CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210867Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210867
Drug Name:	Moxidectin 8 mg administered orally
Indication(s):	Onchocerciasis
Applicant:	Medicines Development for Global Health (MDGH)
Date(s):	Date Submitted: October 13, 2017
	PDUFA Due Date: June 13, 2018
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 4
Statistical Reviewer:	Edward Bein
Concurring Reviewers:	Karen Higgins, Dionne Price
Medical Division:	Division of Anti-infective Products
Clinical Team:	Hiwot Hiruy
Project Manager:	Kristine Park

Introduction

Via the applicant's response to a March 21, 2018 information request, the statistical reviewer learned that a key analysis file data field used for the month 18 efficacy analyses had been incorrectly programmed by the applicant.[1] This data field indicates which participants were expected to be assessed at month 18, given that protocol amendment 3 ended subsequent month 18 assessment. The applicant's response noted that the data field was correctly programmed for sites 1 and 3 but incorrectly programmed for sites 2 and 4, which resulted in 292 participants from the latter sites being incorrectly coded as not having been expected to be assessed at month 18. The applicant's response provided the dates at which protocol amendment 3 was implemented at sites 2 and 4, and this allowed the reviewer to correct the applicant's programming error. According to the original version of the data field, 932 participants (out of 1472 participants in the AR-mITT sample) were intended to be assessed at month 18; per the corrected version of the data field, 1224 in the AR-mITT sample participants were intended to be assessed at month 18.

Of the 1224 participants constituting the AR-mITT-18m sample, 817 were randomly assigned to the moxidectin arm and 407 to the ivermectin arm. Of the AR-mITT-18m participants in the moxidectin arm, 54 had missing mean mf density values at 18 months (6.6%), and of the participants in the ivermectin arm, 20 had missing mean mf density values at 18 months (4.9%).[2]

Having corrected the data field, the reviewer reran the month 18 efficacy analyses, using the corrected AR-mITT-18m sample of 1224 participants instead of the incomplete sample of 932 participants; the corrected sample includes all of the participants from the incomplete sample. In the next section, Tables 6 and 7 from the statistical review are recreated. The tables contain updated results for month 18 but present the original results for months 1, 6, and 12. These original results are included in this addendum for the convenience of the reader.

Revised Tables 6 and 7

[1] The incorrectly programmed data field is *AM3M18FL* in analysis file *adsl.xpt*.
[2] This updates month 18 values in Table 3 in the original review.

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Table 6 (Revised): Reviewer Analyses of Mean MF Density at 1, 6, 12, and 18 Months Using the AR-mITT/AR-mITT-18m Samples

Endpoint	Moxidectin	Ivermectin	Difference/ Ratio of Geometric Means
1 month			
Log(mean mf density + 1)[a]	1.06 (1.04, 1.07)	1.73 (1.61, 1.87)	0.61 (0.57, 0.66) p < .0001
Mean mf density[b]	0.10 (0.06, 0.14)	2.30 (1.68, 2.93)	-2.20 (-2.83, -1.58) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	1.07 (1.05, 1.10)	1.73 (1.61, 1.86)	0.62 (0.58, 0.67) p < .0001
Mean mf density:[b] "Worst Case"	0.31 (0.10, 0.52)	2.29 (1.66, 2.92)	-1.98 (-2.64, -1.32) p < .0001
6 months			
Log(mean mf density + 1)[a]	1.03 (1.02, 1.05)	2.84 (2.62, 3.07)	0.36 (0.34, 0.39) p < .0001
Mean mf density[b]	0.14 (0.02, 0.26)	3.71 (3.18, 4.25)	-3.57 (-4.11, -3.03) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	1.08 (1.05, 1.11)	2.83 (2.62, 3.05)	0.38 (0.35, 0.41) p < .0001
Mean mf density:[b] "Worst Case"	0.55 (0.26, 0.84)	3.70 (3.16, 4.24)	-3.15 (-3.76, -2.54) p < .0001
12 months			
Log(mean mf density + 1)[a]	1.64 (1.56, 1.72)	5.92 (5.41, 6.47)	0.28 (0.25, 0.30) p < .0001
Mean mf density[b]	1.79 (1.35, 2.22)	9.83 (8.81, 10.85)	-8.04 (-9.11, -6.98) p < .0001
Log(mean mf density + 1):[a]	1.77	5.67	0.31

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"Worst Case"	(1.67, 1.87)	(5.17, 6.20)	(0.28, 0.35) p < .0001
Mean mf density:[b] "Worst Case"	2.56 (1.99, 3.13)	9.58 (8.59, 10.57)	-7.02 (-8.12, -5.91) p < .0001
Log(mean mf density + 1):[a] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	2.53 (2.34, 2.73)	7.74 (7.01, 8.54)	0.33 (0.29, 0.37) p < .0001
Mean mf density:[b] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	6.43 (5.43, 7.44)	14.57 (13.03, 16.11)	-8.14 (-9.94, -6.34) p < .0001
18 months			
Log(mean mf density + 1)[a]	2.83 (2.63, 3.04)	8.68 (7.86, 9.58)	0.33 (0.29, 0.36) p < .0001
Mean mf density[b]	5.06 (4.28, 5.84)	15.18 (13.63, 16.74)	-10.13 (-11.74, -8.51) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	3.20 (2.96, 3.47)	7.82 (7.01, 8.72)	0.41 (0.36, 0.46) p < .0001
Mean mf density:[b] "Worst Case"	6.90 (5.90, 7.90)	14.43 (12.89, 15.96)	-7.53 (-9.25, -5.81) p < .0001

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 1224 (817 moxidectin/407 ivermectin) for month 18. Cells contain estimates and 95% confidence intervals. "Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data.

[a] Columns 2 and 3 contain estimates of arms' geometric means for 1+mean mf density, and column 4 contains estimate of ratio of arms' geometric means.

[b] Columns 2 and 3 contain estimates of arms' mean (untransformed) mean mf densities, and column 4 contains estimate of the average treatment effect (i.e., difference in means).

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

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Table 7 (Revised): Reviewer Analysis of Undetectable Skin MF Results at 1, 6, 12, and 18 Months Using the AR-mITT/AR-mITT-18m Samples

Endpoint	Moxidectin	Ivermectin	Difference	Odds Ratio
1 month				
% Undetectable Microfilariae In Skin	83.4% (81.0, 85.8)	42.9% (38.7, 47.1)	40.5% (35.7, 45.3) p < .0001	6.70 (5.26, 8.53)
% Undetectable Microfilariae In Skin: "Worst Case"	83.0% (80.7, 85.3)	43.2% (38.9, 47.4)	39.8% (35.0, 44.7) p < .0001	6.43 (5.07, 8.14)
6 months				
% Undetectable Microfilariae In Skin	91.0% (89.2, 92.8)	11.5% (8.7, 14.2)	79.6% (76.3, 82.9) p < .0001	78.32 (54.93, 111.66)
% Undetectable Microfilariae In Skin: "Worst Case"	89.8% (87.9, 91.7)	11.6% (8.8, 14.5)	78.2% (74.8, 81.5) p < .0001	66.79 (47.38, 94.14)
12 months				
% Undetectable Microfilariae In Skin	45.9% (42.7, 49.0)	5.4% (3.4, 7.5)	40.4% (36.7, 44.1) p < .0001	14.75 (9.63, 22.59)
% Undetectable Microfilariae In Skin: "Worst Case"	44.5% (41.6, 47.5)	7.8% (5.3, 10.2)	36.8% (33.0, 40.6) p < .0001	9.55 (6.65, 13.71)
18 months				
% Undetectable Microfilariae In Skin	27.5% (24.4, 30.5)	4.1% (2.1, 6.0)	23.4% (19.8, 27.0) p < .0001	8.97 (5.17, 15.54)
% Undetectable Microfilariae In Skin: "Worst Case"	26.2% (23.3, 29.2)	8.4% (5.6, 11.1)	17.9% (13.8, 21.9) p < .0001	3.89 (2.61, 5.78)

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 1224 (817 moxidectin/407 ivermectin) for month 18. Cells contain estimates and 95% confidence intervals. Percentages are of participants with undetectable skin mf; i.e., mean mf density = 0.
"Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data.

Though the month 18 results in Tables 6 and 7 change slightly, they still give evidence of the statistically significant superiority of moxidectin to ivermectin at month 18.

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/s/

EDWARD D BEIN
04/11/2018

KAREN M HIGGINS
04/11/2018
I concur.

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1 EXECUTIVE SUMMARY

This review evaluates the strength of the evidence for the efficacy and safety of moxidectin for the treatment of onchocerciasis, based on analyses of data from a Phase 3 multisite double-blinded randomized controlled trial involving 1472 participants in Democratic Republic of Congo, Liberia, and Ghana. The review concludes that there is very strong evidence for the efficacy of moxidectin relative to standard treatment (ivermectin). The reviewer defers to the clinical reviewer regarding the evaluation of safety.[1] There are no efficacy concerns regarding approval of moxidectin for the indication of onchocerciasis.

The analysis of efficacy was based on data from the 1472 participants (977 in the moxidectin arm, 495 in the ivermectin (active control) arm) in the as-randomized modified intention-to-treat (AR-mITT) sample. This sample included all participants who were randomized (per a 2:1 moxidectin:ivermectin ratio) and received study medication, and was analyzed based on the arm to which participants were randomized. Participants in the experimental arm received an oral dose of 8 mg moxidectin on day 1, while participants in the active control arm received an oral dose of ivermectin that depended on body weight on day 1. No additional doses of moxidectin or ivermectin were administered. All participants were followed for 12 months, and a subset for 18 months. The primary efficacy endpoint, density of *Onchocerca volvulus* (*OV*) microfilariae in skin, was assessed at 12 months. Secondary efficacy endpoints included density of microfilariae in skin as assessed at 1, 6, and 18 months; whether or not OV microfilariae in skin were undetectable at 1, 6, 12, and 18 months; and for the subset of 236 participants with high baseline levels of ocular microfilariae, the percent reduction by 12 months.

Data analyses of the primary endpoint by the applicant, and preferred analyses performed by the reviewer, found moxidectin to be significantly superior to ivermectin. Similarly, all analyses of the skin density and undetectability secondary endpoints by the applicant and by the reviewer found moxidectin to be significantly superior. Sensitivity analyses that explored the robustness of these analyses to violations of underlying assumptions also found moxidectin to be significantly superior to ivermectin on these endpoints. However, moxidectin and ivermectin appeared to be comparably effective at reducing ocular microfilariae by 12 months.

Analyses of safety data included the same 1472 participants, but considered the study drug actually received rather than the study drug randomized, as there were 3 participants who were administered the drug they were not randomized to. Only 2 participants in the entire sample did not experience an adverse reaction, and about 6% of adverse reactions in each arm were serious events. Fourteen participants died by 18 months (11 moxidectin (1.1%), 3 ivermectin (0.6%)).

Given the results of the analyses of the efficacy data, approval of moxidectin for the treatment of onchocerciasis is recommended, provided safety is considered acceptable by the clinical reviewer.

[1] Please refer to the clinical reviewer's review for an in-depth analysis of safety data.

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2 INTRODUCTION

2.1 Overview

Moxidectin, an anthelmintic, is used as an anti-parasitic in veterinary medicine. Wyeth and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases sponsored a Phase 2 trial (protocol number 3110A1-200-GH), conducted at a single site in Ghana from 2006-2009, to study the safety, tolerability, pharmacokinetics, and efficacy of orally administered moxidectin for the treatment of onchocerciasis in humans. This was a randomized, double-blind, single-ascending-dose study that used ivermectin, the standard treatment for individuals with *Onchocerca volvulus* (*OV*) infection, as an active control. The study was designed to have 64 participants per moxidectin dose level (2 mg, 4 mg, 8 mg), using a 3:1 randomization ratio of moxidectin to ivermectin. The primary efficacy endpoint was reduction in skin microfilariae density (mf/mg skin) from baseline to 18 months post treatment administration. Secondary endpoints included reductions in skin microfilariae density from baseline to earlier time points, including 1, 6, and 12 months, and whether microfilariae were undetectable at different time points. Starting recruitment for the next higher dose (from 2 mg to 4 mg, from 4 mg to 8 mg) was contingent on a blinded analysis of the safety and microfilariae data obtained during the first 30 days post treatment of all previously enrolled participants.

The Phase 2 trial recruited 127 for the moxidectin arm and 45 for the ivermectin arm (total 172). Data analyses led to the following conclusions.

- No serious adverse events were assessed as related to study treatment.
- Moxidectin 8 mg and 4 mg were significantly superior to ivermectin at 18 months and at all other time points with regard to reduction of skin microfilariae density.
- At months 3 and 6, the participants administered moxidectin 8 mg or 4 mg were more likely to have undetectable skin microfilariae than the participants who were administered ivermectin.

Based on this Phase 2 trial, Wyeth and the World Health Organization (WHO) sponsored the Phase 3 trial (protocol number ONCBL60801) that is reviewed here. It was a randomized, double-blind, four-site trial to study the safety and efficacy of a single oral dose of moxidectin 8 mg for the treatment of onchocerciasis, again using ivermectin as an active control. The study was conducted in three African countries from 2009-2012, and Wyeth withdrew as a sponsor in 2011. Medicines Development for Global Health (MDGH) assumed the role of sponsor in 2014. Data base lock and subsequent unblinding occurred in December 2013. The design, analysis, and results of the Phase 3 trial are reviewed in detail in the sections that follow.

The FDA was not involved in providing feedback on the design or conduct of the Phase 2 and Phase 3 trials, as the sponsors did not initiate an IND process. That is, until the submission of the present NDA, the FDA provided no feedback to the sponsors regarding either trial.

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Table 1: List of all studies included in analysis

Study number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
ONCBL60801	Phase 3	Single oral dose or moxidectin or ivermectin	At least 12 months for all participants; some followed up to 18 months	977 in the moxidectin arm, 495 in the ivermectin arm	Individuals 12 years or older with skin microfilariae density of at least 10 mf/mg

2.2 Data Sources

This review is based on material presented in the Phase 3 trial's June 22, 2017 Clinical Study Report (CSR), the trial's December 18, 2015 final Statistical Analysis Plan (SAP), a June 13, 2016 supplement to the final SAP, and on data contained in ADAM data sets.[2,3] The CSR is given at \\CDSESUB1\evsprod\NDA210867\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\onchocerciasis\5351-stud-rep-contr\studyphaseiii\studyreportbody\study-report-body.pdf. The SAP and supplement are contained in \\CDSESUB1\evsprod\NDA210867\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\onchocerciasis\5351-stud-rep-contr\studyphaseiii\statisticalmethodsinterimanalysisplan\documentation-of-statistical-methods.pdf. The data sets are contained in folder \\CDSESUB1\evsprod\NDA210867\0001\m5\datasets\phaseiii\analysis\adam\datasets. The data sets analyzed are adsl.xpt, adcm.xpt, adzs.xpt, adzq.xpt, adlb.xpt, and adae.xpt.

3 STATISTICAL EVALUATION

This section presents a detailed review of the statistical analyses of primary and secondary efficacy endpoints and safety data from the Phase 3 trial ONCBL60801. Reviewer's comments on the adequacy of the applicant's analysis are given in italics.

3.1 Data and Analysis Quality

The applicant's ADAM data sets were adequately documented, and it was possible to straightforwardly recreate the applicant's primary and secondary efficacy endpoints, as presented in the SAP and CSR. As discussed in detail below, the applicant's data analyses were flawed and

[2] The SAP and supplement are dated after data base unblinding. The prior version of the SAP was finalized prior to unblinding. When MDGH became the sponsor in 2014, it initiated a review of the prior SAP and made a small number of changes to it. The main change was to add the AR-mITT sample for analysis of the primary and secondary efficacy endpoints. The SAP supplement later added sensitivity analyses to investigate the robustness of efficacy analyses to different possible missing data mechanisms.

[3] A brief efficacy analysis of a subset of the Phase 2 trial (3110A1-200-GH) data is presented in subsection 5.2; all other analyses in the review are of the Phase 3 trial data.

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the reviewer did not attempt to replicate them. Instead, the reviewer performed corrected versions of the applicant's analyses, also described in detail below.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Phase 3 trial ONCBL60801 is a multisite, double-blind, randomized trial to investigate the efficacy and safety of a single 8 mg dose of moxidectin for the treatment of *OV* infection. Four sites participated, two in the Democratic Republic of Congo and one each in Liberia and Ghana. These sites met two pre-specified criteria: (i) Community for Directed Treatment with ivermectin not yet implemented or implemented with low geographic or therapeutic coverage, and (ii) Not co-endemic for loiasis. Each site was to enroll between 200 and 700 participants. Participants were randomized in a 2:1 ratio to the moxidectin arm or to the single-dose ivermectin active control arm (where dose was dependent on participant's weight). The randomization was stratified by sex and by two-level baseline microfilariae density (< 20 microfilariae per milligram skin vs. >= 20 mf/mg skin). Randomization was implemented manually, by an unblinded pharmacist, using applicant-generated tables of randomization codes with blocks of size 6; there was one such table for each of the four strata (e.g., stratum containing males with >= 20 mf/mg skin).

Inclusion criteria included age >= 12 years, weight >= 30 kg with *OV* infection at a density of at least 10 microfilariae/mg skin (this was implemented as at least 9.5 mf/mg skin). Exclusion criteria included prior treatment (within 6 months of study entry) with anti-nematodal drugs known or suspected to have an effect on *OV*, acute disease during the week prior to study drug administration, pregnancy, breast-feeding, and coincidental infection with Loa loa.

Participants were assessed for efficacy at months 1, 6, and 12 post study drug administration; some participants were additionally assessed at 18 months. The participants who were to be assessed at 18 months were those whose month 18 study visit was due prior to the adoption of protocol amendment 3 (which eliminated the month 18 visit) or due prior to December 31, 2011, whichever came last. Participants were assessed for safety for the first 4 days post study drug administration, at days 6 and 14, and at months 1, 3, and 6. Post-study-drug-administration use of anti-nematodal drugs diethylcarbamazine, suramin, ivermectin, albendazole, or levamisole was considered a protocol violation.

Efficacy Endpoints

The primary efficacy endpoint is *OV* mean microfilariae (mf) density (mf/mg skin) at 12 months. Skin snips were taken at four sites (left and right sides of the iliac crest and calf), microfilariae density was computed at each site, and the average of the four densities was the mean microfilariae density. If the density at one of the four sites could not be computed, then the mean density was the average of the densities at the other three sites; if the density could not be computed at two or more sites, then the mean density was considered missing.

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Secondary efficacy endpoints include

- Mean microfilariae density in skin at 1, 6, and 18 months.
- Binary variable indicating whether skin microfilariae are detectable (i.e., mean density = 0) at 1, 6, 12, and 18 months.
- For the subsample of participants with the sum of (live or dead) microfilariae in the anterior chambers of the eyes > 10 at baseline, the percentage reduction in this sum at 12 months.

3.2.2 Statistical Methodologies

Analysis Populations

Analyses of the primary and secondary efficacy endpoints were performed on the Analyzed as Randomized Modified Intent-to-Treat (AR-mITT) population. This includes all participants who received a single dose of study medication (moxidectin or ivermectin), with analyses conducted based on the arm to which participants were randomized.

The primary efficacy endpoint was also analyzed using the Modified Intent-to-Treat (mITT) population. This is the same exact set of participants as the AR-mITT population, but with analyses conducted based on the treatment which participants actually received. The mITT population was also used for analyses of safety.

Compliance Windows

The study protocol specifies that the 1 month assessment be conducted at 1 month plus-or-minus 5 days; the 3 month assessment at 3 months plus-or-minus 2 weeks; the 6 month assessment at 6 months plus-or-minus 1 month; the 12 month assessment at 12 months plus-or-minus 1 month; and the 18 month assessment at 18 months plus-or-minus 2 months.

However, the windows used for conducting data analyses differed from the compliance windows. An endpoint value was considered a 1-month outcome if it was assessed between days 22-45; considered a 3-month outcome if it was assessed between days 46-135; considered a 6-month outcome if it was assessed between days 136-270; considered a 12-month outcome if it was assessed between days 271-450; considered an 18-month outcome if it was assessed after day 450.

Overview of Statistical Analyses

The applicant specified random intercept models to analyze the primary and secondary efficacy endpoints, as described below. These models rely on normality assumptions, and the applicant noted that if residual analysis suggested this assumption failed, then a permutation test would be used in place of the multilevel model.

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For all analyses, two-sided hypothesis tests were performed, with alpha = .05.

Analysis of the Primary Efficacy Endpoint

Let j index sites (j = 1,…,4) and i index participants within sites. Let $Y12_{ij}$ represent the natural logarithm of 1 plus the 12-month primary efficacy endpoint value for the ith participant at site j; $Ybase_{ij}$ represent the natural logarithm of 1 plus the corresponding baseline value for the same participant; T_{ij} represent treatment arm assignment (1=moxidectin, 0=ivermectin) for the participant; sex_{ij} represent the sex (1=male, 0=female) of the participant; and ε_{ij} and e_j are participant-level and site-level error terms, respectively. The hierarchical linear model used to perform the applicant's analysis of the primary endpoint is

Level 1

$$Y12_{ij} = \beta_j + \beta_1 T_{ij} + \beta_2 Ybase_{ij} + \beta_3 sex_{ij} + \varepsilon_{ij}$$

Level 2

$$\beta_j = \beta_0 + e_j$$

Variance components

$$\varepsilon_{ij} \sim N\left(0, \sigma_\varepsilon^2\right); e_j \sim N(0, \sigma_e^2)$$

where all error terms are independent. β_1 gives the average treatment effect. Further, given the definition of $Y12_{ij}$, $\exp(\beta_1)$ can be interpreted as the ratio of the population geometric mean of 1+mean mf density under the moxidectin condition to the population geometric mean of 1+mean mf density under the ivermectin condition.[4] REML was used to estimate the model's parameters.

Analysis of the Secondary Efficacy Endpoints

Undetectable Microfilariae at 1, 6, 12, and 18 months

Let $undm_{ij}$ be the indicator of undetectable levels of skin microfilariae at month m (m=1, 6, 12, 18) for the ith participant at site j, where 1=undetectable, 0=detectable. Separate hierarchical logistic regression models were used to perform the analysis of each of the four undetectable indicator endpoints.

Level 1

[4] The geometric mean of a set of n positive numbers is the nth root of their product. For example, the geometric mean of a pair of positive numbers is the square root of their product.

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$$logit(undm_{ij} | T_{ij}, Ybase_{ij}, sex_{ij}, e_j) = \beta_j + \beta_1 T_{ij} + \beta_2 Ybase_{ij} + \beta_3 sex_{ij}$$

Level 2

$$\beta_j = \beta_0 + e_j$$

Variance components

$$e_j \sim N(0, \sigma_e^2)$$

where the site-level error terms are independent. The applicant understood β_1 to represent the log odds ratio of the treatment effect.

Mean Microfilariae Density at 1, 6, and 18 months

Let m index time of assessment (m=1, 6, 12, 18 months). Let Ym_{ij} represent the natural logarithm of 1 plus the mean skin microfilariae density at month m for the ith participant in site j; let $time(m)_{ij}$ indicate whether it is the month m assessment (m=1,6,12) for the ith participant in site j; and let εm_{ij} be an error term for the month m assessment of the same participant. A single repeated-measures hierarchical linear model was used to perform the analysis of these four mean density endpoints.[5]

Level 1

$$Ym_{ij} = \beta_j + \beta_1 T_{ij} + \sum_m \alpha_m time(m)_{ij} + \sum_m \gamma_m T_{ij} * time(m)_{ij} + \beta_2 Ybase_{ij} + \beta_3 sex_{ij} + \varepsilon m_{ij}$$

Level 2

$$\beta_j = \beta_0 + e_j$$

Variance components

[5] Note that the primary endpoint, mean mf density at 12 months, was included in this repeated measures analysis. Thus, the average treatment effect at 12 months was estimated twice, in the 12-month-only analysis described previously and in this repeated-measures analysis. The SAP treats the estimate of the 12-month average treatment effect from the 12-month-only analysis as definitive.

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$$\varepsilon m_{ij} \sim N\left(0, \sigma_m^2\right);\ e_j \sim N\left(0, \sigma_e^2\right); Cov\left(\varepsilon m_{ij}, \varepsilon m'_{ij}\right) = \theta_{mm'} \text{ for } m \neq m'$$

and level-1 errors are independent of level-2 errors. REML was used to estimate the model's parameters. $\beta_1 + \gamma_m$ gives the average treatment effect at month m, and exp $(\beta_1 + \gamma_m)$ can be interpreted as the ratio of the population geometric mean of 1+mean mf density under the moxidectin condition to the population geometric mean of 1+mean mf density under the ivermectin condition at month m.

Percent Reduction of Ocular Microfilariae

A hierarchical linear model analogous to the model for the primary efficacy endpoint was used, with log-transformed baseline ocular mf count used in place of log-transformed baseline mean skin mf density.

Adjustments for multiplicity

No adjustment was needed for the single primary efficacy endpoint. No adjustment was specified for the secondary efficacy endpoints.

Handling missing data

The applicant assumed that missing data were missing at random (MAR). For example, in the context of the analysis of the primary endpoint, this assumes that, within strata defined by site, sex, and baseline mean mf density, the distribution of unobserved endpoint values is identical to the distribution of observed endpoint values. Under the MAR assumption, the specified statistical models are valid in the face of missing endpoint data. Since the MAR assumption is not testable, a supplementary SAP specified several 12-month mean mf density sensitivity analyses that embodied other assumptions about missingness. In particular, it described a so-called "conditional worst case" sensitivity analysis, in which missing endpoint values in the moxidectin arm are replaced with the participant's baseline value, and missing endpoint values in the ivermectin arm are replaced with the participant's most recent endpoint observation.

Reviewer Comments

There are several grounds for questioning the adequacy of the statistical analyses:

First, multilevel models with site-level random intercepts were used to analyze primary and secondary efficacy endpoints, but these models are inappropriate given the small number of sites in the study. To quote two texts on multilevel modeling:

> *A random-effects approach should be used only if there is a sufficient number of clusters [i.e., sites] in the sample, typically more than 10 or 20. The reason for this is that the between-cluster variance ψ is poorly estimated if there are few clusters. Poor estimation of ψ translates to poor estimation of the standard error of $\hat{\beta}$ [i.e., the vector of regression coefficients].*

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Rabe-Hesketh and Skrondal (2012, p.97)[6]

This rule [of thumb] mainly depends on N, the number of groups [i.e., sites] in the data. If N is small, say N < 10, then use the analysis of covariance approach: the problem with viewing the groups as a sample from a population in this case is that the data will contain only scant information about this population.
Snijders and Bosker (2012, p. 48)[7]

Because the study only used four sites, it would be better to perform the efficacy analyses using analysis of covariance (ANCOVA) models (or their analogue for logistic regression) with site fixed effects and computing robust or nonparametric bootstrap standard errors. Such ANCOVA models have the additional important benefit that, in randomized controlled trials (RCTs), they yield consistent (i.e., asymptotically unbiased) treatment effect estimates without relying on distributional or homoskedasticity assumptions, even when the model is misspecified (Yang & Tsiatis, 2001; Tsiatis, Davidian, Zhang, & Lu, 2008).[8]

Second, regarding the undetectable microfilariae logistic regression model presented above, whether in its multilevel or analogous fixed-effects version, $exp(\beta_1)$ *is not, in general, the marginal (i.e., population-wide) odds ratio for the treatment effect. This is a consequence of the fact that the odds ratio is usually "non-collapsible;" see Agresti (2013, section 2.3.6).*[9] *Instead, use of the "standardization" or "g-computation" estimator of the marginal odds ratio yields a consistent odds ratio estimate in RCTs, even if the underlying logistic regression model is misspecified (Moore & van der Laan, 2009; further discussed below).*[10] *Additionally,* $exp(\beta_1)$ *in the fixed-effect logistic regression is a valid conditional odds ratio only under the strong assumption that all strata defined in terms of site, sex, and baseline mean mf density share a common odds ratio.*

Third, the repeated-measures analysis of the secondary mean mf density endpoints presupposes that (i) the linear relation between each longitudinal endpoint and baseline mf density, controlling for the other covariates, is the same at all timepoints, and (ii) the linear relation between each longitudinal endpoint and sex, controlling for the other covariates, is the same at all timepoints. If these do not, in fact, hold, then the model yields biased estimates of the treatment effect. It would be better to perform separate ANCOVA analyses at each timepoint, for the reasons discussed in the first reviewer comment.

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[6] Rabe-Hesketh & Skrondal (2012). *Multilevel and Longitudinal Modeling Using Stata. Volume I: Continuous Responses* (3rd ed.).
[7] Snijders & Bosker (2012). *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling* (2nd ed.).
[8] Yang & Tsiatis (2001). Efficiency study of estimators for a treatment effect in a pretest-posttest trial. American Statistician, 55, 314-321.
Tsiatis, Davidian, Zhang, & Lu (2008). Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: A principled yet flexible approach. Statistics in Medicine, 27, 4658–4677.
[9] Agresti (2013). *Categorical Data Analysis* (3rd ed.).
[10] Moore & van der Laan (2009). Covariate adjustment in randomized trials with binary outcomes: Target maximum likelihood estimation. Statistics in Medicine, 28, 39-64.

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Fourth, the analyses of 18 month endpoints included 18 month endpoint values that should have been excluded. As discussed above, protocol amendment 3 limited the number of AR-mITT participants who were intended to be assessed at 18 months. However, there were 253 additional AR-mITT participants who were not intended to be assessed at 18 months who nonetheless were assessed then and so have observed 18 month endpoint values. Because the collection of these endpoint values was contrary to the amended protocol, inclusion of these values in data analyses introduced the possibility of selection bias and so should have been avoided.

Fifth, the SAP does not address how to handle endpoints that are measured after a death or medication protocol violation. A participant's death should be considered a treatment failure, so endpoints that are assessed after death should be assigned a value indicative of treatment failure. Similarly, a medication protocol violation should be considered a treatment failure, and endpoints that are assessed after the protocol violation should be assigned a value indicative of treatment failure.

Sixth, lack of multiplicity adjustment for secondary efficacy endpoints means that, in effect, they should be considered exploratory endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In the Phase 3 trial, 1499 participants were randomized to one of the two arms, and 1472 of these received study medication. The latter set of participants constitutes the AR-mITT sample. All of the 27 participants who were randomized but did not receive study medication were from site 1, and they included the final 22 participants and 25 of the final 28 participants who were randomized at that site.

The AR-mITT sample included three participants who failed inclusion-exclusion criteria.[11] They have been retained for the data analyses reported below in order to guard against the possibility that they were singled out for extra scrutiny by study staff. The AR-mITT sample contained 977 participants randomized to the moxidectin arm and 495 participants randomized to the ivermectin arm. Site 1 contained 460 participants, site 2 contained 472, site 3 contained 299, and site 4 contained 241.

By design, all of the AR-mITT sample members were to be followed through the 12-month assessment, but, as just discussed, only a subset was intended to be followed through the 18 month assessment. This latter subset is termed the AR-mITT-18m sample. It contained 932 participants, of which 622 were randomized to the moxidectin arm and 310 randomized to the ivermectin arm. No participants from site 4 were included in the AR-mITT-18m sample; this site was the last to begin recruitment.

Baseline Characteristics

[11] The IDs of these participants are (b) (6) All were from site 3.

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Table 2 compares the moxidectin and ivermectin arms in the AR-mITT sample on baseline characteristics.[12]

Table 2: **Comparing Moxidectin and Ivermectin Arms on Baseline Characteristics in the AR-mITT Sample**

Variable	moxidectin arm	ivermectin arm	Standardized Difference[1]
gender			
male	64.0%	63.8%	.003
age			
age in years	42.1	43.3	-.078
adult (18+)	94.6%	95.2%	-.026
site			
Site 1	31.1%	31.5%	-.009
Site 2	32.2%	31.7%	.011
Site 3	20.6%	19.8%	.019
Site 4	16.1%	17.0%	-.024
baseline infection in skin[2]			
mean mf density	38.70	41.15	-.079
< 20 mf/mg	30.3%	30.5%	-.004
>=20 mf/mg to <50 mf/mg	45.4%	37.6%	.159
>=50 mf/mg to <80 mf/mg	16.1%	21.4%	-.137
>=80 mf/mg	8.2%	10.5%	-.079
baseline ocular infection (count)[3]			
>= 10 mf	15.5%	17.3%	-.047

Notes. All variables are assessed at baseline. The AR-mITT sample includes 1472 participants, with 977 in the moxidectin arm and 495 in the ivermectin arm.

[1] The standardized difference is the difference between the means in the two arms (for a binary variable, the difference in proportions) divided by the square root of a pooled standard deviation term. It gives the effect size difference between the two arms. For a binary variable, the standardized difference in arms' proportions taking the value 1 is equal to -1 times the standardized difference in arms' proportions taking the value 0. For example, the standardized difference for proportion male is .003 and the standardized difference for proportion female is -.003.

[2] One participant was missing a baseline skin infection value.

[3] Seven participants were missing baseline ocular infection values.

The largest (in absolute value) standardized differences occurred with regard to level of baseline mean mf density in skin: the moxidectin arm had a larger proportion of participants at the ">=20 mf/mg to <50 mf/mg" level, while the ivermectin arm had a larger proportion at the next highest level, ">=50 mf/mg to <80 mf/mg". Overall, the ivermectin arm had a slightly higher skin infection level.

Missing Data and Related Issues

[12] Unless otherwise noted, the results presented in the review's tables were computed by the reviewer.

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Sex, site membership, and baseline mean mf density were the covariates used in the efficacy analyses for the mean mf density and the undetectability of mf endpoints. Sex and site membership were observed for all participants in the AR-mITT sample, and one participant was missing baseline mean mf density. Baseline ocular mf count was a covariate in the analysis of the ocular percent reduction endpoint, and seven participants in the AR-mITT sample had missing values here.

Table 3 presents the amount of missing mean mf density data at different time points. Missing data rates were very small at all time points.

Table 3: **Missing Mean Microfilariae Density Endpoint Data in the AR-mITT/AR-mITT-18m Samples**

Time Point	Moxidectin	Ivermectin
1 month	5 (0.5%)	2 (0.4%)
6 months	13 (1.3%)	1 (0.2%)
12 months	27 (2.8%)	12 (2.4%)
18 months	19 (3.1%)	6 (1.9%)

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18. Number of missing endpoint values computed after filling in values for participants who died or committed medication protocol violations (explained in next section).

Table 4 presents the number of deaths at different time points. This is discussed further in the section on safety analysis, but is addressed here because it has implications for handling apparent missing endpoint data. As discussed in the reviewer's comments above, for a patient who died during the study, he/she should be treated as a treatment failure at subsequent assessment occasions, even though no endpoint value is observed at those occasions.

Table 4: **Number of Deaths in the AR-mITT/AR-mITT-18m Samples**

Time Point	Moxidectin	Ivermectin
1 month	0 (0%)	0 (0%)
6 months	3 (0.2%)	2 (0.4%)
12 months	8 (0.5%)	2 (0.4%)
18 months	8 (1.3%)	2 (0.6%)

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18.

Table 5 presents the number of medication protocol violations by different time points. This is addressed here because it has implications for handling apparent missing endpoint data. As discussed in the reviewer's comments above, for a patient who used proscribed concomitant

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medication during the study, he/she should be treated as a treatment failure at subsequent assessment occasions, whether or not an endpoint value is observed at those occasions.

Table 5: **Number of Medication Protocol Violations in the AR-mITT/AR-mITT-18m Samples**

Time Point	Moxidectin	Ivermectin
1 month	0 (0%)	0 (0%)
6 months	0 (0%)	0 (0%)
12 months	2 (0.2%)	0 (0%)
18 months	3 (0.5%)	0 (0%)

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18. There were 100 instances of the use of proscribed medication prior to study entry. Such instances were, per the protocol, examined to determine whether exclusion criteria were met. Additionally, there were 26 individuals (19 moxidectin, 7 ivermectin) whose use of proscribed medication had missing start dates, and these uses were assumed to have occurred prior to study entry.

3.2.4 Results and Conclusions

This section presents results for the primary and secondary efficacy endpoints. As discussed above, because the applicant did not specify a method for multiplicity adjustment for secondary endpoints, their analyses should, in theory, be considered exploratory. At the same time, one could argue that it would be reasonable to apply the most conservative of the standard multiplicity adjustment methods, namely, the Bonferroni adjustment, to the tests of the secondary endpoints. There are 8 secondary endpoints examined in this review, and per the Bonferroni adjustment, a test-specific alpha = .05/8 = .00625 would control the familywise error rate at .05. Further, because of limitations in the applicant's analyses, the analyses were redone by the reviewer, using the AR-mITT and AR-mITT-18m samples, via somewhat different statistical methods but retaining the same covariates. The re-analysis methods are described now, followed by a presentation of their results.

Re-analysis of Primary and Secondary Efficacy Endpoints

Prior to the re-analysis of an endpoint, the reviewer determined which participants died or committed a medication protocol violation prior to the endpoint measurement. These participants were treated as treatment failures by assigning their baseline value to the endpoint.

In analyzing mean mf density at 1, 6, 12, or 18 months, the reviewer performed ANCOVAs with randomly assigned arm (moxidectin or ivermectin), baseline mean mf density, sex, and site indicators as predictors, and computed nonparametric bootstrap standard errors for the estimators of the average treatment effect (i.e., population difference in the arm's mean endpoint values) and for the arms' mean endpoint values. The estimate of the average treatment effect is the estimated linear regression coefficient for arm. The standard error estimates were based on 2000 bootstrap samples, where each bootstrap sample was created by combining separate bootstrap

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subsamples from the two arms. This preserved the overall 2:1 randomization ratio for each bootstrap sample. Hypothesis tests were performed and 95% confidence intervals constructed based on the assumed approximate normality of the average treatment effect and mean arm value estimators.

At each of the four time points, mean mf density was analyzed in four ways. The first analysis used as the outcome variable the applicant's preferred transformation of adding 1 to the mean mf density and then taking the natural logarithm. In this analysis, the same transformation was applied to the baseline mean mf density. The second analysis used the mean mf density as is as the outcome variable, and did not transform baseline mean mf density. The analysis of the untransformed endpoint yields results that are more naturally and easily interpreted than the analysis of the transformed endpoint, but using the transformed endpoint appeared to provide more powerful hypothesis tests. If one analysis showed statistical significance but the other did not, then the analysis using the applicant's transformed endpoint was considered dispositive. These two analyses relied on the MAR assumption. The third and fourth were sensitivity analyses that redid the first two, but after filling in missing mean mf density endpoint values according to a "worst case scenario" scheme that is more severe than the applicant's proposed "conditional worst case" approach. In this scheme, missing endpoint values in the moxidectin arm were filled in with the participant's baseline value (as with the applicant's approach), indicative of treatment failure, but missing endpoint values in the ivermectin arm were filled in with zero, indicative of complete treatment success. If such a sensitivity analysis yields statistically significant results, then the corresponding analysis using (if only possible) the true though unobserved values would almost certainly also yields statistically significant results, and with larger estimated treatment effects.

One additional sensitivity analysis, suggested by the clinical reviewer, was performed for the primary efficacy endpoint. The clinical reviewer noted several medications, in addition to those proscribed by the study protocol, whose use was likely to reduce mf density. These are doxycycline, tetracycline, and mebendazole. In this sensitivity analysis, these medications were also treated as proscribed if used after study entry, and any post-study-entry use prior to 12 months was treated as indicative of treatment failure at 12 months. Further, missing 12 month endpoint values were filled in using the reviewer's "worst case scenario" scheme. This sensitivity analysis was performed twice, using the transformed and untransformed primary endpoint.

In analyzing whether mf were undetectable in skin at 1, 6, 12, or 18 months, the reviewer computed the "standardization" or "g-computation" estimate of the average treatment effect (Agresti, 2013, pp. 191-192; Snowden, Rose, & Mortimer, 2011) at each time point, using an underlying logistic regression model with arm, untransformed baseline mean mf density, sex, and site indicators as predictors, and computing nonparametric bootstrap standard errors as described above.[13] To compute the g-computation estimate, the underlying logistic regression is estimated and then, for each participant, the predicted probabilities of undetectability under each of the arms are estimated. Thus, two probabilities are estimated for each participant, irrespective

[13] Snowden, Rose, & Mortimer. (2011). Implementation of g-computation on a simulated data set: Demonstration of a causal inference technique. American Journal of Epidemiology, 173, 731-738.

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of the arm to which the participant was actually assigned. The average of the predicted probabilities for the moxidectin arm minus the average of the predicted probabilities for the ivermectin arm gives the g-computation estimate of the average treatment effect, which is consistent in an RCT even under model misspecification. Again, hypothesis tests were performed and 95% confidence intervals constructed based on the assumed approximate normality of the average treatment effect and mean arm value estimators. While the average treatment effect was targeted because of its straightforward interpretation, the g-computation estimate of the odds ratio was also computed and a 95% confidence interval was constructed for it.[14]

At each of the four time points, undetectability was analyzed in two ways. The first analysis was performed as just described, and the second was a "worst case scenario" sensitivity analysis, along the lines described above.

In analyzing percent reduction in ocular mf count by 12 months, the sample was restricted to participants with baseline ocular mf counts of 10 or greater. Then, similar to the analysis of mean mf density, percent reduction was analyzed via an ANCOVA with arm, baseline ocular mf count, sex, and site indicators as predictors. The analysis was performed twice, with log-transformed percent reduction and baseline ocular mf count, and again with the untransformed values. As discussed below, neither analysis yielded statistically significant results, so no sensitivity analyses were performed.

Results

Detailed results for reviewer analyses of the primary efficacy endpoint, the secondary endpoints for mean mf density, the secondary endpoints for undetectable mf, and the secondary endpoint of percent reduction of ocular mf by 12 months are given in Tables 6, 7, and 8. To summarize the main results:

- Primary efficacy endpoint: all analyses, of the transformed endpoint, the untransformed endpoint, and the "worst case" scenarios, yielded statistically significant results, $p < .0001$, in favor of the superiority of moxidectin over ivermectin at 12 months. Per the 12-month subtable of Table 6, the estimate of the untransformed average treatment effect is 8.04 fewer mf per mg skin using moxidectin vs. using ivermectin, with a 95% confidence interval of 6.98-9.11 fewer mf per mg skin. The corresponding estimated ratio of geometric means is 0.276, with a 95% confidence interval of 0.251-0.304.

- Secondary mean mf density endpoints: all analyses at 1, 6, and 18 months, of the transformed endpoint, the untransformed endpoint, and the "worst case" scenarios, yielded statistically significant results, $p < .0001$, in favor of the superiority of moxidectin over ivermectin.

- Secondary undetectable mf endpoints: all analyses at 1, 6, 12, and 18 months, including the "worst case" scenarios, yielded statistically significant results, $p < .0001$, in favor of

[14] Based on the normal approximation and bootstrap standard errors, a confidence interval was constructed for the log odds ratio, and then the endpoints were exponentiated to obtain a confidence interval for the odds ratio.

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the superiority of moxidectin over ivermectin. Per the 12-month subtable of Table 7, the estimate of the average treatment effect at 12 months is 40.4% more individuals with undetectable mf using moxidectin vs. using ivermectin, with a 95% confidence interval of 36.7%-44.1%. The corresponding odds ratio estimate is 14.75, with a 95% confidence interval of 9.63-22.59.

- Both analyses of percent reduction of ocular mf by 12 months yielded nonsignificant results, $p > .9$.

- All of the secondary endpoint results that are statistically significant would remain significant if the Bonferroni test-specific alpha = .00625 were used.

- The results of the reviewer's analyses, for the primary efficacy endpoint and for all of the secondary endpoints, were qualitatively similar to the applicant's analyses.

    i. For the primary endpoint at 12 months, the applicant's analysis of the AR-mITT sample yielded an estimated ratio of geometric means of 0.270, with 95% confidence interval of 0.249-0.293. This is almost identical to the results of the reviewer's analysis, as just presented. The applicant's result was also statistically significant at $p < .0001$.
    ii. Both the reviewer and the applicant found nonsignificant differences in percent reduction of ocular mf by 12 months.
    iii. Both the reviewer and applicant analyses of all other secondary endpoints yielded statistically significant results in favor of the superiority of moxidectin vs. ivermectin, $p < .0001$.

Table 6: Reviewer Analyses of Mean MF Density at 1, 6, 12, and 18 Months Using the AR-mITT/AR-mITT-18m Samples

Endpoint	Moxidectin	Ivermectin	Difference/ Ratio of Geometric Means
1 month			
Log(mean mf density + 1)[a]	1.06 (1.04, 1.07)	1.73 (1.61, 1.87)	0.61 (0.57, 0.66) p < .0001
Mean mf density[b]	0.10 (0.06, 0.14)	2.30 (1.68, 2.93)	-2.20 (-2.83, -1.58) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	1.07 (1.05, 1.10)	1.73 (1.61, 1.86)	0.62 (0.58, 0.67) p < .0001
Mean mf density:[b] "Worst Case"	0.31 (0.10, 0.52)	2.29 (1.66, 2.92)	-1.98 (-2.64, -1.32) p < .0001
6 months			
Log(mean mf density + 1)[a]	1.03 (1.02, 1.05)	2.84 (2.62, 3.07)	0.36 (0.34, 0.39) p < .0001
Mean mf density[b]	0.14 (0.02, 0.26)	3.71 (3.18, 4.25)	-3.57 (-4.11, -3.03) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	1.08 (1.05, 1.11)	2.83 (2.62, 3.05)	0.38 (0.35, 0.41) p < .0001
Mean mf density:[b] "Worst Case"	0.55 (0.26, 0.84)	3.70 (3.16, 4.24)	-3.15 (-3.76, -2.54) p < .0001
12 months			
Log(mean mf density + 1)[a]	1.64 (1.56, 1.72)	5.92 (5.41, 6.47)	0.28 (0.25, 0.30) p < .0001
Mean mf density[b]	1.79 (1.35, 2.22)	9.83 (8.81, 10.85)	-8.04 (-9.11, -6.98) p < .0001
Log(mean mf density + 1):[a]	1.77	5.67	0.31

"Worst Case"	(1.67, 1.87)	(5.17, 6.20)	(0.28, 0.35) p < .0001
Mean mf density:[b] "Worst Case"	2.56 (1.99, 3.13)	9.58 (8.59, 10.57)	-7.02 (-8.12, -5.91) p < .0001
Log(mean mf density + 1):[a] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	2.53 (2.34, 2.73)	7.74 (7.01, 8.54)	0.33 (0.29, 0.37) p < .0001
Mean mf density:[b] Expanded proscribed Concomitant medications[c] Plus "Worst Case"	6.43 (5.43, 7.44)	14.57 (13.03, 16.11)	-8.14 (-9.94, -6.34) p < .0001
18 months			
Log(mean mf density + 1)[a]	2.57 (2.36, 2.79)	7.60 (6.77, 8.53)	0.34 (0.30, 0.38) p < .0001
Mean mf density[b]	4.48 (3.60, 5.36)	14.20 (12.39, 16.01)	-9.72 (-11.63, -7.81) p < .0001
Log(mean mf density + 1):[a] "Worst Case"	2.77 (2.55, 3.01)	7.32 (6.48, 8.27)	0.38 (0.33, 0.43) p < .0001
Mean mf density:[b] "Worst Case"	5.27 (4.34, 6.20)	13.95 (12.15, 15.75)	-8.68 (-10.57, -6.78) p < .0001

Notes. N = 1472 (977 moxidectin/495 ivermectin) for months 1, 6, and 12. N = 932 (622 moxidectin/310 ivermectin) for month 18. Cells contain estimates and 95% confidence intervals. "Worst case" refers to sensitivity analyses using the reviewer's "worst case" approach to missing endpoint data.

[a] Columns 2 and 3 contain estimates of arms' geometric means for 1+mean mf density, and column 4 contains estimate of ratio of arms' geometric means.

[b] Columns 2 and 3 contain estimates of arms' mean (untransformed) mean mf densities, and column 4 contains estimate of the average treatment effect (i.e., difference in means).

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

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Table 7: Reviewer Analysis of Undetectable Skin MF Results at 1, 6, 12, and 18 Months Using the AR-mITT/AR-mITT-18m Samples

Endpoint	Moxidectin	Ivermectin	Difference	Odds Ratio
1 month				
% Undetectable Microfilariae In Skin	83.4% (81.0, 85.8)	42.9% (38.7, 47.1)	40.5% (35.7, 45.3) p < .0001	6.70 (5.26, 8.53)
% Undetectable Microfilariae In Skin: "Worst Case"	83.0% (80.7, 85.3)	43.2% (38.9, 47.4)	39.8% (35.0, 44.7) p < .0001	6.43 (5.07, 8.14)
6 months				
% Undetectable Microfilariae In Skin	91.0% (89.2, 92.8)	11.5% (8.7, 14.2)	79.6% (76.3, 82.9) p < .0001	78.32 (54.93, 111.66)
% Undetectable Microfilariae In Skin: "Worst Case"	89.8% (87.9, 91.7)	11.6% (8.8, 14.5)	78.2% (74.8, 81.5) p < .0001	66.79 (47.38, 94.14)
12 months				
% Undetectable Microfilariae In Skin	45.9% (42.7, 49.0)	5.4% (3.4, 7.5)	40.4% (36.7, 44.1) p < .0001	14.75 (9.63, 22.59)
% Undetectable Microfilariae In Skin: "Worst Case"	44.5% (41.6, 47.5)	7.8% (5.3, 10.2)	36.8% (33.0, 40.6) p < .0001	9.55 (6.65, 13.71)
18 months				
% Undetectable Microfilariae In Skin	30.5% (26.8, 34.1)	4.9% (2.4, 7.4)	25.5% (21.2, 29.8) p < .0001	8.43 (4.75, 14.98)
% Undetectable Microfilariae In Skin: "Worst Case"	29.4% (26.0, 32.8)	6.8% (4.0, 9.6)	22.6% (18.2, 27.0) p < .0001	5.72 (3.52, 9.30)

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

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Table 8: Reviewer Analysis of Percent Reduction in Ocular MF Count from Baseline to 12 months for Participants with High Baseline Ocular MF Count

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

Notes. Analysis restricted to participants in AR-mITT sample with baseline ocular mf count >= 10. N = 236 (151 moxidectin/85 ivermectin); there were 34 other participants with missing baseline ocular mf counts. 11 of the 236 participants had missing ocular mf counts at 12 months (4.7%). Cells contain estimates and 95% confidence intervals.

[a] Columns 2 and 3 contain estimates of arms' geometric means for 1+percent reduction in ocular mf, and column 4 contains estimate of ratio of arms' geometric means.

[b] Columns 2 and 3 contain estimates of arms' mean (untransformed) ocular mf counts, and column 4 contains estimate of the average treatment effect (i.e., difference in means).

3.3 Evaluation of Safety

Table 9 provides an overview of adverse events in the safety sample at 12 months, presenting data obtained from the clinical reviewer or the CSR. The membership of the safety sample is identical to the membership of the AR-mITT sample, but now participants are categorized by the medication (moxidectin or ivermectin) they actually used, rather than the medication they were assigned to use. Two participants randomly assigned to ivermectin actually were administered moxidectin and one participant assigned to moxidectin actually was administered ivermectin.

Table 9: **Overview of Adverse Events in Safety Sample at 12 Months**

Variable	Moxidectin	Ivermectin	Total
	N=978	N=494	N=1472
At least 1 treatment emergent adverse event	978 (100%)	492 (99.6%)	1470 (99.9%)
Any Mazzotti reaction	968 (99.0%)	478 (96.8%)	1446 (98.2%)
Grade 4 Mazzotti reaction	334 (34.2%)	187 (37.9%)	521 (35.4%)
At least 1 serious adverse event	60 (6.1%)	29 (5.9%)	89 (6.0%)
Death	8 (0.8%)	2 (0.4%)	10 (0.7%)

Notes. Cells in columns 2-4 give number of participants and % of participants in arm or sample.

Fourteen deaths were observed by 18 months, including several in participants who did not belong to the AR-mITT-18m sample (recall that members of the AR-mITT-18m sample were

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intended to be followed for 18 months, but some additional participants were also followed through 18 months). Of the 14 deaths observed, 11 (1.1%) were from the moxidectin arm and 3 (0.6%) from the ivermectin arm.

Please refer to the clinical reviewer's review for an in-depth analysis of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 10 presents the results of subgroup analyses of the untransformed primary efficacy endpoint; the untransformed endpoint was chosen for ease of interpretability. Besides estimating and testing efficacy within each subgroup, tests of subgroup differences in efficacy were performed. The reader should be aware that the study was not designed to have high power for detecting such differences, so nonsignificant findings here should be interpreted cautiously.

Table 10 shows that moxidectin was significantly superior to ivermectin in all of the subgroups examined, $p < .01$. More exactly, moxidectin was superior at $p < .0001$ except for the adolescent subgroup, which only contained 77 participants and hence had lower power to detect moxidectin-vs-ivermectin differences.

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Table 10: 12 month mean mf density within subgroups of AR-mITT Sample

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

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

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

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

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[c] Age group differences in efficacy are not significant, $p > .8$.
[d] Baseline infection level differences in efficacy are significant, $p < .0001$. Sample size sums to 1471 because one participant had missing baseline infection level.

4.1 Gender, Race, Age, and Geographic Region

The demographic variables examined are site attended, sex, and age group. Due to the homogeneity of the sample, race/ethnicity was not examined. See Table 10 for results. Significant site differences in efficacy were found, $p < .0001$.

4.2 Other Special/Subgroup Populations

Baseline mean mf density subgroups were examined. See Table 10 for results. Significant baseline mean mf density level subgroup differences in efficacy were found, $p < .0001$. Because of this significant finding, Table 10 includes a column providing each subgroup's overall baseline mean mf density.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer's comments in subsection 3.2.2 discuss limitations in the applicant's statistical methods for the primary and secondary efficacy endpoints. Because of these limitations, the reviewer redid the analyses, using somewhat different methods but retaining the same covariates, and obtained results that were qualitatively very similar to the applicant's results. That is, the applicant's analyses of the primary and secondary endpoints yielded statistically significant results if and only if the same held for the reviewer's analyses, and in all cases of significant results $p < .0001$. For the transformed primary endpoint, the applicant's and reviewer's point estimates and 95% confidence intervals were almost identical. Additionally, the reviewer performed "worst case" missing data sensitivity analyses that were somewhat more demanding than those proposed by the applicant, and all of the original analyses that were statistically significant remained significant in the sensitivity analyses.

Hence, the applicant's imperfect analysis of the primary endpoint does not result in incorrect inference regarding the superiority of moxidectin to ivermectin. Because the applicant did not specify an approach for multiplicity adjustment, the results of the secondary endpoint analyses should, strictly speaking, be considered exploratory. However, if the conservative Bonferroni adjustment is applied, then the significant secondary endpoint analysis results retain significance under the stricter alpha. If use of the Bonferroni adjustment seems warranted, as the reviewer believes, then it is also the case that the applicant's imperfect analysis of the secondary endpoints still results in qualitatively correct inferences regarding the relative merits of the rival medications.

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5.2 Collective Evidence

To this point, this review has entirely been based on the analysis of efficacy and safety data from the single Phase 3 trial ONCBL60801. It should be noted that all analyses of demographic and baseline mf infection level subgroups yielded statistically significant results in favor of moxidectin over ivermectin on the untransformed primary endpoint. Ten such subgroup efficacy analyses were performed, and if a conservative Bonferroni multiplicity adjustment is applied to this set of analyses (using per-test alpha = .05/10 = .005), then all ten analyses still yield significant results. These subgroup analyses therefore provide evidence of the utility of moxidectin vs. ivermectin over different geographic regions, genders, ages, and baseline infection levels.

The reviewer additionally analyzed 12-month endpoint data from a subsample from the Phase 2 (3110A1-200-GH) trial. Recall that this was a single-site trial examining moxidectin at doses of 2 mg, 4 mg, and 8 mg. The subsample included the 37 participants randomly assigned to the moxidectin 8 mg arm and the 15 participants randomly assigned to the contemporaneous ivermectin arm who had observed 12-month mean mf density data (1 additional participant assigned to the moxidectin 8 mg arm did not). Per the Phase 2 SAP, the 12-month endpoint was baseline-to-12 months mean mf density change scores, using transformed mean mf density values. The reviewer conducted a linear regression analysis of the 12 month endpoint, using arm randomized to, sex, and ordinal baseline level of mean mf density (0< to <10 mf/mg skin, 10-20, >20) as predictors and computing the nonparametric bootstrap standard error. The estimated average treatment effect (i.e., the estimated regression coefficient for arm) was .84, 95% confidence interval (based on assuming normality of the average treatment effect estimator) was (.39, 1.28), with $p < .001$. As a check that didn't rely on a normality assumption, a randomization test was also performed. This involved repeatedly (250,000 times) randomly partitioning the subsample into 37-participant and 15-participant groups, rerunning the linear regression, and recording the resulting average treatment effect estimate. The p-value was obtained by dividing the number of recorded average treatment effect estimates greater than or equal to .84 by 250,000 (Imbens and Rubin, 2015, chapter 5).[15] This randomization test yielded $p < .0001$. In sum, these Phase 2 results also provide strong evidence of the superiority of moxidectin 8 mg relative to ivermectin.

5.3 Conclusions and Recommendations

Analyses of the primary and secondary efficacy endpoints provide very strong evidence of the superiority of moxidectin vs. ivermectin during the first year post drug administration. This superiority is demonstrated across transformed and untransformed endpoints and in regular and sensitivity efficacy analyses. Therefore, approval of moxidectin for the treatment of onchocerciasis is recommended, provided safety is considered acceptable by the clinical reviewer.

[15] Imbens, G. W., & Rubin, D. B. (2015). *Causal Inference for Statistics, Social, and Biomedical Sciences: An Introduction*.

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5.4 Labeling Recommendations

It is recommended that the following be included in the label:

The assessment of safety and efficacy of MOXIDECTIN 8 mg in the treatment of onchocerciasis (b) (4) based on data from a Phase 3 randomized, multisite, double-blind, active-controlled study in 1472 patients with *Onchocerca volvulus* infection. Patients in the trial received a single oral dose of moxidectin or of ivermectin, the active control medication.

Efficacy was assessed by skin microfilariae density (microfilariae/mg skin) from the mean of 4 skin snips per person per time point up to 18 months post-treatment.

(b) (4) adult and adolescent subjects ≥ 12 years with a body weight ≥ 30 kg, ≥ 10 microfilariae per mg skin, (b) (4) 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 microfilariae per mg skin was 39.5 (± 30.7), 69.6% had ≥ 20 microfilariae/mg skin and 39.7% had at least one ocular microfilaria.

(b) (4) were recruited from the sub-Saharan African region (Democratic Republic of Congo, Liberia, Ghana) who were not previously exposed to ivermectin community directed treatment programs. The table below reports mean skin microfilariae density and the proportion of (b) (4) with undetectable skin microfilariae at Months 1, 6, 12, and 18.

(b) (4)

Endpoint	Moxidectin N=977	Ivermectin N=495	Difference
1 month			
Mean Microfilariae Density In Skin	0.10	2.30	-2.20 (-2.83, -1.58) p < .0001
% Undetectable Microfilariae (b) (4)	83.4%	42.9%	40.5% (35.7, 45.3) p < .0001
6 months			
Mean Microfilariae Density (b) (4)	0.14	3.71	-3.57 (-4.11, -3.03) p < .0001
% Undetectable Microfilariae (b) (4)	91.0%	11.5%	79.6% (76.3, 82.9) p < .0001
12 months			
Mean Microfilariae Density (b) (4)	1.79	9.83	-8.04 (-9.11, -6.98) p < .0001
% Undetectable Microfilariae (b) (4)	45.9%	5.4%	40.4% (36.7, 44.1) p < .0001

(b) (4)

Additionally, (b) (4) 2 study was conducted in adult (b) (4) in Ghana aged ≥ 18 to ≤ 60 years, (b) (4) Analysis of the baseline-to-12-month change in skin mf density showed that moxidectin 8mg was significantly superior to ivermectin, p < .001.

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/s/

EDWARD D BEIN
03/23/2018

KAREN M HIGGINS
03/23/2018
I concur.

DIONNE L PRICE
03/23/2018
Concur with conclusions