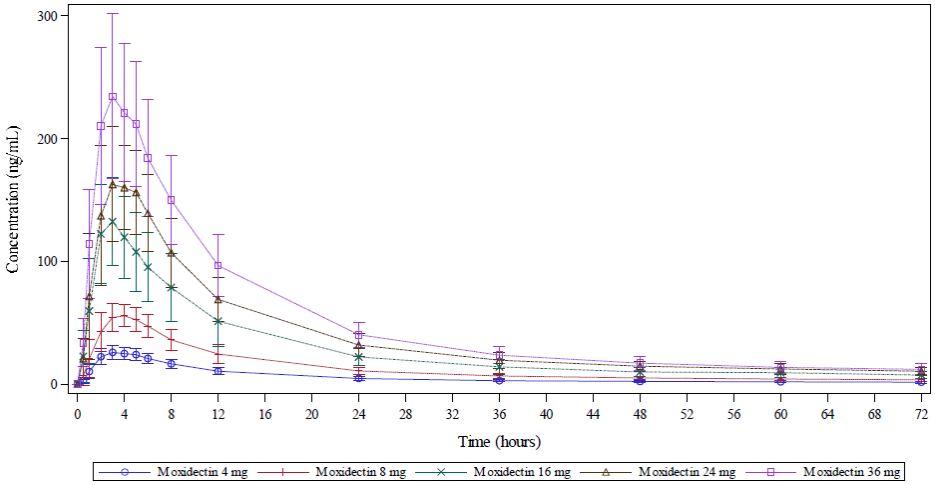
No deaths or serious treatment emergent adverse events (TEAEs) were reported during the study. There were no TEAEs leading to study drug or study discontinuation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 1 (moxidectin). C_{max} and AUC values in the QT study were 4.4-fold higher following administration of 36 mg compared with 8 mg, the intended clinical dose.

Figure 1: Time-course of mean ± SD for moxidectin plasma concentration



Source: CSR, Figure 11-6, Page 78

Table 1: Summary of PK parameters for moxidectin plasma concentration

Parameter (units)	Group 1 Moxidectin 4 mg	Group 2 Moxidectin 8 mg	Group 3 Moxidectin 16 mg	Group 4 Moxidectin 24 mg	Group 5 Moxidectin 36 mg
Number of subjects	10	10	10	10	10
C_{max} (ng/mL)	27.2 (18.9)	56.7 (20.8)	133 (27.1)	176 (18.7)	247 (19.7)
T_{max} (h)	3.08 (2.08-5.08)	4.08 (2.08-5.08)	3.08 (2.08-4.08)	3.08 (2.08-6.08)	3.08 (2.08-5.08)
$AUC_{0\text{-last}}$ (h*ng/mL)	730.9 (26.9)	1677 (29.7)	3553 (37.7)	5181 (31.2)	5659 (47.2)
$AUC_{0\text{-}24}$ (h*ng/mL)	284.8 (20.6)	632.6 (22.4)	1354 (36.2)	1873 (22.0)	2613 (19.6)
$AUC_{0\text{-}48}$ (h*ng/mL)	353.7 (21.8)	797.7 (23.8)	1685 (37.5)	2359 (23.6)	3209 (21.1)
$AUC_{0\text{-}72}$ (h*ng/mL)	395.0 (23.0)	893.3 (24.6)	1883 (38.1)	2645 (24.4)	3531 (22.0)
$AUC_{24\text{-}48}$ (h*ng/mL)	68.32 (29.1)	163.8 (32.2)	328.7 (44.6)	480.7 (34.6)	592.4 (29.3)
$AUC_{48\text{-}72}$ (h*ng/mL)	40.67 (35.5)	94.51 (34.7)	195.7 (46.1)	279.6 (40.0)	317.0 (36.8)

Abbreviations: CV%, percent coefficient of variation; PK, pharmacokinetic.
Note: T_{max} was reported as median (minimum-maximum).

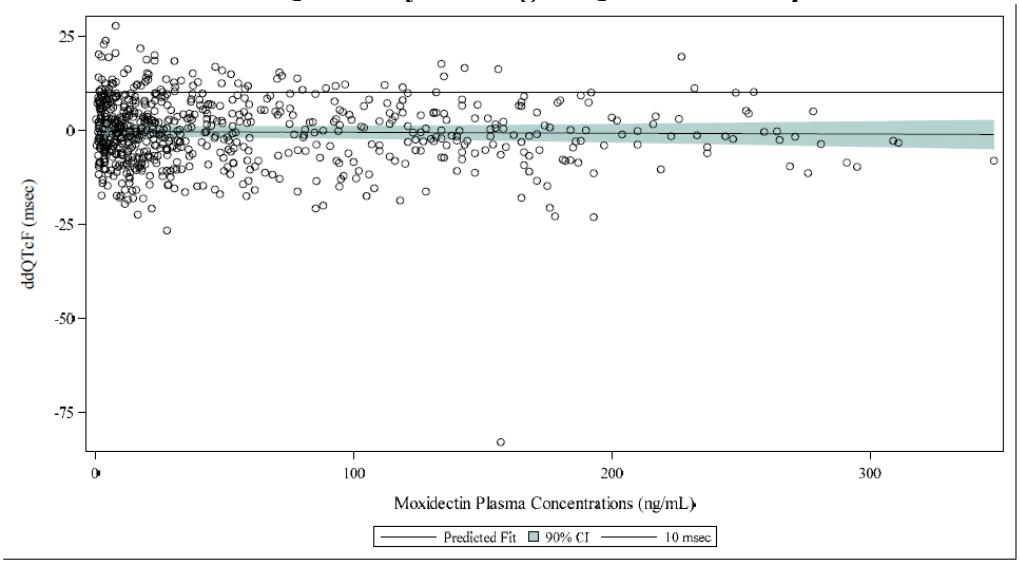
Source: CSR, Table 11-3, Page 79

4.2.8.4.2 Exposure-Response Analysis

An assessment for hysteresis (ddQTcF [baseline and placebo subtracted QTcF] change delayed after Tmax) was carried out as described in the SAP. Since there was only a single ddQTcF value at a single time point in a single treatment cohort that exceeded 5 msec, criteria for further hysteresis assessment were not met and it was concluded that hysteresis was not present.

The model used by the sponsor for the primary analysis deviates significantly from the recommended linear mixed effects model, e.g. the sponsor included an interaction between treatment and time (SAP, Page 28). The reviewer is therefore presenting the secondary analysis (double-delta model).

Figure 2: Concentration-QTc analysis using ΔΔQTcF as the dependent variable



Source: Concentration-QTc report, Figure 6, Page 12

Reviewer's Analysis: The reviewer evaluated the relationship between moxidectin and QTcF using the recommended pre-specified linear mixed effects model (Garnett et al., J Pharmacokinet Pharmacodyn 2017). The results of this analysis are similar to the sponsor's secondary analysis that is presented above, see section 5.3 for additional details.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e., mean changes ≤10 bpm (section 5.3). Therefore, no assessment of the QT/RR correction methodology is necessary.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Moxidectin

The exposure-response analysis was used for primary analysis. The findings of the study can be found in section 4.2.8.4.2. By time-point statistical analysis was not conducted due to small number of subjects in each group.

5.2.1.2 Assay Sensitivity Analysis

Not Applicable

5.2.1.3 Categorical Analysis

The reviewer used the mean of the triplicate for the categorical analysis, which is the reason for the small discrepancies compared to the sponsor's analysis, which considered both individual ECGs and the mean of the triplicates. No subjects had QTcF >450 ms. No subject's change from baseline in QTcF (ΔQTcF) was above 30 ms.

5.2.2 HR Analysis

The outlier analysis results for HR are presented in Table 2.

Table 2: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	60	60 (100%)	0 (0.0%)	60 (100%)	0 (0.0%)
Moxidectin 4 mg	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)
Moxidectin 8 mg	10	9 (90.0%)	1 (10.0%)	10 (100%)	0 (0.0%)
Moxidectin 16 mg	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)
Moxidectin 24 mg	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)
Moxidectin 36 mg	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)
Placebo	10	10 (100%)	0 (0.0%)	10 (100%)	0 (0.0%)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 3. There were no subjects who experienced PR >220 ms.

Table 3: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	60	60	59 (98.3%)	59 (98.3%)	1 (1.7%)	1 (1.7%)
Moxidectin 4 mg	10	140	9 (90.0%)	139 (99.3%)	1 (10.0%)	1 (0.7%)
Moxidectin 8 mg	10	140	10 (100%)	140 (100%)	0 (0.0%)	0 (0.0%)
Moxidectin 16 mg	10	140	10 (100%)	140 (100%)	0 (0.0%)	0 (0.0%)
Moxidectin 24 mg	10	140	9 (90.0%)	128 (91.4%)	1 (10.0%)	12 (8.6%)
Moxidectin 36 mg	10	140	10 (100%)	140 (100%)	0 (0.0%)	0 (0.0%)
Placebo	10	140	9 (90.0%)	131 (93.6%)	1 (10.0%)	9 (6.4%)

5.2.4 QRS Analysis

The outlier analysis results for QRS are presented in Table 4.

Table 4: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	60	60	56 (93.3%)	56 (93.3%)	4 (6.7%)	4 (6.7%)
Moxidectin 4 mg	10	140	8 (80.0%)	132 (94.3%)	2 (20.0%)	8 (5.7%)

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Moxidectin 8 mg	10	140	9 (90.0%)	139 (99.3%)	1 (10.0%)	1 (0.7%)
Moxidectin 16 mg	10	140	9 (90.0%)	127 (90.7%)	1 (10.0%)	13 (9.3%)
Moxidectin 24 mg	10	140	7 (70.0%)	132 (94.3%)	3 (30.0%)	8 (5.7%)
Moxidectin 36 mg	10	140	9 (90.0%)	138 (98.6%)	1 (10.0%)	2 (1.4%)
Placebo	10	140	10 (100%)	140 (100%)	0 (0.0%)	0 (0.0%)

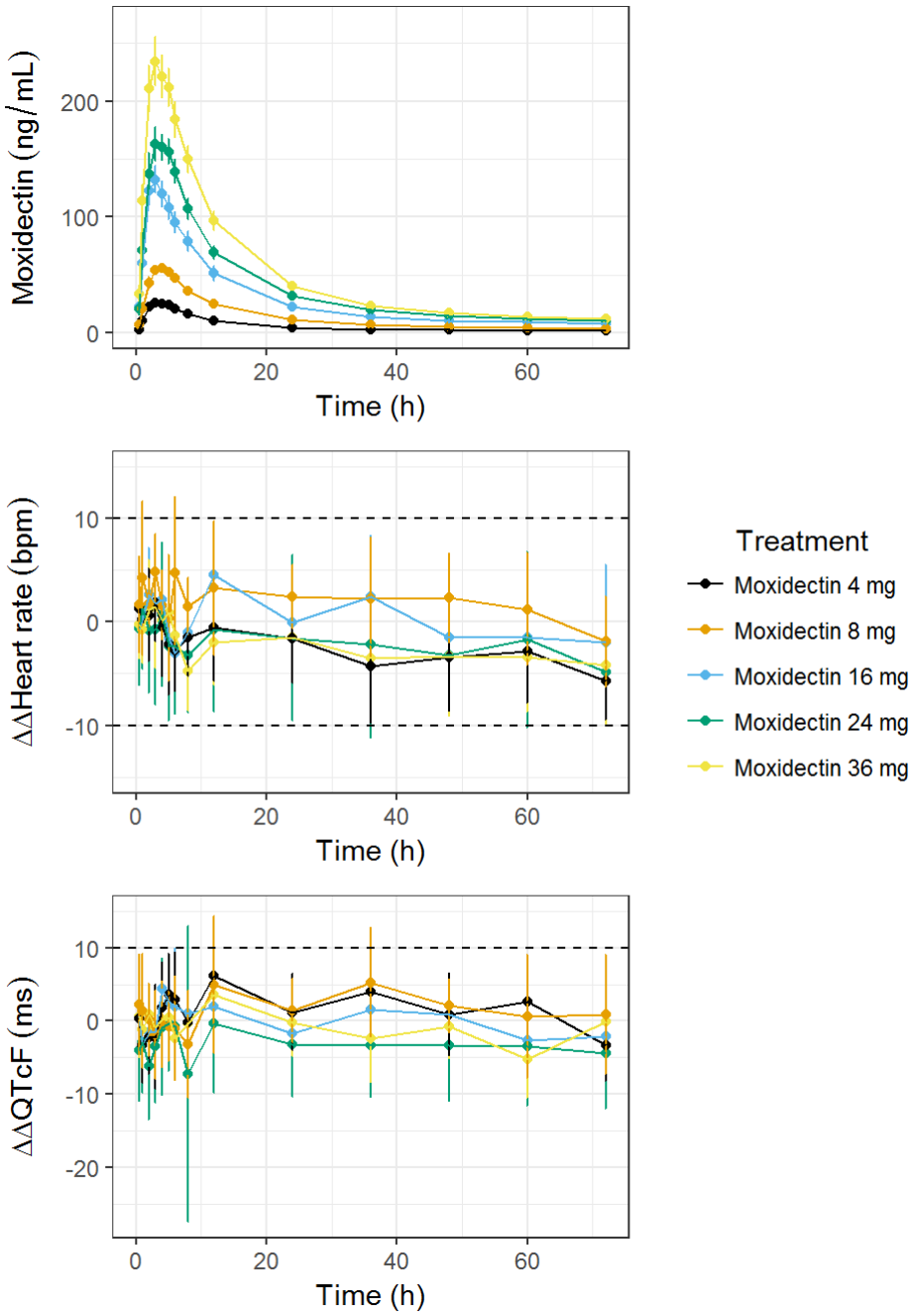
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between moxidectin concentration and ΔΔQTcF using the linear prespecified mixed effects model.

Prior to applying the prespecified model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔΔQTcF and 3) presence of non-linear relationship.

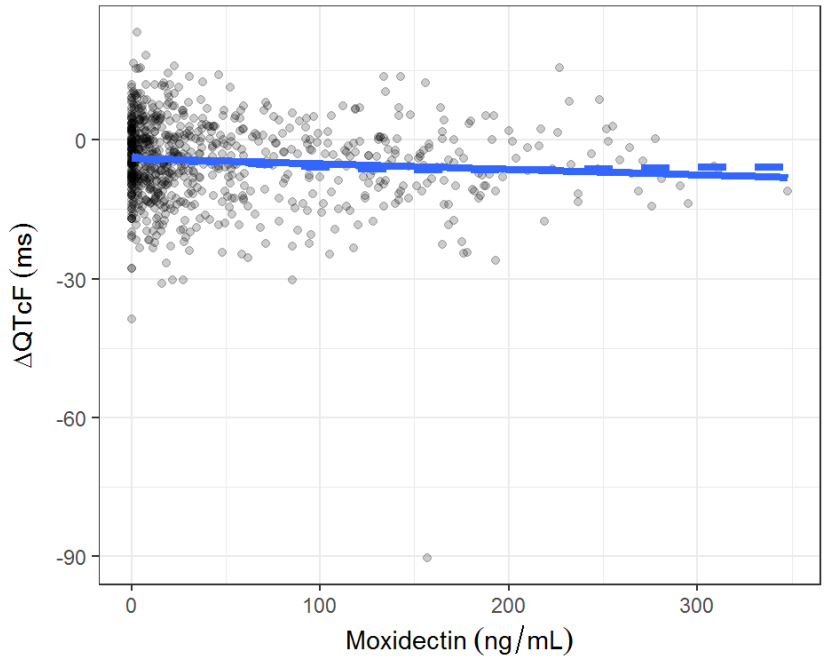
An evaluation of the time-course of moxidectin pharmacokinetics and changes in ΔΔHR and ΔΔQTcF is shown in Figure 3, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

Figure 3: Time-course of moxidectin (top), ΔΔHR (middle) and ΔΔQTcF (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between moxidectin concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 4 shows the relationship between moxidectin concentration and ΔQTcF and supports the appropriateness of a linear model.

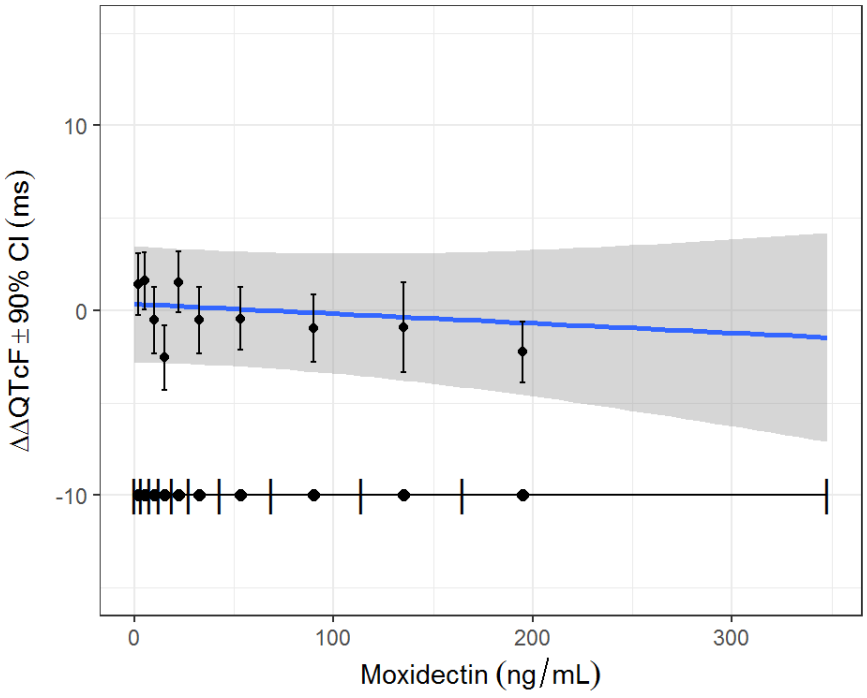
Figure 4: Evaluation of the relationship between moxidectin concentration and ΔQTcF. The blue lines represent a linear fit (solid) and loess fit (dashed).



Finally, the linear prespecified mixed effects model was applied to the data and the goodness-of-fit plot is shown in

Figure 5, which shows an absence of a relationship between moxidectin concentration and ΔΔQTcF.

Figure 5: Goodness-of-fit plot for final model



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this phase 1 study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 Other ECG Intervals

No clinically relevant changes on the PR or QRS intervals were observed in this study.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Source: IND 126876, SDN 5

Therapeutic dose and exposure	8 mg per oral given as a single dose to patients with *O. volvulus* infection (Study 3110A1-200-GH): Mean (CV%) Cmax = 63.1 (32%) ng/mL Mean (CV%) AUC = 2738 (59%) ng x hr/mL Moxidectin is to be given as a single dose. Therefore steady state parameters are not applicable.	
Maximum tolerated dose	36 mg was the maximum dose studied in 5 healthy volunteers (HV) (Study 3110A1-100-EU). None of the subjects experienced SAEs (including death) or safety-related discontinuations of study participation. However, 4 subjects experienced the adverse events of somnolence (lethargy) or dizziness. These adverse events led to the decision to terminate the study prior to enrolling the 54 mg group.	
Principal adverse events	Common AE's at 8 mg: no SAEs or life-threatening adverse events were reported in Phase I, and no treatment-related deaths occurred during the phase II or III studies. Frequently occurring adverse events (i.e., experienced by ≥ 10% of subjects) in subjects who took moxidectin included headache (35%), infection (29%), pharyngitis (16%), leukopenia (13%), dizziness (13%), and pain, SGOT increased, SGPT increased, somnolence, rhinitis, and cough increased (10%).	
Maximum dose tested	Single Dose	36 mg per oral, liquid formulation given fasted and fed
	Multiple Dose	Not applicable; Moxidectin has only been studied under single-dose conditions

Exposures Achieved at Maximum Tested Dose	Single Dose
	Mean (CV%)
		Study 3110A1-100-EU, HV, liquid formulation:
		• 36 mg fasted (n=5):
		  • Cmax (ng/mL) = 294 (15)
		  • AUC_{inf} (ng x hr/mL) = 10158 (22)
		• 36 mg fed (n=5):
		  • Cmax (ng/mL) = 296 (16)
		  • AUC_{inf} (ng x hr/mL) = 14972 (15)

	Multiple Dose	Not applicable
Range of linear PK	2-36 mg	

Accumulation at steady state	Not applicable	
Metabolites	In radiolabeled ADME studies in rats, moxidectin radioactivity was eliminated primarily in the feces after oral dosing. Most of the radioactivity was comprised of moxidectin, although oxidative metabolites were also detected. Urinary excretion was low (<2%) in rats. These data indicate that moxidectin is likely cleared by a combination of biliary excretion of unchanged drug, and oxidative metabolism. Moxidectin metabolism was assessed in rat and human liver microsomes; the same metabolites were detected in both species. Four moxidectin-related peaks were detected in liver microsomes in the presence of cofactors and were characterized by LC/MS/MS as apparent hydroxylations at the C-4-methyl, C6-C19, C-28-methyl, and C-14 methyl positions. Three additional oxidative metabolites (O-demethyl-C14-hydroxylmethyl, C-24-hydroxylmethyl, and 23-keto) were detected in rat tissues, urine and/or feces after oral administration of moxidectin. A study to evaluate moxidectin and its major metabolites in plasma and excreta following an 8 mg single oral dose in healthy volunteers is currently being designed.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability has not been determined in humans. Relative bioavailability: The mean Cmax and AUC of the liquid formulation was 1.2 x higher than the tablet formulation. Mean Tmax of the tablet formulation was 3.2 hr versus 2.3 hrs for the liquid formulation.
	Tmax (hours)	Patients, 8 mg (Study 30110A1-200-GH, n=31): • Mean ± SD: 3.37 ± 0.99 hours HV, 8 mg fasted (Study 30110A1-1005-EU, n=27): • Median (range): 4 (2-8) hours
Distribution	Vd/F (L) Mean (CV%)	Patients, 8 mg (Study 30110A1-200-GH, n=31): • 2421 (68) L
	% bound	Protein-binding data are not available for moxidectin due to >80% nonspecific binding of moxidectin to matrices (dialysis membranes and centrifuge tubes).

Elimination	Route	Moxidectin has limited metabolism and low renal excretion *in vitro* in rat and human systems and *in vitro* and *in vivo* in a wide variety of animal species. A study to evaluate the metabolism and excretion of a single 8 mg dose of moxidectin in healthy volunteers is currently being prepared. Plasma, urine and fecal concentrations of moxidectin and its metabolites are planned to be measured over a three day period using validated assay methodology. This information on the metabolism and excretion of moxidectin and its main metabolites in humans will be provided as part of the NDA submission.
	Terminal t½ (hr) Mean (CV%)	Patients, 8 mg (Study 30110A1-200-GH, n=31): • 559 (94%) hours HV, 8 mg fasted (Study 30110A1-1005-EU, n=27): • 784 (44%) hours
	CL/F (L/h) Mean (CV%)	Patients, 8 mg (Study 30110A1-200-GH, n=31): • 3.5 (35%) L/hr
Intrinsic Factors	Age	Based on a preliminary population PK analysis of the phase II data in patients, a relationship between weight (WT) and volume of the central (V2/F) and peripheral (V4/F) compartment (V2/F) and distributional clearance (Q4/F) was seen. Further, Q4/F and V4/F were higher in females but V2/F values were lower in females. No relationships were identified for CL/F, or other volume or clearance parameters. The covariates accounted for 34.3% (CV% 21.6 to 14.2) of the inter-individual variability (IIV) for V2/F, 23.3 % (CV% 57.2 to 43.8) of the IIV for Q4/F and 62.8% (CV% 41.7 to 15.5) of the IIV for V4/F. However the difference in V2/F, V4/F or Q4/F are not expected to significantly impact the exposure and to cause concern for dose adjustment based on weight or between males and females.
	Sex	
	Race	
	Hepatic & Renal Impairment	Has not been evaluated.

Extrinsic Factors	Drug interactions	Moxidectin has limited metabolism *in vitro* in rat and human systems. No *in vivo* DDI studies have been conducted with moxidectin as a substrate and is considered unlikely to be a victim of DDIs Moxidectin was evaluated in a clinical study with midazolam and did not alter the PK of midazolam or its metabolites.
	Food Effects	Administration of 8 mg moxidectin with a standard FDA high fat meal resulted in an increase in Cmax and AUC of 34 and 39%, respectively, compared to the fasted state. Moxidectin is to be administered in a fasted state
Expected High Clinical Exposure Scenario	Moxidectin is intended to be given as a single dose. The expected clinical scenarios which could increase moxidectin concentrations are described below. At this time, the most likely scenario which could increase exposure (by approximately 36%) would be if moxidectin were to be administered after a high fat meal. However, given the diet of patients in onchocerciasis endemic areas, and the controlled administration of moxidectin, in addition to the proposed administration of moxidectin (2 hours before or 2 hours after a meal), the likely incidence of moxidectin administration in a high fat environment is rare. The other scenarios at this time are unknown. However, restrictions can be incorporated into labeling to mitigate risk in susceptible populations until dedicated studies are available. <u>8 mg moxidectin with food:</u> Cmax increased by 34% compared to fasted AUC increased by 39% compared to fasted <u>Patients with renal or hepatic impairment</u> Dedicated studies have not been conducted in patients with renal or hepatic impairment, therefore the impact on exposure in these patients is unknown. Effect of organ impairment will be evaluated in the population PK analyses and as part of a safety analyses. Initial labeling will be supported by the organ impairment groups for which data is known. The need for dedicated organ impairment studies will be decided upon after completion of the healthy patient study which will characterize the PK and elimination (feces and urine) of a single 8 mg dose.	

	Drug Drug Interactions No *in vivo* DDI studies have been conducted to evaluate moxidectin as a victim of DDIs. Moxidectin has limited metabolism *in vitro* in rat and human systems. CYP phenotyping studies will indicate if dedicated studies with CYP450 inhibitors are needed. The effect of CYP inhibitors will be evaluated in a population PK and safety analysis of coadministered agents during the phase 2 and 3 studies. Overdose An unlikely clinical scenario given the proposed administration of a single dose.
Preclinical Cardiac Safety	*In vitro* The potential effects of moxidectin on I_{Kr} were examined in an *in vitro* hERG potassium ion channel assay. The concentrations of moxidectin for *in vitro* studies spanned a broad range (1, 3 and 10 μM), covering and exceeding the anticipated maximal therapeutic plasma concentrations by 101-fold (10 μM - 6398 ng/mL; C_{max} = 63.1 ± 20.0 ng/mL). Precipitate was observed at concentrations greater than 10 μM, and therefore, they were not tested. Moxidectin inhibited the hERG potassium ion current 4.9% ± 0.8% (mean ± standard deviation [SD]; n = 3) at 1 μM, 17.8% ± 5.0% (n = 4) at 3 μM, and 19.7% ± 3.5% (n = 3) at 10 μM which suggested that the potential for hERG inhibition had plateaued. The positive control resulted in 82.3% ± 0.5% (n = 2) inhibition. The results for the controls in this study were within the range of historical control data from the testing facility. *In vivo* Moxidectin was administered to male and female dogs as a single oral (capsule) dose of 0 or 1 mg/kg according to a parallel dosing paradigm (3/gender/group). The control group received the vehicle consisting of an empty size-13 gelatin capsule. Parameters collected using radiotelemetry consisted of arterial blood pressures (systolic, diastolic, and mean), heart rate, and ECG. The telemetry data were collected for 60-second periods every 5 minutes for 25 hours prior to and 72 hours after dosing. Administration of 1 mg/kg moxidectin to dogs resulted in a statistically significant decrease in heart rate, but no consistent, statistically significant changes in systolic, diastolic, or mean arterial blood pressure, and no effects on the ECG, including the

	QTc interval. The decrease in heart rate was not considered adverse based on the small magnitude of change and the absence of a corresponding change in blood pressure or associated clinical observations. The no observed adverse effect level (NOAEL) for cardiovascular effects was the only dose tested, 1 mg/kg, as higher doses were not being explored. The average C_{max} (616 ng/mL) and AUC (31200 ng•h/mL) in juvenile male and female dogs after a dose of 1 mg/kg (from Report 73592) were 16.5- and 24.7-times the C_{max} and AUC in infected adults after an 8 mg dose. Thus, moxidectin has not exhibited any significant cardiovascular or other safety concerns in animals.
Clinical Cardiac Safety	The safety of moxidectin has been assessed in 194 healthy volunteers in five Phase I studies, and in 1105 patients with onchocerciasis in one Phase II and one Phase III study. The moxidectin dosage regimen for all studies has been a single oral dose. Safety information relevant to cardiac safety are summarized below. Twelve (12)-lead ECGs were performed at various time points during the studies (including Screening). A physician experienced in evaluating ECGs provided the interpretations of all ECGs. The evaluation included the rhythm, rate, PR, QRS and QT intervals. Potentially clinically important (PCI) ECG changes and vital signs were also examined (study-specific criteria). A brief summary of the cardiac safety events per study is included below. A more detailed discussion can be found in the Type C briefing document in Section 4.5 <u>Study 3110A1-100-EU</u>: This was a first in human study in healthy volunteers which tested single doses of moxidectin (or placebo) up to 36 mg. None of the subjects were discontinued from the study because of an adverse event. There were no clinically significant changes in vital signs or ECGs <u>Study 3110A1 101 EU</u>: This was a relative bioavailability study in healthy volunteers which tested single 10 mg doses of Moxidectin tablet and liquid formulation. No serious adverse events or deaths occurred in this study. No subjects discontinued as a result of an adverse event. A total of 36 (62.1%) subjects had treatment-emergent adverse events during the study, all of which were mild to moderate in intensity, and none were considered to be related to treatment. No clinically meaningful abnormalities

	were observed in vital sign measurements, ECGs, or laboratory tests during the study. One subject (Subject (b) (6)) had a Baseline QTc value of 453 msec on Day 1 that remained under 450 msec throughout the study, except for one occasion on Day 1 (4 hours after dose administration) when a value of 452 msec was observed. There was no significant prolongation of QTc after the dose in this subject and the day 180 QTc value was 414 msec. 3110A1 1002 EU: This was a lactation study in healthy lactating females which tested a single 8 mg dose of Moxidectin. No SAE or death occurred during the course of this study. No subject was withdrawn from the study because of safety-related adverse events. Nine subjects reported adverse events, all of which were considered treatment-emergent. No treatment emergent adverse events (TEAE) were reported during the study that were considered to be drug related. No clinically significant changes in laboratory test results, vital signs measurement and ECG findings occurred during the study. No subject had any potentially clinically important (PCI) change in ECG parameters. Study B1751002 / 3110A1-1004-EU: This was a midazolam drug:drug interaction (DDI) study with four periods. Period 2 was when only moxidectin (8 mg) was administered. No SAE or death occurred during the course of this study. A total of 18 (46.2%) subjects reported adverse events, all of which were considered TEAEs. All drug-related TEAEs were mild or moderate in nature. Six were considered related to moxidectin and one related to midazolam (nausea, vomiting, and headache). No subject was withdrawn from the study because of a safety-related adverse events. The Principal Investigator performed an overall reading of ECGs, which was reviewed by the study Medical Monitor. There were no ECG findings of clinical importance. Study 3110A1 1005 EU: This was a food effect study in healthy male volunteers (fed or fasted) administered a single 8 mg dose of moxidectin. No SAEs or deaths occurred during the course of this study. No subject was withdrawn from the study because of a safety-related adverse events. Adverse events were experienced by 33 (61.1%) subjects of whom 29 (53.7%) subjects experienced TEAEs. Of the 29 subjects who experienced TEAEs during the entire study, 11 events (20.4%) were considered by the Investigator to be drug related. All drug related TEAEs were mild in severity. There were no clinically relevant changes in ECGs, vital signs or safety laboratory tests (in particular, there were no increases in liver enzymes) during the study.

	Twenty-six (48.1%) of subjects had at least one ECG measurement that exceeded the ECG criteria for potential clinical importance at some time during the study. Of these 26 subjects, 21 subjects had PCI changes in ECG measurements before dose administration and 22 subjects had PCI changes in ECG measurements after dose administration; 10 (37.0%) from the fasted cohort and 12 (44.4%) from the fed cohort. The medical monitor determined the PCI ECG values were not of individual clinical importance. Analyses of QTc were performed using population specific Q wave-T wave correction (QTcN) and Q wave-T wave correction using Fridericia's formula/Fridericia's correction (QTcF). The model included fed/fasted status, hour, and fed/fasted status by hour interaction as fixed effects, with baseline as a covariate and subject as a random effect. The dependent variable was the time-matched difference from baseline. Model based point estimates and 90% confidence interval (CI) were calculated at each time point. Statistical analysis of the ECG QTc interval using QTcN and QTcF showed neither a time point having a statistically significant increase in QTc, nor an upper bound greater than 10 msec for either analysis. Therefore, no prolongation of the QTc interval was demonstrated in this study of healthy male subjects after administration of a single 8 mg oral dose of moxidectin. Study 3110A1-200-GH: This was a phase II dose ranging study evaluating both efficacy and safety in patients who were randomized to receive 2, 4 or 8 mg of moxidectin or ivermectin. Eight subjects (4.7%) in the moxidectin treatment groups reported 13 SAEs. Of the 13 events, typhoid fever and pneumonia occurred in two patients each. Other events occurred once. None of the events were assessed as related to treatment. One subject (Subject (b) (6)) died following a snakebite post dose Day 319. An extensive review of the ECGs and AEs are included in Section 4.5.3.6 of the Type C briefing document. No subject in any of the treatment groups had a QTc interval greater than 500 msec. There was no statistically significant differences observed between the moxidectin and ivermectin treatment groups for any of the QTc interval changes evaluated, including greater than 30 msec or 60 msec, or with values greater than 450 msec, 480 msec or 500 msec.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 5, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210867
Product Name and Strength:	Moxidectin Tablets, 2 mg
Applicant/Sponsor Name:	Medicines Development for Global Health
FDA Received Date:	February 1, 2018
OSE RCM #:	2017-2171-1
DMEPA Safety Evaluator:	Deborah Myers, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label for moxidectin (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label for moxidectin is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Myers, D. Label and Labeling Review for Moxidectin (NDA 210867). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 26. RCM No.: 20017-2171.

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/s/

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02/05/2018

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02/06/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 26, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 210867
Product Name and Strength:	Moxidectin Tablets, 2 mg
Product Type:	Single-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Medicines Development for Global Health
Submission Date:	October 13, 2017 and December 19, 2017
OSE RCM #:	2017-2171
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the NDA approval process for moxidectin tablets, 2 mg, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label and prescribing information to identify areas of vulnerability that may lead to medication errors.

2 BACKGROUND/REGULATORY HISTORY (IF APPLICABLE) MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below includes the identified medication error issues with the submitted container label and prescribing information, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	None		
Highlights of Prescribing Information			
1.	None		

Full Prescribing Information (FPI), Section 2, *Dosage and Administration*			
1.	We note that the recommended dosage information is identical; "single dose of 8 mg (four 2 mg tablets) taken orally with or without food" in both Section 2.1 (b) (4) and Section 2.2 (b) (4).	To provide clarity and streamline dosing information.	Consider combining the dosage information from the proposed Section 2.1 (b) (4) and Section 2.2 (b) (4) under a single heading titled "*Recommended Dosage in Patients 12 Years of Age and Older*."
FPI, Section 16, *How Supplied/Storage and Handling.*			
1.	The statement "(b) (4)." is included in the PI, Section 16, *How Supplied/Storage and Handling*. However, this information related to handling and disposal is not included on the container label.	Specific information for appropriate handling of the drug product to maintain its identity, strength, quality, and purity should be included on the container label.	DMEPA defers to the Office of Pharmaceutical Quality (OPQ) to determine the appropriateness of the statement "(b) (4)." If OPQ deems this, or a similar statement in Section 16 as appropriate, we recommend that OPQ additionally request inclusion of the statement on the side panel of the container label.
2.	The statement "(b) (4)" is included in the PI, Section 16, *How Supplied/Storage and Handling*. However, this dispensing information is not included on the container label.	Specific information for appropriate dispensing of the drug product to maintain its identity, strength, quality, and purity should be included on the container label.	DMEPA defers to OPQ to determine the appropriateness of the statement "(b) (4)." If OPQ deems this, or similar statement in Section 16 as appropriate, we recommend that OPQ additionally request inclusion of the statement on the side panel of the container label.

Table 3: Identified Issues and Recommendations for Medicines Development for Global Health (entire table to be conveyed to Applicant)

Container Label			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	As currently presented the proprietary name is denoted as "(b) (4)."	N/A	You note in Section 1.18 Proprietary Names of your October 13, 2017 submission that "A proprietary name for moxidectin has not been established. The sponsor is currently considering name options and may elect to establish a proprietary name at a future date." While a proprietary name is not required, if you intend to have a proprietary name for your product we recommend that you submit your request for FDA review of your proposed proprietary name. The content requirements for such a submission can be found in the Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf. If instead you do not intend to submit a proprietary name for this product, delete "(b) (4)" and revise "moxidectin tablets" to be the most prominent information on the label.

2.	As currently presented the National Drug Code (NDC) is denoted by a placeholder (XXXX-XX-XX). However, we note that the proposed Full Prescribing Information, Section 16, *How Supplied/Storage and Handling* lists the NDC as 71705-050-01.	N/A	Add the intended NDC number to the container label and submit for our review.
3.	Currently the statement "(b) (4) " appears on the side panel of the label. In addition, this statement is inconsistent with the discard statement in the proposed Full Prescribing Information, Section 16, *How Supplied/Storage and Handling* which states, "Once open, the full contents of the container should be used within 24 hours with any unused content discarded."	Once the bottle is opened, the unused contents must be discarded after 24 hours. If the user misses the discard information, it could result in the dispensing or administration of deteriorated product.	To increase the prominence of the discard information, we recommend moving the information to the principal display panel (PDP). We recommend including a space for healthcare providers to add the date and time that the product was opened along with the reminder that the contents should be discarded 24 hours after opening. In addition, we recommend changing the color of the font, surrounding this information with a box, and/or highlighting the information to draw attention to this important information (see example below):

			Full contents of the container should be used within 24 hours with any unused content discarded. **Date and Time of first opening:** **__/__/__** **__:__ AM/PM**
4.	Currently the storage statement on the label reads (b) (4) [redacted]."	This information does not include the actual storage temperature and is not aligned with the Section 16, *How Supplied/Storage and Handling* of the proposed Prescribing Information (PI) which states, "Store below 30°C (86°F)." This omission and inconsistency could lead to improper storage.	Include the storage temperature on the container label and ensure that it is consistent with the storage information included in the PI.
5.	A drug barcode is not currently included.	The drug barcode is an important safety feature that should be part of the label whenever possible.	Add the product barcode as required per 21CFR 201.25(c)(2). Additionally, we recommend that the barcode be oriented in the vertical position to improve scannability, as barcodes placed in a horizontal position may not scan due to the curvature of the container.
6.	As currently presented the net quantity statement (500 tablets) appears directly below the product strength (2 mg).	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	We note there is no numeric overlap between the proposed strength and quantity; however, other strengths or quantities could be introduced in the future. Therefore, we recommend you relocate the net quantity statement away from the

			product strength, such as to the bottom of the principal display panel.
7.	As currently presented the “Rx only” statement appears to be the same font size (height) as the established name and strength.	The “Rx Only” statement appears more prominent than the established name and strength on the principal display panel.	Decrease the prominence of the “Rx Only” statement.
8.	As currently presented there is no “protect from light” statement on the container label. However, “Protect from light.” is included in the PI, Section 16, *How Supplied/Storage and Handling*.	Where light subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label should bear the appropriate instructions to protect the article from light.[a]	For consistency and to instruct users on proper storage, add the statement “Protect from light.” to the side panel.

4 CONCLUSION

DMEPA’s evaluation of the proposed container label and prescribing information identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 above and ask that the Division conveys the entire table to Medicines Development for Global Health so that our recommendations are implemented prior to approval of this NDA.

[a] USP General Chapter <659> Packaging and Storage Requirements

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for moxidectin that Medicines Development for Global Health submitted on December 19, 2017.

Table 4. Relevant Product Information for moxidectin	
Initial Approval Date	N/A
Active Ingredient	moxidectin
Indication	treatment of onchocerciasis due to (b) (4) *Onchocerca volvulus*
Route of Administration	oral
Dosage Form	tablet
Strength	2 mg
Dose and Frequency	8 mg (four 2 mg tablets) to be taken as a single oral dose, with or without food
How Supplied	Each high-density polyethylene bottle contains 500 tablets, a silica gel desiccant and polyester coil.
Storage	Store below 30°C (86°F). • Protect from light. • (b) (4) • Once open, the full contents of the container should be used within 24 hours with an unused content discarded. • (b) (4)
Container Closure	(b) (4) closure with (b) (4) induction liner.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 9, 2017, we searched the L:drive and AIMS using the terms, moxidectin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified zero previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following moxidectin labels and labeling submitted by Medicines Development for Global Health on October 13, 2017 (container label) and December 19, 2017 (prescribing information).

- Container label
- Prescribing Information – available at the following link: \\cdsesub1\evsprod\nda210867\0006\m1\us\draft-label-text.docx

F.2 Label Image

- Container label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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