CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#:	208398
Supplement #:	SDN 1, Sequence Number 0000
Proposed Drug Name:	VERMOX® Chewable (mebendazole) 500 mg Tablets
Indication(s):	Treatment of [(b) (4)] gastrointestinal [(b) (4)] by whipworm, large roundworm, [(b) (4)]
Applicant:	Janssen Research & Development, LLC
Date(s):	April 19, 2016 (Stamp Date)
Review Priority:	6 months
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Keywords: cure rates, data transformation, geometric mean, literature review

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1 EXECUTIVE SUMMARY

This is a statistical review of a New Drug Application (NDA208389), submitted by Janssen Research and Development (hereafter referred to as the Applicant) for VERMOX® Chewable (mebendazole) 500 mg Tablets, an anthelmintic to be indicated for (b) (4) gastrointestinal (b) (4) by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); and (b) (4) The submission contains the results from four studies conducted by the Applicant: a relative bioavailability and pharmacokinetic study in healthy volunteers, a Phase 3 single-arm, open-label study, a Phase 1 food effect study and a Phase 3 efficacy and safety study. In addition, the Applicant submits a literature review based on published studies as supportive data of the efficacy of the product in the proposed indication. The main objective of this review is to investigate whether the efficacy findings of the single Phase 3 efficacy and safety study and publications included in the submission support the indication sought by the Applicant. Additionally, this review provides recommendations, in Section 5.4, for the US Prescribing Information (USPI) to be considered by the Division of Anti-Infective Products (DAIP) should mebendazole be approved.

The trial under review, referred to as GAI3003, is a prospective, randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy and safety of mebendazole compared to placebo in pediatric patients in Africa (specifically, Ethiopia and Rwanda) who are infected with single- or mixed-infections with large roundworm or whipworm, including patients also infected with hookworm. It should be noted that patients infected with hookworm only were excluded from this trial by design. In this trial, 295 pediatric patients, aged 1 to 16 years, were randomized (1:1) to receive a single-dose of mebendazole (149 patients) or placebo (146 patients). Clinical response is assessed at the test-of-cure (TOC) visit (Day 19). Clinical cure, the primary endpoint in the study, is defined as an egg count of zero at Day 19 in patients with stool samples that were positive for eggs of the respective worm(s) at baseline. Patients with missing stool samples at Day 19 are considered as failures in the analyses.

The clinical cure rates for large roundworm, whipworm, (b) (4) from GAI3003 are presented in Table 1 by each treatment arm; the difference in cure rates and associated 95% confidence intervals are also provided in this table. As shown in the table, there is a statistically significant better clinical cure rate with mebendazole compared to placebo in the treatment of large roundworm (83.7% vs. 11.1%) and whipworm (33.9% vs. 7.6%). The observed cure rates for whipworm is lower than for roundworm, however, these rates are within the range for assumed rates for whipworm at the design of the study. (b) (4)

The efficacy of mebendazole for the treatment of mixed-infection indication from study GAI3003 is evaluated in 109 patients (59 mebendazole and 50 placebo) who were infected with both large roundworm and whipworm. Among these patients, the clinical cure rate, i.e.

percentage of patients with zero egg count for both worms, is 37.2% for mebendazole and 6.0% for placebo, resulting in a difference in cure rate of 31.3%; 95% CI (12.7%, 48.2%). (b) (4)

Table 1 Clinical Cure Rates for Large Roundworm, Whipworm, and Hookworm

Infection Type	Mebendazole n/N (%)	Placebo n/N (%)	Difference[1] (95% CI)
Large Roundworm	72/86 (83.7)	9/81 (11.1)	72.6 (62.3, 82.7)
Whipworm	42/124 (33.9)	9/119 (7.6)	26.2 (16.7, 35.6)
(b) (4)			

[1] Difference in cure rates, expressed in percentages, and based on Mantel Haenzel methods to account for stratification by site, for large roundworm and whipworm; and based on (b) (4).
Failures include patients who tested positive for the worm at Day 19 or positive for the worm at baseline and had missing stool sample at Day 19.
Source: Created by the statistical reviewer using dataset "adeff xpt"

In 6 placebo-controlled studies from the literature, the efficacy of single-dose mebendazole 500 mg (oral tablet formulation) was evaluated in 571 mebendazole patients and 557 placebo patients with single- or mixed-infections with hookworm; *refer to clinical pharmacology review for the comparability of formulation used in published placebo-controlled trials to the proposed 500 mg mebendazole chewable tablet in this NDA.* (b) (4) The ages of patients varied between 2 to 71 years. The reported cure rates are highly variable and ranged from 2.9% to 91.1% for mebendazole and from 0% to 33% for placebo across all of these studies. The multiple sources of heterogeneity in the publications (such as, differences in designs, patient populations, geographic locations, intensity of infection, and endpoint ascertainment) limits the ability to further summarize this data, for example, through meta-analytic statistical methods to obtain an overall treatment effect estimate for mebendazole in the treatment of hookworm.

In conclusion, the results of the analyses of GAI3003 that are presented in this statistical review suggest that mebendazole is superior to placebo and provide evidence to support the efficacy of mebendazole for the treatment of single- or mixed-infection with large roundworm and whipworm. (b) (4)

(b) (4)

2 INTRODUCTION

2.1 Overview and Regulatory Background

This is a statistical review of a New Drug Application (NDA) that was submitted by Janssen Research & Development (JRD), hereafter referred to as the Applicant, on April 19, 2016 for VERMOX® Chewable (mebendazole) 500 mg Tablets. VERMOX® is a broad-spectrum anthelminthic that is currently available in many countries (not including the US) as a 20mg/mL oral suspension and as swallowable tablets, each containing 100 mg or 500 mg of mebendazole. Multi-dose (i.e. 100 mg administered twice daily for 3 or more days) and single-dose (i.e. 500 mg) mebendazole regimens have been used globally to treat soil-transmitted helminth (STH) infections for over 40 years. However, the 500 mg solid oral swallowable tablet formulation is only available for children 5 years or older.

The NDA currently under review proposes a newly formulated 500 mg tablet to be administered as a single-dose chewable tablet in patients 1 year or older. Additionally, for children that have difficulty chewing the tablet, it can be placed in a spoon and softened with approximately 2 to 3 mL of drinking water, which then can be easily ingested by the child. The proposed indication for this newly formulated 500 mg mebendazole chewable tablet is for the treatment of [redacted] (b) (4) gastrointestinal [redacted] (b) (4) by *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (large roundworm), [redacted] (b) (4) The Applicant is seeking regulatory approval for mebendazole 500 mg chewable tablets to facilitate access to a therapy which can help reduce morbidity and mortality associated with neglected tropical diseases not endemic in the United States (US).

In accordance with the discussions at the pre-NDA meeting[1], the Applicant submits safety and efficacy data from the following four clinical studies to support the NDA for the newly proposed 500 mg mebendazole chewable tablet:

- MEBENDAZOLGAI1001: a relative bioavailability and pharmacokinetic study in healthy volunteers
- MEBENDAZOLGAI3002: a Phase 3 single-arm, open-label safety study
- MEBENDAZOLGAI1002: a Phase 1 food-effect study
- MEBENDAZOLGAI3003: a Phase 3 efficacy and safety study

In addition, the Applicant submits a literature review based on published studies as supportive data of the efficacy of the product in the proposed indication.

This statistical review focuses mainly on an assessment of the efficacy findings from study MEBENDAZOLGAI3003, also referred to as GAI3003, titled "A Double-Blind, Randomized, Multi-Center, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of a 500-mg Chewable Tablet of Mebendazole in the Treatment of Soil-Transmitted

[1] Refer to Pre-NDA Meeting Minutes dated April 4, 2016.

Helminth Infections (*Ascaris lumbricoides* and *Trichuris trichiura*) in Pediatric Subjects". The study was designed to assess the efficacy and safety of treatment with a single 500-mg chewable mebendazole or matching placebo in pediatric patients (aged 1 to 16 years) infected with large roundworm, or whipworm. It should be noted that patients who were infected with only hookworm were not to be enrolled in the study, but were to be referred through the appropriate health care system for further evaluation, treatment, and follow-up. Patients with hookworm as well as large roundworm or whipworm were enrolled in the study.

The Applicant proposes to include findings from this study into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy for mebendazole in treatment of large roundworm, whipworm, (b) (4) Given the limited information for patients with hookworm infection in GAI3003, (b) (4) This review investigates whether the findings from the two data sources, GAI3003 and published placebo-controlled studies (b) (4) included in the submission, support the proposed indication for treatment of whipworm, large roundworm, (b) (4) and, provides recommendations for the USPI to be considered by the Division of Anti-Infective Products (DAIP) if the product is approved.

Reviewers Comment: ***Given the extent of data provided for whipworm and roundworm in GAI3003, evaluation of mebendazole efficacy in these worms based on publications included in the submission is not performed in this review.***

Refer to reviews by other disciplines for assessments of the findings from the other three clinical studies submitted as part of the NDA.

2.2 Data Sources

The application was submitted electronically and includes a full study report as well as analysis datasets that are relevant for the analyses of GAI3003 that are presented in this review. Datasets and corresponding definition files can be found at the following locations:

\\CDSESUB1\evsprod\NDA208398\0000\m5\datasets\bimo-gai3003
\\CDSESUB1\evsprod\NDA208398\0002\m5\datasets\mebendazolgai3003[2]

The following datasets are used in this statistical review:

- adae.xpt contains the adverse events data
- adsl.xpt contains the demographic data
- adeff.xpt contains the original efficacy data of clinical responses
- adeff2.xpt contains the efficacy data requested by the microbiology reviewer
- ds.xpt contains the disposition data

[2] Dataset submitted in response to request from microbiology reviewer dated April 28, 2016.

Publications of placebo-controlled studies included in the submission that investigate the efficacy of mebendazole for single- or mixed-infection with hookworm are also reviewed.

The quality and integrity of the data included in the submission will be discussed in Section 3.1.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are no major issues identified regarding the submitted data and quality of the analysis performed by the Applicant for large roundworm and whipworm in study GAI3003. It is noted that the Applicant has proposed to include cure rate estimates for large roundworm and whipworm as well as p-values from corresponding statistical analyses in the USPI. To describe the variability associated with these estimates, 95% confidence intervals are also presented in this review and recommended for the USPI should the product be approved for this indication. Additionally, given the skewed distributions of egg counts in each STH worm and the paired nature of the data, egg count reduction rates based on median of the relative change in egg count from baseline to test of cure are recommended as alternatives to the rates based on arithmetic means proposed by the Applicant for the USPI.

(b) (4)

3.2 Evaluation of Efficacy

This section presents the statistical evaluation of efficacy from study GAI3003. A review of efficacy data from published placebo-controlled studies referenced in the submission in support of hookworm indication is also described in this section. Refer to review by Dr. Sheral Patel for clinical review of efficacy.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The trial, GAI3003 that is under review in this document, is a randomized, multi-center, double-blind, parallel-group, placebo-controlled study in pediatric patients aged 1 to 16 years; at least 25 patients were to be in the 1 to 3 year age group. In addition, to be eligible for the trial, patients

had to be male or female children with confirmed soil-transmitted helminth (STH) infestations due to whipworm or large roundworm. Parents or guardians of patients must have signed an informed consent document indicating that they understood the purpose of and procedures required for the trial and were willing to have their child participate in the trial. Patients with only hookworm infestation were not enrolled in the trial, but were to be referred through the appropriate health care system for further evaluation, treatment, and follow-up. However, patients with multiple infestations that include hookworm were eligible for trial participation. The protocol lists 5 additional inclusion criteria and 11 exclusion criteria.

Reviewer's Comment: A subset of patients enrolled in the trial was selected for participation in a pharmacokinetic (PK) sub-study; refer to review from clinical pharmacology for assessment of findings from the PK sub-study.

The study was conducted in three phases: a screening phase (Visit 1), a double-blind treatment phase (Baseline/Visit 2, Double-Blind/Visit3, and Visit 4 only for patients in the PK sub-study), and a post-treatment follow-up phase (Visit 5). During the screening phase, all patients supplied a stool sample on which two Kato-Katz smears were performed. Only patients with an average positive egg count for either large roundworm or whipworm returned to the site at Visit 2 for baseline measurements and randomization. Patients with confirmed STH infection were randomly assigned to treatment with a single-dose of mebendazole or matching placebo based on a computer-generated randomization schedule prepared before the trial. The randomization was to be balanced by using randomly permuted blocks and patients were to be stratified by site and type of worm (i.e. large roundworm or whipworm). If a patient was infected with both worms, the patient was to be assigned to the stratum of large roundworm until the desired sample size was achieved for this worm; afterward such patients were to be included in the whipworm stratum. At Visit 3 (on Day 19), a second stool sample was obtained and two Kato-Katz smears were performed on this sample. All patients received a single-dose of 500 mg mebendazole chewable tablets at this visit after stool sample collection. The post-treatment follow-up visit to assess safety occurred approximately 7 days after Visit 3. Figure 1 shows the schedule of procedures and detailed assessments that were planned during the trial.

Reviewer's Comment: Defer to microbiology review by Dr. Shukal Bala for adequacy of the Kato Katz procedures implemented in this study.

Figure 1 Schedule of Procedures and Assessments for Trial GAI3003

Phase	Screening	Treatment			Posttreatment	
Period	Screening	Baseline	Double-Blind	PK Visit	Follow-up	Early Withdrawal[a]
Visit	1[b]	2[c]	3[c,d]	4 (PK subject subset only)	5 (All subjects)	
Day	-3 to -1	1	19[e]	20[f]	26[g]	
Screening/Administrative						
Informed consent	X					
Informed assent[h]	X					
Inclusion/exclusion criteria	X					
Medical history	X					
Urine pregnancy test[i]	X		X			
Hemoglobin[j]	X					
Study Drug						
Randomization		X				
Drug Administration		X[k]	X[l]			
Study Drug Accountability		X	X			
Stool sample collection for egg count analysis	X[m]		X[n]			X[o]
Safety						
Physical examination	X		X		X	X
Height	X					
Weight	X		X		X	X
BMI	X		X		X	X
Vital signs[p]	X	X	X	X	X	X
Blood samples for PK analysis			X[q,r]	X[s]		
Adverse event monitoring[t]	X	X	X	X	X	X
Concomitant therapy[u]	X	X	X	X	X	X

a Every effort will be made to perform final assessments for all subjects who withdraw from the study at any time before Visit 3.
b Only subjects with a positive egg count for any STH will be enrolled in the study.
c Subjects will be observed 3 hours posttreatment for safety evaluations.
d Subjects who come for Visit 3 and have their stool sample collected will be considered as "completers" for the study efficacy analysis.
e Day listed is an approximation. Actual day is Day 19±2 days.
f Day listed is an approximation. Actual day occurs 1 day after Visit 3.
g Day listed is an approximation. Actual day occurs 7±1 days after Visit 3.
h For children ≥6 years old.
i Female subjects who are ≥9 years old will have a urine pregnancy. If needed, the investigator may conduct additional pregnancy tests to confirm the absence of pregnancy at any time during the study. If at any time the results of the pregnancy test are positive, study drug administration will be discontinued, the subject will be followed for safety, and the pregnancy outcome will be assessed.
j Fingerstick testing using Hemocue machine.
k Subject will receive either a 500-mg chewable tablet of mebendazole or matching placebo tablet after all screening assessments are performed and results reviewed.
l All subjects will receive a 500-mg chewable tablet of mebendazole in the open-label manner.
m Two Kato-Katz smears will be performed on the stool sample. Only subjects with an average positive egg count for either STH will return for Visit 2.
n Stool collection will occur before 2nd dose of 500-mg mebendazole chewable tablet. Two Kato-Katz smears will be performed on the stool sample.
o Two Kato-Katz smears will be performed on the stool sample.
p Include heart rate, respiration rate, body temperature, and blood pressure.
q Capillary blood samples for PK analysis will be collected at the following timepoints: predose, 1, 2, 3, 5, and 8 hours posttreatment.
r One venous blood sample will be taken at the 3-hour timepoint posttreatment from each subject ages 7 to 16 years.
s The last PK blood samples (both capillary and venous collections) will be obtained 24 hours posttreatment.
t Adverse events will be assessed by direct observations of the investigator, or reported by the subject, parent, or guardian.
u Will be recorded from time the ICF is signed throughout the Follow-up visit after the last dose of the study drug administration.

Source: Extracted from the protocol (pages 15-16)

Patients were to be discontinued from study medication for various reasons including:

- If upon review of reported adverse reactions, significant safety reasons were detected
- The investigator decision
- If at any visit a patient had significant wasting (i.e. greater than 2 standard deviations below the mean WHO Child Growth Standards for weight-for-height or BMI)

If a patient discontinued study treatment before Visit 3, early withdrawal assessments were to be obtained as shown in Figure 1.

Patients could have been withdrawn from the trial because of lost to follow-up before Visit 5 or withdrawal of consent. In the case of lost to follow-up, every possible effort was to be made by the study site personnel to contact the patient and determine the reason for withdrawal.

An independent data monitoring committee (DMC) was established to provide safety oversight during the course of the trial.

3.2.1.2 Efficacy Objectives and Endpoints

This section summarizes the efficacy objectives and endpoints that are of interest in this statistical review.

The primary objective of the trial is to compare the efficacy and safety of a single dose of a 500-mg mebendazole chewable tablet and placebo in the treatment of large roundworm and whipworm in pediatrics. The two primary efficacy endpoints defined in the protocol are the cure rate for large roundworm and whipworm at the end of the double-blind treatment period. For each worm type, clinical cure is defined as an average post-treatment egg count of zero in patients who had an average positive egg count for that STH at baseline.

The two secondary efficacy endpoints defined in the protocol are egg count reduction for large roundworm and whipworm for those patients with an average positive egg count for that STH at baseline.

(b) (4)

3.2.2 **Statistical Methodologies**

This section describes the efficacy analyses performed by the Applicant, as described in the Statistical Analysis Plan (SAP) and by the statistical reviewer for the efficacy endpoints defined in Section 3.2.1.2. These analyses are based on findings during the double-blind treatment period of the trial. All statistical analyses are performed at the 0.05 significance level (two-sided).

3.2.2.1 Analysis Populations

The primary analysis population in this review is the intent-to-treat (ITT) population, which comprises all randomized patients with an average positive pre-treatment stool sample. This population is used for the analyses of the 2 primary efficacy endpoints. The analysis of each primary endpoint includes only those patients with a positive pre-treatment stool sample for the particular STH being tested. The ITT population is also used for testing of the secondary efficacy endpoints.

(b) (4)

3.2.2.2 Analyses of Efficacy Endpoints

Analyses of Primary Efficacy Endpoints

The SAP defines the following two null hypotheses for the primary endpoints:

- Null Hypothesis 1: Cure rate of large roundworm is comparable following treatment with a single dose of 500 mg chewable mebendazole compared to placebo in children infected with large roundworm, i.e. no difference in cure rates between the treatment arms.

- Null Hypothesis 2: Cure rate of whipworm is comparable following treatment with a single dose of 500 mg chewable mebendazole compared to placebo in children infected with whipworm, i.e. no difference in cure rates between the treatment arms.

These hypotheses are tested sequentially in order to preserve the overall Type I error rate at 0.05 (two-sided), i.e. superiority for the first primary endpoint (cure for large roundworm) must be established before testing of superiority on the second primary endpoint (cure for whipworm).

The Applicant's planned analysis for each primary endpoint is based on a stratified Cochran-Mantel-Haenszel (CMH) test, i.e. controlling the effect of site, and performed in ITT patients positive for the particular STH being tested. In this review, difference in cure rates for each primary endpoint is also presented based on Mantel Haenzel methods to account for stratification by site along with corresponding 95% confidence interval (CI) for the difference in cure rates between the two treatment groups. For the analyses of the primary endpoints, ITT patients with missing post-treatment stool samples are considered failures in the analysis of the respective STH.

Analysis of the Secondary Efficacy Endpoints

For the analysis of each secondary endpoint, a logarithmic transformation is first performed on the baseline and post-treatment average patient level egg counts to account for the positively skewed distribution of the egg count data. As there are patients with an egg count of zero eggs in the post-treatment stool sample, i.e. cures, a value of 1 is added to egg count at baseline and egg

count at post-treatment so that the logarithmic transformation can be applied. The geometric mean, average of logarithmic transformed data, is used to summarize the mean egg count at baseline and post-treatment visits for the treatment arms. For each STH present at baseline, relative change in egg count from baseline to post-treatment is determined for each patient, to account for the paired nature of the data, as follows:

$$\frac{\text{(egg count at post-treatment – egg count at baseline)}}{\text{egg count at baseline}} \times 100\%$$

The overall egg count reduction rate for each STH is then calculated as the median of the relative change in egg count from baseline to post-treatment and presented for each treatment arm.

Reviewer's Comment: The Applicant presents overall egg count reduction rate for each STH based on a group mean change from baseline to post-treatment that does not take into account the paired nature of the data.

Treatment differences in mean egg count are evaluated by an analysis of covariance (ANCOVA), in which the logarithm of the egg count at post-treatment is the dependent variable, site and treatment as fixed effect, and the logarithm of the average egg count at baseline is the covariate. Baseline values are used for patients with missing post-treatment data in the analyses presented in this review; according to the study report, no imputation was performed by the Applicant for the missing values.

Analysis of Exploratory Endpoint and Subgroup Analyses

For the exploratory hookworm endpoints, cure rate estimates for each treatment group and 95% CI for the difference in cure rates are presented using exact methods to account for the small sample of patients with positive baseline stool sample for hookworm infection. In addition, descriptive summaries are provided for percent egg count reduction for each treatment group.

Cure rate estimates and 95% CI for the difference in cure rates for large roundworm and whipworm are presented separately in the following subgroups defined at baseline:

- Age group: less than 2 years, 2 to 5 years, 5 to 11 years, 11 to 15 years
- Sex: male, female
- Country and site
- Intensity of infection: light, moderate, severe

The cure rate estimates and 95% CIs are also presented for single- v. mixed-infections at baseline. For mixed-infections, a patient is considered to be cured if the post-treatment egg count is zero for all STH that were present at baseline, otherwise considered a failure.

Normal approximations, i.e. without stratification by site, are utilized for all subgroup analyses. Subgroup analyses are based on exact methods for small samples.

All efficacy analyses presented in this review are performed using in SAS Version 9.4.

3.2.3 **Patient Disposition, Demographic and Baseline Characteristics**

Study GAI3003 randomized a total of 295 patients (149 randomized to mebendazole and 146 randomized to placebo) at 2 sites in Ethiopia and 1 site in Rwanda; approximately 86% of patients are from the Ethiopian sites. There were 167 patients (86 randomized to mebendazole and 81 to placebo) confirmed with large roundworm at baseline and 243 patients (124 randomized to mebendazole and 119 to placebo) confirmed with whipworm at baseline. Only 13 of the randomized patients were confirmed with hookworm at baseline.

The majority of patients (approximately 94%) in both treatment groups completed the double-blind treatment period; see Table 2. There were 17 patients (8 mebendazole and 9 placebo) who were withdrawn from the trial prior to completion of the double-blind treatment period. The most commonly reported reason for withdrawal from the trial was "withdrawal by subject".

Table 2 Patient Status at End of Double-blind Treatment Period

	Mebendazole N=149	**Placebo N=146**
Patient Status, n (%)		
Completed	141 (94.6)	137 (93.8)
Withdrawn	8 (5.4)	9 (6.7)
Reported Reasons for Withdrawal, n (%)		
Withdrawal by subject	7 (4.7)	5 (3.4)
Lost to follow-up	0 (0)	3 (2.1)
Physician Decision	0 (0)	1 (0.7)
Protocol Violation	1 (0.7)	0 (0)

Source: Created by the Statistical Reviewer using dataset "adsl xpt" and "ds xpt"

The distributions of demographic characteristics were similar across the mebendazole and placebo treatment arms; refer to Table 3. Most subjects were between 5 and 11 years; 27 subjects (13 mebendazole and 14 placebo) were 1 to 3 years old per study design requirement that at least 25 subjects in this age group.

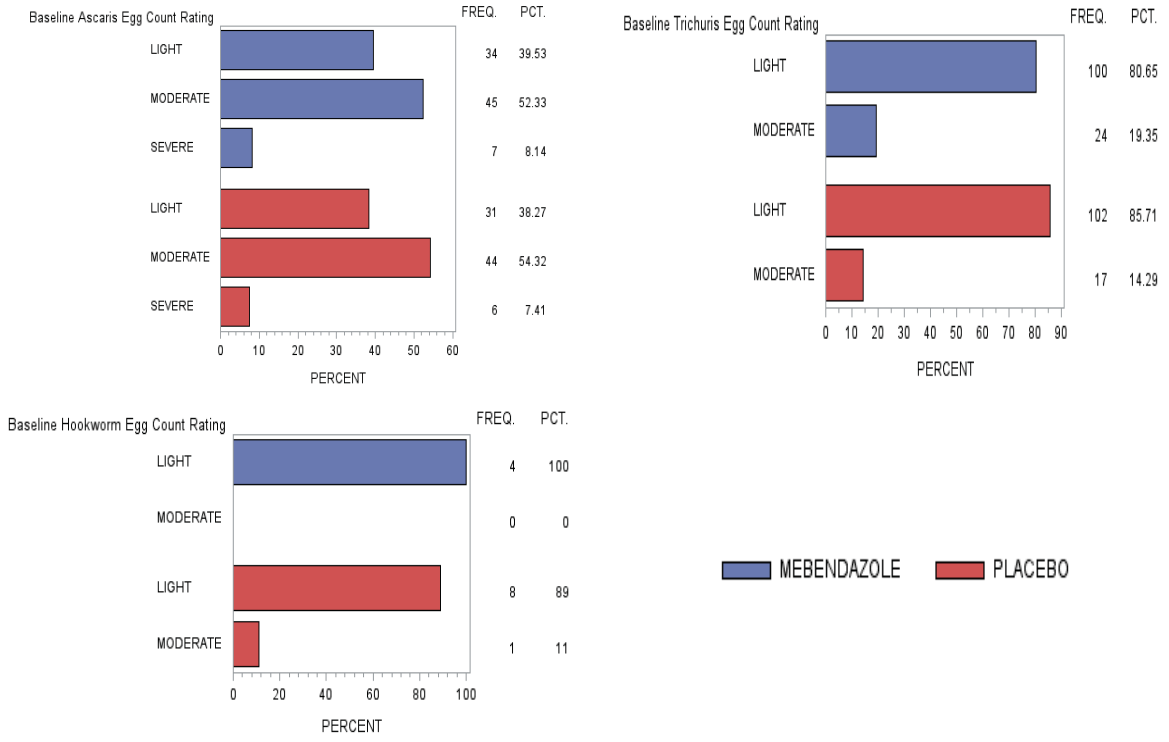
The distributions in intensity were generally similar between treatment groups for each of the STH present at baseline; see Figure 2. The majority of patients had light to moderate intensity across all STH infestations present at baseline.

Table 3 Distribution of Baseline Characteristics

Baseline Characteristics	Mebendazole N=149	Placebo N=146
Sex, n (%)		
Female	78 (53.4)	74 (50.7)
Male	71 (47.6)	72 (49.3)
Age Group, n (%)		
Less than 2	7 (4.7)	7 (4.8)
2 – 5	15 (10.1)	12 (8.2)
5 – 11	99 (66.4)	106 (72.6)
11 – 16	28 (18.8)	21 (14.4)
Age, in years		
Mean (SD)	7.9 (3.3)	7.7 (3.1)
Median (Range)	8 (1 – 15)	8 (1 – 15)
Country, n (%)		
Ethiopia	128 (85.9)	127 (87.0)
Rwanda	21 (14.1)	19 (13.0)

All patients in study reported as "Black or African American".
Source: Created by the Statistical Reviewer using dataset "adsl.xpt"

Figure 2 Distribution of STH Intensity at Baseline



Ascaris=large roundworm, Trichuris=whipworm, FREQ=number of patients, PCT=percent patients per treatment arm
Intensity based on the following egg count categories defined in the study report: light (1-4999), moderate (5000-49999), and severe (≥50,000) for large roundworm; light (1-999), moderate (1000-9999), and severe (≥10000) for whipworm; and light (1-1999), moderate (2,000-3999), and severe (≥4000) for hookworm.
Source: Created by the Statistical Reviewer using "adsl.xpt"

3.2.4 **Results and Conclusions**

3.2.4.1 Results and Conclusions from GAI3003

This section summarizes the findings from the reviewer's analyses of cure rate and egg count reduction for large roundworm and whipworm as well as exploratory analyses for hookworm from GAI3003. Results for all subgroup analyses, including those for mixed infections, are presented in Section 4 of this review.

Results from Analyses of Primary Endpoints: Clinical Cure

For large roundworm, the clinical cure rate observed in the mebendazole arm (83.7%) is statistically significantly better than the cure rate observed in the placebo arm (11.1%) for the ITT population at the TOC time point; see Table 4. The difference in cure rates is 72.6% with 95% CI (62.3%, 82.7%). These findings support the superiority of mebendazole over placebo in treatment of large roundworm infection.

The findings for whipworm are also shown in Table 4. For this STH worm, the clinical cure rate observed in the mebendazole arm (33.9%) is statistically significantly better than the cure rate observed in the placebo arm (7.6%) for the ITT population at the TOC time point. The difference in cure rates is 26.2% with 95% CI (16.7%, 35.6%). These findings support the superiority claim of mebendazole over placebo in treatment of large roundworm infection.

Reviewer's Comment: ***The observed cure rates for whipworm are notably lower than observed for large roundworm. Nonetheless, these lower cure rates are within the range of the assumed rates for whipworm at the design stage of this trial as described in the SAP.***

Table 4 Clinical Response Rate at Day 19 for Large Roundworm and Whipworm

STH Infection Type	**Mebendazole All=149**	**Placebo All=146**	**Difference[1] (95% CI)**
Large Roundworm	**N= 86**	**N=81**	
	n (%)	**n (%)**	
Cure	72 (83.7)	9 (11.1)	**72.6 (62.3, 82.7)[2]**
Failure	9 (10.5)	67 (82.7)	
Missing	5 (5.8)	5 (6.2)	
Whipworm	**N=124**	**N=119**	
	n (%)	**n (%)**	
Cure	42 (33.9)	9 (7.6)	**26.2 (16.7, 35.6) [2]**
Failure	76 (61.3)	103 (86.6)	
Missing	6 (4.8)	7 (5.8)	

[1]Difference in cure rates, expressed as percentages, based on using Mantel Haenzel methods to account for stratification by site. Similar findings without stratification, the difference in cure rate is 72.6%, 95% CI (62.2%, 83.0%) for large roundworm and 26.3%, 95% CI (16.7%, 35.9%) for whipworm.
[2]P-value <0.001 based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
Failures include patients who tested positive for the worm at Visit 3 (Day 19, i.e. test-of-cure)..
Source: Created by the statistical reviewer using dataset "adeff.xpt"

Results from Analyses of Secondary Endpoints: Egg Count Reduction

A statistically significant higher mean egg count is observed for mebendazole compared to placebo; see Table 5. The egg count reduction rate for mebendazole arm (100%) is higher than the egg count reduction rate observed in the placebo arm (30%) at Day 19. These findings provide supportive data of the efficacy of mebendazole for treatment of large roundworm infection.

Table 5 Egg Count Reduction Rate at Day 19 for Large Roundworm

	Mebendazole	**Placebo**
Baseline, (eggs/g)		
N	86	81
Geometric Mean	5801.3	6259.0
Median (Range)	9389.6 (48; 117384)	10560.0 (36; 90840)
Post-treatment, (eggs/g)		
N	81	76
Geometric Mean	1.9*	2116.4
Median (Range)	0 (0; 20064)	5932.9 (0; 143040)
Egg Count Reduction Rate	100%	30%

Geometric mean, median, and range calculated from log transformed data. Egg count reduction rate based on median of the individual relative change in egg count from baseline to post-treatment; see definition in Section 3.2.1.2. *p-value<0.001 for difference in mean egg counts, based on analysis of covariance in which the log transformed post-treatment egg count is the dependent variable with site and treatment as fixed effects and the log transformed baseline egg count as a covariate.
In the ANCOVA model and egg count reduction rate, the baseline egg count is used for 10 patients (5 mebendazole and 5 placebo) with missing data at Day 19.
Source: Created by the statistical reviewer using "dataset adeff2.xpt"

As shown in Table 6, the secondary analysis for whipworm results in a statistically significant difference in mean egg count for mebendazole patients compared to placebo patients. The egg count reduction rate for mebendazole is 81.2% and for placebo is 27.4% at Day 19. These findings provide supportive data of the efficacy of mebendazole for treatment of whipworm infection.

Reviewer's Comment: Given the small number of patients with missing post-treatment data, the findings from the secondary analyses performed by the reviewer which utilizes baseline data for those patients with missing post-treatment data, are comparable to those obtained by the Applicant whereby no imputation is performed for missing data.

Table 6 Egg Count Reduction Rate at Day 19 for Whipworm

	Mebendazole	**Placebo**
Baseline, (eggs/g)		
N	124	119
Geometric Mean	209.2	270.8
Median (Range)	168 (12; 8808)	264 (12; 5916)
Post-treatment, (eggs/g)		
N	118	112
Geometric Mean	23.4*	150.2
Median (Range)	53.7 (0; 10536)	209.9 (0; 7704)
Egg Count Reduction Rate	81.2%	27.4%

Geometric mean, median, and range calculated from log transformed data. Egg count reduction rate based on median of the individual relative change in egg count from baseline to post-treatment; see definition in Section 3.2.1.2.
*p-value<0.001 for difference in mean egg counts, based on analysis of covariance in which the log transformed post-treatment egg count is the dependent variable with site and treatment as fixed effects and the log transformed baseline egg count as a covariate.
In the ANCOVA model and estimation of egg count reduction rate, baseline egg count is used for 13 patients (6 mebendazole and 7 placebo) with missing data at Day 19.
Source: Created by the statistical reviewer using "dataset adeff2.xpt"

Results from Exploratory Endpoint Analyses

Among the 13 patients with confirmed hookworm infestation at baseline, the cure rate is (4/4 or 100%) in patients randomized to mebendazole and (2/9 or 22.2%) in patients randomized to placebo; difference in cure rates of 77.8% and 95% CI (17.1%, 99.4%). In addition, a higher egg count reduction rate is observed for patients with hookworm infection at baseline who were randomized to mebendazole (100%) compared to placebo patients (10.9%). Given the limited number of patients with hookworm at baseline; further examination of the efficacy findings from placebo-controlled studies from publications included in the submission is performed in the section that follows.

3.2.4.2 Literature Review of Placebo-Controlled Studies

There are 6 placebo-controlled studies investigating the efficacy of single-dose 500 mg mebendazole oral tablet (571 patients) compared to placebo (557 patients) for treatment of single- or mixed-infection with hookworm that are contained in the submission. A summary of the designs of these studies is presented in the Appendix of this review. Defer to clinical pharmacology review for the comparability of formulations used in published placebo-controlled trials to the proposed 500 mg mebendazole chewable tablet in this NDA.

Reviewer's Comment: ***The Appendix presents 8 publications which are referred to by the Applicant as placebo-controlled studies in the submission. However, two of these studies are omitted from this review: one study by Albonico et al. 2002 is omitted because it is an uncontrolled study and one study by Larocque 2006 is omitted because it is a study assessing***

low birth weight in pregnant women; cure rates are not provided for the placebo arm in this study.

There are multiple sources of variability in the designs of these studies, such as, differences in age groups, blinding (single- vs. double-blind), species of hookworm evaluated, sample size, geographic locations, and endpoint ascertainment. Additionally, various techniques (e.g. arithmetic means vs. geometric means) are utilized for summarizing the mean egg counts. Furthermore, it appears that the reported cure rates and egg count reduction rates in some studies (namely, Sacko *et al.*, Albonico *et al*. and Charoenlarp *et al.)* do not incorporate data from all patients infected with hookworm at baseline and randomized to treatment, but based only on those patients with fecal samples available at the test-of-cure time points. For these reasons, meta-analytic methods are not employed in this review to estimate an overall treatment effect, such as overall mean cure rate or egg count reduction rate, from these studies and such overall effects, as proposed by the Applicant, are not recommended for the USPI. Additionally, given that there are studies in which reported rates appear to exclude patients based on post-randomization factors, confidence intervals s around the rate estimates for the individual studies are not presented in this review. Instead, what follows is a discussion of descriptive summaries based on reported cure rates and egg count reduction rates for the individual studies as well as a summary of the range of cure rates for each treatment arm across all studies.

Table 7 shows the reported cure rates and egg count reduction rates across the 6 placebo-controlled trials reviewed separated by geographic location. The cure rates for mebendazole appears to be notably better than placebo in two studies, one study by Sacko *et al.* conducted in Africa in which the reported cure rate for mebendazole is 51.4% compared to placebo rate of 16.7% and one study by K. Abadi conducted in Asia in which the cure rate for mebendazole is 91.1% compared to 0% for placebo. Similarly, mebendazole appears better than placebo in reducing egg count for these two studies. Three studies (Charoenlarp *et al.*, Albonico *et al.*, and Flohr et al.) all conducted in Asia, which have the largest sample sizes of the placebo-controlled studies and conducted entirely in pediatric patients, report small differences in cure rates (less than 5%) between mebendazole and placebo; more favorable differences are noted for mebendazole compared to placebo based on egg count reduction rates. The remaining study by De Clercq *et al*. which was conducted in Africa reports essentially no difference in cure rates between the treatment arms and the reported egg count reduction rates suggest that egg count actually increased for mebendazole but decreased for placebo. It should be noted that rates are not provided based on patient subgroups across all publications; as such, it is unclear whether the variable results observed are due to differences in age, geographic location, (b) (4) or other factors.

Table 7 Cure Rates and Egg Count Reduction Rates in Published Placebo Controlled Studies

Location	Author, Publication year	Age in years	Treatment Arm	Number Analyzed	CR in %	ERR* in %
Africa	De Clercq, D. *et al.* 1997	3 to 71	MBZ	35	22.9	-6.5
			PBO	31	22.6	32.7
	Sacko, M. *et al.* 1998	3 to 71	MBZ	35	51.4	68.5
			PBO	36	16.7	-38.9
Asia	Abadi, K. 1985	2 to 70	MBZ	45	91.1	98.3
			PBO	43	0	13.5
	Charoenlarp, P. *et al.* 1993	6 to 14	MBZ	130	2.9	68.6 (median)
			PBO	127	0.7	21.5 (median)
	Albonico, M. *et al.* 2003	schoolchildren	MBZ	236	7.6	52.1 (geometric)
			PBO	242	3.4	16.0 (geometric)
	Flohr, C. *et al.* 2007	6 to 11	MBZ	90	38	52
			PBO	78	33	41

CR=cure rate, ERR=egg count reduction rate
*Egg count reduction rate based on arithmetic mean, unless otherwise specified. Negative reduction rate indicates increased egg count.
Source: Created by the statistical reviewer from publications of placebo-controlled studies referenced in submission.

In sum, the reported cure rates for mebendazole are generally higher than placebo across all 6 studies; (b) (4) . A single range for egg count reduction rates is not described given the different methods used in determining the mean egg count. (b) (4) . As such, the reviewer defers to clinical expertise on the ability to rely on the efficacy of whipworm and round worm (b) (4)

3.3 Evaluation of Safety

This section presents descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), using MedDRA preferred terms version 18.0, for each treatment arm based on data from trial GAI3003 only. These summaries are provided for the double-blind safety analysis set, which is defined in the SAP as all randomized patients who receive 1 dose of study medication at baseline. It should be noted that there are no safety endpoints defined in the protocol or by the clinical team that require statistical analysis for this trial.

The double-blind safety analysis set comprises 284 patients, 144 mebendazole and 140 placebo. The percentages of these patients who reported a TEAE during the double-blind period of the trial are low and comparable between the treatment arms: 9/144 (6.3%) in mebendazole and 8/140 (5.7%) placebo. None of these events are reported as serious events and there were no deaths reported in the study

***Reviewer's Comment**: No further assessments of safety are provided in this statistical review; defer to clinical review by Dr. Sheral Patel for detailed assessment of mebendazole safety from all available data in the submission.*

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the results of analyses conducted by the reviewer to assess clinical cure at Day 19 in GAI3003 within the specified subgroups; all subgroups are defined based on pre-treatment measurements. There are no adjustments for the multiple comparisons presented in this section; therefore, these analyses are conducted for descriptive purposes only and should be interpreted with caution.

4.1 Age, Gender, and Country

Table 8 shows results from subgroup analyses of clinical cure for large roundworm by age, gender, and country; within each country, site-level analyses are also presented. Recall that all patients were reported as "Black or African American" in this trial, so analyses by race are not applicable. As shown in the table, there are no apparent differences in clinical cure rates based these subgroups; findings are generally consistent with the overall results for this worm.

Table 8 Clinical Cure Rates for Large Roundworm by Age, Gender, and Country

Subgroup	**Cure Rate**		**% Difference (95% CI)**
	Mebendazole n/N (%)	**Placebo n/N (%)**	
Gender			
Female	39/44 (88.6)	6/42 (14.3)	74.4 (60.2, 88.5)
Male	33/42 (78.6)	3/39 (7.7)	70.9 (53.2,84.2)*
Age Group, in years			
Less than 2	5/6 (83.3)	0/4 (0)	83.3 (17.2, 99.6)*
2 – 5	5/6 (83.3)	3/8 (37.5)	45.8 (-9.9, 83.0)*
5 – 11	52/60 (86.7)	6/52 (11.5)	75.1 (62.9, 87.4)
11 – 16	10/14 (71.4)	0/17 (0)	71.4 (39.2, 91.6)*
Country			
Ethiopia	59/68 (86.8)	6/66 (9.1)	77.7 (67.0, 88.3)
Site 251001	*27/33 (81.8)*	*1/33 (3.0)*	*78.8 (58.7, 91.3)**
Site 251002	*32/35 (91.4)*	*5/33 (15.2)*	*76.3 (60.9, 91.6)*
Rwanda (Site 250001)	13/18 (72.2)	3/15 (20.0)	52.2 (18.3, 77.3)*
Overall	**72/86 (83.7)**	**9/81 (11.1)**	**72.6 (62.2, 83.0)**

Patients with missing Day 19 Kato Katz measurements treated as failures for this analysis.
*Exact confidence interval provided; otherwise based on normal approximation to the binomial.
Source: Created by the statistical reviewer using dataset "adeff xpt"

Table 9 shows no apparent differences in clinical cure rates in whipworm for the age, gender, and region subgroups; findings are generally consistent with the overall results for this worm.

Table 9 Clinical Cure Rates for Whipworm by Age, Gender, and Country

Subgroup	Cure Rate		% Difference (95% CI)
	Mebendazole n/N (%)	Placebo n/N (%)	
Gender			
Female	28/64 (43.8)	4/60 (6.7)	37.1 (19.7,52.8)*
Male	14/60 (23.3)	5/59 (8.5)	14.9 (2.0, 27.7)
Age Group, in years			
Less than 2	1/2 (50.0)	1/5 (20.0)	30.0 (-52.0, 89.9)*
2 – 5	2/11 (18.2)	0/9 (0)	18.2 (-26.6, 57.4)*
5 – 11	30/85 (35.3)	8/88 (9.1)	26.2 (14.4, 38.0)
11 – 16	9/26 (34.6)	0/17 (0)	34.6 (4.6, 60.6)*
Country			
Ethiopia	35/103 (34.0)	8/101 (7.9)	26.1 (15.5, 36.6)
Site 251001	*14/31 (45.2)*	*5/29 (17.2)*	*27.9 (5.7, 50.2)*
Site 251002	*21/72 (29.2)*	*3/72 (4.2)*	*25.0 (8.1, 40.8)**
Rwanda (Site 250001)	7/21 (33.3)	1/18 (5.6)	27.8 (-4.7, 56.7)*
Overall	**42/124 (33.9)**	**9/119 (7.6)**	**26.3 (16.7, 35.9)**

Patients with missing Day 19 Kato Katz measurements treated as failures for these analyses.
*Exact confidence interval provided; otherwise based on normal approximation to the binomial.
Source: Created by the statistical reviewer using dataset "adeff xpt"

4.2 Other Special/Subgroup Populations

Table 10 shows the findings for clinical cure rate by intensity of each STH infestation at baseline.

Table 10 Clinical Cure Rates for Large Roundworm and Whipworm by Intensity

	Cure Rate		% Difference (95% CI)
	Mebendazole n/N (%)	Placebo n/N (%)	
Intensity of Large Roundworm			
Light (1 – 4,999)	29/34 (85.3)	6/31 (19.4)	65.9 (47.6, 84.3)
Moderate (5,000 – 49, 999)	38/45 (84.4)	3/44 (6.8)	77.6 (64.7, 90.6)
Severe (≥50,000)	5/7 (71.4)	0/6 (0)	71.4 (18.1, 96.3)*
Intensity for Whipworm			
Light (1 – 999)	39/100 (39.0)	9/102 (8.8)	30.2 (19.2, 41.2)
Moderate (1000 – 9999)	3/24 (12.5)	0/17 (0.0)	12.5 (-18.6, 90.6)*

Patients with missing Day 19 Kato Katz measurements treated as failures for these analyses. Intensity determined based egg count categories defined in the study protocol.
*Exact confidence interval provided; otherwise based on normal approximation to the binomial.
Source: Created by the statistical reviewer using dataset "adeff.xpt"

Of importance in this statistical review is to assess whether the data from trial GAI3003 support an indication for treatment of single- or mixed-infections with whipworm or large roundworm as

proposed by the Applicant. For these assessments, to be considered a cure a patient with mixed-infections must be cured at Day 19 of all STH that were present at baseline; otherwise, patient is considered a failure. Also, a single-infection means that each patient has exactly one STH present at baseline. This differs from the analyses presented in Section 3.2.4 whereby a patient could have multiple STH at baseline, but clinical cure of each STH is analyzed separately. Recall that there are only 13 patients with hookworm infection in GAI3003, therefore, subgroup analyses by multiple-infection that includes hookworm (e.g. hookworm and whipworm) are not informative and omitted from this review.

The results presented in Table 11 show that the clinical cure rate for mebendazole is higher than placebo in single-infections with large roundworm or whipworm; these findings are consistent with those presented in Section 3.2.4. There were 109 patients (59 mebendazole and 50 placebo) in the study who were infected with both worms, i.e. mixed-infections. Among these patients, the clinical cure rate, i.e. percentage of patients with zero egg count for both worms, was 37.2% for mebendazole and 6.0% for placebo, resulting in a difference in cure rate of 31.3%; 95% CI (12.7%, 48.2%).

Table 11 Clinical Cure Rates by Single- vs. Mixed-Infection

Type of Infection at Baseline	Cure* Rate		% Difference (95% CI)
	Mebendazole n/N (%)	Placebo n/N (%)	
Single-Worm Infection[1]			
Large Roundworm Only	21/24 (87.5)	0/25 (0)	87.5 (66.2, 97.3)**
Whipworm Only	20/62 (32.3)	3/62 (4.8)	27.4 (9.2, 44.3)**
Mixed-Worm Infection*			
Large Roundworm & whipworm	22/59 (37.2)	3/50 (6.0)	31.3 (12.7, 48.2)**

17 patients with missing Day 19 Kato Katz measurements treated as failures for these analyses.
*For patients with mixed-worm infections, cure means all worms present at baseline have been cleared at Day 19.
[1]By study design, there were no patients with only hookworm randomized in Trial GAI3003.
**CI based on exact method.
Source: Created by the statistical reviewer using dataset "adeff2 xpt"

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are some important statistical issues to be considered when interpreting the findings of this review. (b) (4)

(b) (4) Recall this is the primary comparative study conducted by the Applicant to provide evidence for safety and efficacy of mebendazole for the proposed indication. However, by design of this study, patients

who were infected with hookworm alone were excluded from the study. Given this design constraint, only 13 patients (4 mebendazole and 9 placebo) were infected with hookworm (along with whipworm or large roundworm) in the trial, (b) (4)

Secondly, the Applicant has proposed to include in the USPI overall weighted mean cure rates and egg count reduction rates for the mebendazole arm alone from 24 publications as well as these overall estimates for mebendazole and placebo arms from 8 "placebo-controlled" studies. There are a few notable concerns, described below, which make reliance of these overall weighted estimates for demonstrating efficacy of mebendazole problematic:

- Clinical response from the mebendazole arm alone from the 24 publications does not demonstrate the clinical benefit of the product over comparator. It is noted that even if comparative assessments had been proposed, interpretation would be challenging given the multiple comparators among all of these publications.

- Two out of the 8 publications of placebo-controlled studies referenced in the submission and proposed for the USPI are considered not adequate for assessing the efficacy of mebendazole: one study was actually a non-comparative study and one study assessed low birth weight in pregnant women.

- There are multiple sources variability in the designs of the remaining 6 placebo-controlled studies, such as, differences in age groups, species of hookworm evaluated, sample size, geographic locations, and endpoint ascertainment. Additionally, various techniques (e.g. arithmetic means vs. geometric means) are utilized for summarizing the mean egg counts. Furthermore, there is uncertainty of the extent to which patients and investigators are blinded in these studies and cure rates and egg count reduction rates in some publications are based only on those patients with fecal samples available at the test-of-cure time points, rather than all patients positive for hookworm at baseline.

5.2 Collective Evidence

This review evaluates the efficacy of mebendazole in two data sources, namely, trial GAI3003 and 6 publications of placebo-controlled studies in hookworm included in the submission. The results from trial GAI3003 show that the clinical cure rate (the primary endpoint in the study) for mebendazole is superior to placebo; and therefore, provide evidence to support the proposed indication for the treatment of single- or mixed-infections with large roundworm or whipworm.

For hookworm, the results from trial GAI3003 suggests a significant difference in cure rates between mebendazole and placebo; however, this result is based only on 13 patients with mixed infections (b) (4) In the publications of 6 placebo-controlled trials reviewed, the reported cure rates for mebendazole are generally higher than placebo across all studies; however, the rates were quite variable and ranged from 2.9% to 91.1% in mebendazole patients and from 0% to 33% in placebo patients. A notably higher rate for mebandazole compared to placebo was reported in two studies, one study by Sacko *et al.* conducted in Africa in which the reported cure rate for

mebendazole is 51.4% compared to placebo rate of 16.7% and one study by K. Abadi conducted in Asia in which the cure rate for mebendazole is 91.1% compared to 0% for placebo. However, the cure rates for mebendazole was only slightly higher (<5%) than placebo in the remaining four studies. It is unclear whether the variable results observed are due to differences in age, geographic location, species of hookworm, or intensity of hookworm, or other factors.

5.3 Conclusions and Recommendations

Given the findings from the analyses presented in this review for trial GAI3003, mebendazole has been shown to be superior to placebo for treatment of single- or mixed-infections with large roundworm or whipworm.

Regarding the hookworm indication, the observed cure rates for mebendazole are generally higher than placebo across the 6 published placebo-controlled studies reviewed and in study GAI3003 conducted by the Applicant. However, given the variability in the observed clinical cure rates in these two data sources, heterogeneous study designs in the publications and limited data on hookworm in GAI3003, it is difficult to adequately assess, from a statistical perspective, the strength of these findings to support an indication for treatment of single- or mixed-infection with hookworm. (b) (4)

5.4 Labeling Recommendations

This section summarizes the major labeling recommendations for Section 14 ("Clinical Studies") of the VERMOX® USPI should the product be approved for (b) (4) with *Ascaris lumbricoides* (large roundworm), *Trichuris trichiura* (whipworm), (b) (4) *Note that label negotiations are ongoing at the time of this statistical review.*

(b) (4) The recommended table for the USPI is shown in Table 13 and includes all responses (cures, failures, and missing) for each of these infection types as well as the 95% confidence intervals to illustrate the variability around the estimated cure rates.

(b) (4)

Table 13 Recommended Table for Large Roundworm and Whipworm for the USPI

Infection Type	VERMOX™ Chewable 500 mg All Patients=149	Placebo All Patients=146	Difference[1] (95% CI)
	N= 86	**N=81**	
Ascaris lumbricoides	**n (%)**	**n (%)**	
Cure	72 (83.7)	9 (11.1)	**72.6 (62.3, 82.7)[2]**
Failure	9 (10.5)	67 (82.7)	
Missing	5 (5.8)	5 (6.2)	
	N=124	**N=119**	
Trichuris trichiura	**n (%)**	**n (%)**	
Cure	42 (33.9)	9 (7.6)	**26.2 (16.7, 35.6)[2]**
Failure	76 (61.3)	103 (86.6)	
Missing	6 (4.8)	7 (5.8)	

[1]Difference in cure rates, expressed in percentages, and based on Mantel Haenzel methods to account for stratification by site.
[2]P-value <0.001 based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
Failures include patients who tested positive for the worm at Visit 3 (Day 19, i.e. test-of-cure).

(b) (4)

(b) (4)

(b) (4)

Given the concerns raised in this review with the referenced publications in the submission, the recommended language for the USPI if the hookworm indication is granted is as follows:

The efficacy of mebendazole 500 mg single-dose for the treatment of mixed and/or single infections with *Ancylostoma duodenale* or *Necator americanus* (hookworm) has been evaluated in 6 placebo-controlled trials. In these 6 studies, a total of 571 mebendazole patients and 557 placebo patients were evaluated for clearance of hookworm eggs at the end of the respective treatment follow-up periods. Treatment follow-up varied from 2 weeks up to 4 weeks and ages of patients ranged from 2 to 71 years. Reported clinical cure rates ranged from 2.9% to 91.1% for mebendazole and from 0% to 33% for placebo across all of these studies.

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/s/

JANELLE K CHARLES
09/23/2016

KAREN M HIGGINS
09/23/2016
I concur.