CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208398Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	208398
Link to EDR	EDR Link
Submission Date	April 19,2016
Submission Type	Priority
Brand Name	Vermox Chewable
Generic Name	Mebendazole
Dosage Form and Strength	500 mg Chewable Tablet
Route of Administration	Oral
Proposed Indication	Treatment of single or mixed gastrointestinal infections by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); (b) (4) [redacted]
Proposed Dosing Regimen	One 500 mg Vermox Chewable tablet as a one-time dose
Applicant	Janssen Pharmaceuticals, Inc.
Associated IND	115959
OCP Review Team	Abhay Joshi, PhD
OCP Team Leader	Philip Colangelo, PharmD, PhD

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1. EXECUTIVE SUMMARY

This NDA 208398 is for Vermox Chewable, which is a rapidly disintegrating 500 mg mebendazole chewable tablet. The Applicant is seeking approval for the treatment of (b) (4) gastrointestinal infections by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); (b) (4) The proposed dosing regimen is one 500 mg Vermox Chewable tablet as a one-time dose in adult and pediatric patients 1 year of age and older.

A chewable tablet formulation containing 100 mg mebendazole was approved in the US in 1974 for the treatment of *T. trichiura*, *A. lumbricoides*, *Enterobius vermicularis*, and *A. duodenale* and *N. americanus* (hookworm) in single or mixed infections at a dosage regimen of 100 mg BID x 3 days for a total dose of 600 mg. This tablet formulation has been discontinued from the US market. The 500 mg solid oral Vermox tablet is not marketed in the US, however, the Applicant states that this formulation is currently being donated to World Health Organization (WHO) for use in preventive chemotherapy programs for soil transmitted helminth (STH) infections in school-age children in approximately 60 countries.

The currently proposed drug product, i.e., 500 mg Vermox Chewable tablet formulation, has been developed by the Applicant to address the WHO recommendations of improving the ease of use in young children who may not be able to swallow the 500 mg solid oral tablet. This formulation is specifically designed to be a single-dose, age-appropriate formulation to allow for the treatment of children down to 1 year of age.

Under the clinical development program, the Applicant has conducted four clinical studies in support of the proposed drug product; specifically, one bioavailability study (phase 1), one food effect study (phase 1), one safety study (phase 3), and one safety & efficacy study (phase 3). From these clinical studies, three studies had pharmacokinetic (PK) assessments. However, these three studies assessed the PK of two different formulations: (1) One study with an investigational chewable formulation and is referred as "Previous Chewable" formulation and, (2) Two studies with the final to-be-marketed chewable formulation, which is a fast disintegrating chewable tablet and is referred as "New Chewable" formulation. The relative BA / PK of the "New Chewable" tablet was determined by historical comparison to the PK of the "Previous Chewable" tablet by the Applicant.

For the proposed drug product, the intended site of action is gastrointestinal tract (GI tract) for the proposed treatment and the extent of systemic exposure is not expected to relate directly with the proposed drug product's efficacy; however, to compare the abovementioned formulations, the systemic exposure results were evaluated.

From a Clinical Pharmacology perspective, the following are key review issues:

(1) Higher systemic exposure to mebendazole from the proposed 500 mg chewable tablet formulation in younger children 1 to < 3 years of age as compared to systemic exposure in older children ≥3 years of age and adults.
(2) Food effect on systemic exposure to mebendazole following administration of Vermox Chewable tablet.
(3) Evaluation of capillary sampling as a surrogate for traditional venous PK plasma sampling in pediatric and adult patients.

1.1 Recommendations

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends that NDA 208398 for Vermox Chewable be approved for the treatment of (b) (4) gastrointestinal infections by *T. trichiura* (whipworm); *A. lumbricoides* (large roundworm); (b) (4) From a Clinical Pharmacology perspective, the primary concern was the observed higher exposure in the youngest pediatric patients (1 to < 3 years) than the older pediatric patients (3 to 16 years) and adults. However, the Clinical Pharmacology recommendation was based on the absence of association between higher systemic exposure and safety findings in the Applicant provided clinical study reports (Medical Review by S. Patel, MD).

	Review Issues	Review Issues Recommendations and Comments
1	Higher mebendazole systemic exposure in young pediatric patients (age 1 to < 3 years)	The mean mebendazole systemic exposure from a single dose of 500 mg mebendazole chewable tablet was approximately 4-fold higher in the youngest pediatric patients (1 to < 3 years) than the older pediatric patients (3 to < 7 years and 7 to 16 years) and adults. The higher exposure was partially attributed to the fixed ("non-weight normalized") dosing strategy of one 500 mg chewable tablet as a one-time dose. However, the observed higher exposure in pediatrics (>1 years) was deemed clinically insignificant based on the safety data from the same study. Thus, the proposed single one-time 500 mg dose of Vermox Chewable in pediatric patients is acceptable from a Clinical Pharmacology perspective.
2	Food effect	In healthy volunteers, administration of the newer to-be-marketed mebendazole chewable tablet formulation with a high fat breakfast resulted in approximately 3- to 4-fold higher systemic exposure compared to when administered under fasted conditions. However, there was no apparent association between higher systemic exposure and safety findings, based on review of safety data from the same study. Thus, Vermox Chewable tablets will be recommended to be given without regard to meals/food.
3	Capillary sampling method in pediatric and adult patients	The Applicant's proposal to use whole blood mebendazole concentrations from fingerstick capillary samples as a surrogate for venous PK plasma sampling was not acceptable because of the observed sporadic higher concentrations in some capillary samples, in both pediatrics and adults. For the majority of inconsistences, mebendazole concentrations in capillary fingerstick samples were higher than concentrations in respective venous plasma samples; therefore, it can be approximated that the mebendazole plasma levels will be equal or lower than the levels that are detected in the fingerstick samples. Therefore, the Reviewer agrees with the Applicant's proposed approach of using mebendazole concentrations in whole blood capillary fingerstick samples as "worst case" or "maximum" estimates for the systemic PK exposure to mebendazole.

The Reviewer's proposed labeling changes/recommendations in **Section 2.3** will be forwarded to the Applicant.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Under the clinical development program, the Applicant has conducted four clinical studies in support of the proposed drug product; out of which, three studies had pharmacokinetic (PK) assessments. However, these three studies assessed the PK of two different formulations: (1) One study used an investigational chewable formulation, which is referred as "Previous Chewable" formulation and, (2) Two studies used the final to-be-marketed chewable formulation, which is a fast disintegrating chewable tablet and is referred as "New Chewable" formulation. The summary of each clinical study is listed in Table 1 below with the information on respective formulations that were tested. In addition, the Applicant has also provided a literature-based Clinical Pharmacology summary for mebendazole.

Table 1: List of Clinical Studies Conducted in Support of the New 500 mg Mebendazole Chewable Tablet (source: Module 2 5 Clinical Overview Table 1)

Study / Formulation	Dosing / Treatment Model	Planned / Actual Number of Subjects	Study Design	Primary Objective
MEBENDAZOLGAI1001 Previous Chewable	A single 500-mg oral dose of VERMOX tablet vs single 500-mg oral dose of mebendazole chewable tablet	20/19	An open-label, single-dose, relative bioavailability, randomized, 2-way crossover design study	To determine the relative bioavailability of a new chewable tablet formulation of mebendazole with respect to the currently marketed tablet in healthy adult subjects
MEBENDAZOLGAI1002 New Chewable	Treatment A (Reference): A single 500-mg dose of mebendazole, fast disintegrating chewable tablet formulation, in the fasted condition. Treatment B (Test): A single 500-mg dose of mebendazole, fast disintegrating chewable tablet formulation, just after ingestion of a high-fat breakfast	16/16	A Phase 1, open-label, randomized, single-center, single-dose, 2-way crossover study	To evaluate the effect of food on the bioavailability of mebendazole from a single 500-mg oral dose of a rapidly disintegrating chewable tablet formulation of mebendazole in healthy adult subjects
MEBENDAZOLGAI3002 Previous Chewable	A single mebendazole 500-mg chewable tablet on Day 1 followed by 30 min of observation. Subjects returned to the study center 3 days (±1 day) postdose for safety assessments	375/396	An open-label, single-center, single-dose, single-arm safety study	To assess the safety and tolerability of a mebendazole 500-mg chewable tablet formulation in a pediatric population (children 2 to 10 years of age, inclusive)
MEBENDAZOLGAI3003 New Chewable	A single mebendazole 500-mg rapidly disintegrating chewable tablet or a matching placebo was given after screening and baseline assessments. All subjects were given a single mebendazole 500-mg fast disintegrating chewable tablet at Day 19 followed by PK assessments in a subpopulation of subjects	250/295	A randomized, multicenter, double-blind, parallel-group, placebo-controlled study	To compare the efficacy and safety of a single dose of a new 500-mg rapidly disintegrating chewable tablet of mebendazole and placebo in the treatment of *A. lumbricoides* and *T. trichiura* in pediatric subjects aged between 1and 16 yrs followed by PK assessments in a subpopulation of subjects

It is noteworthy from Table 1 that although the relative BA of the "Previous Chewable" tablet was compared to the Vermox solid oral tablet, the relative BA comparison was not done between the "New Chewable" to the "Previous Chewable" tablet formulation, or between the "New Chewable" to the Vermox solid oral tablet formulation. However, there was a food effect study conducted with the "New Chewable" tablet (see Section 2.1.4 below), and efficacy and safety were determined with both the "New Chewable" and "Previous Chewable" tablet formulations in pediatric patients. The relative BA / PK of the "New Chewable" tablet was determined by historical comparison to the PK of the "Previous Chewable" tablet and Vermox solid oral tablet (see Section 2.1.3 below), by the Applicant.

The Vermox solid oral tablet has established safety and efficacy. In addition, based on internal discussion with the Medical reviewer, this formulation has been used extensively in pediatrics. The relative BA / PK results between Vermox solid oral tablet and of the "Previous Chewable" tablet suggests that the BA from the latter formulation is higher (mean Cmax↑ by 50% and mean AUC↑ by 68%). Since, the reported mebendazole systemic exposure from the "Previous Chewable" tablet (BA study, GAI1001) was similar to the reported exposure from the "New Chewable" tablet (Food effect study, GAI1002), it can be approximated that the "New Chewable" tablet will also have similar BA. In addition, the efficacy and safety of both chewable tablet formulations were deemed acceptable by the Medical Reviewer (S. Patel, MD) in clinical studies MEBENDOZOLGAI3002 and -3003 (see Table 1 above). In addition, despite of the higher exposure from the chewable formulation, no notable differences in safety were detected (based on internal discussion).

Therefore, based on the abovementioned assessments, the Applicant proposed link between the PK of the "New Chewable" tablet to the PK of the "Previous Chewable" tablet, and to the Vermox solid oral tablet are deemed to be acceptable by the Clinical Pharmacology review team.

2.1 Pharmacology and Clinical Pharmacokinetics

The following are the key Clinical Pharmacology relevant findings from the studies that were conducted in support of the proposed drug product. Literature based Clinical Pharmacology information on mebendazole is summarized in Section 3.1.

2.1.1 Measurement of Systemic Mebendazole Exposure by Fingerstick Capillary Sampling

To assess the systemic exposure to mebendazole in pediatric patients, the Applicant proposed to use whole blood mebendazole concentrations determined from fingerstick capillary samples as a surrogate of plasma concentrations from venous samples. However, results that were submitted in support of the proposed relationship/surrogacy had inconsistencies; specifically, the drug concentrations determined in some capillary fingerstick samples were sporadically higher than the concentrations determined in the respective venous plasma samples. These sporadic inconsistencies were observed in the PK data from two clinical studies; specifically, the adult PK data from study GAI1002 and the pediatric PK data from study GAI3003. Therefore, the proposed relationship cannot be used for any definitive quantitative inferences or for any additional assessments such as effect of weight or age on PK/clearance. However, given that in most inconsistences, capillary fingerstick samples had higher concentrations than the respective venous plasma samples, it can be approximated that the mebendazole plasma levels will be equal or lower than the levels that are detected in the fingerstick samples. Therefore, the Reviewer agrees with the Applicant's proposed approach of using mebendazole concentrations in whole blood capillary fingerstick samples as "worst case" or "maximum" estimates of the systemic PK exposure to mebendazole.

2.1.2 Comparison of Exposure to Mebendazole in Adult Subjects and Pediatric Patients

The reported information on the adult exposure from the New 500 mg Vermox Chewable tablet was derived from the venous plasma sampling. However, fingerstick capillary sampling was used to derive parameter estimates for mebendazole systemic PK exposure in pediatric patients following administration of the New 500 mg Vermox Chewable tablet. In patients who were < 3 years of age, the mean systemic exposure was substantially higher (> 3-fold) than in patients who were ≥ 3 years of age (Table 2*). However, in pediatric patients who were 3 to 16 years of age, mean systemic exposure to mebendazole was similar or lower than adult exposure (Table 2*). The Applicant has partially attributed the observed higher mebendazole exposure in the younger pediatric patients to the fixed ("non-weight normalized") dosing strategy, i.e., one single 500 mg mebendazole chewable tablet. In addition, as noted previously, the drug concentrations in capillary fingerstick samples were sporadically higher than concentrations in venous plasma samples; therefore, these reported exposure parameter estimates could be overestimated.

Table 2: Mean Capillary Whole Blood Mebendazole Pharmacokinetic Parameters by Age Group and Comparison with the Plasma Pharmacokinetic Parameter Estimates in Adults*

	Reported Estimates				Compared to Adult Estimates (Fold increase)		
	1 to <3 years# (N = 20)	≥3 to <7 years# (N = 12)	≥7 to 16 years# (N = 10)	Adults$ (N = 16)	1 to <3 years	≥3 to <7 years	≥7 to 16 years
Mean C_{max} (ng/mL)	174	49.9	34.2	56.2	3.7	0.9	0.6
Maximum C_{max} (ng/mL)	881	101	52.1	156	5.6	0.6	0.3
Mean AUC_{Last} (ng*h/mL)	1320	416	387	456	2.9	0.9	0.8
Maximum AUC_{Last} (ng*h/mL)	4076	874	747	986	4.1	0.9	0.8

$Adult PK parameter estimates are calculated from plasma samples in fed condition
#Pediatric PK parameter estimates are calculated from whole blood capillary fingerstick samples and most administrations were with food

Nevertheless, there was no apparent association between higher mebendazole systemic exposure and safety findings observed in Study GAI3003 (see Safety Results under Individual Study Report Section 4.2.3 below and Medical Officer's review).

2.1.3 Relative Bioavailability of the Proposed Formulation

The proposed final to-be-marketed formulation, i.e., "New Chewable" formulation is a fast-disintegrating chewable tablet that contains 500 mg mebendazole. However, the "New Chewable" tablet was not compared directly to the solid oral tablet formulation, which is currently being used in more than 60

* The PK information in Table 2 is revised information, which is also presented later in this Review (Section 4.2.3 on page 33). These revisions are based on the updated information that was provided by the Applicant in a subsequent submission that affects GAI3003 PK sub-study results. As per the updates, two subjects were excluded (Subjects 251001272 and 251002233) from the PK analysis based on protocol violations; however, these exclusions do not have any significant impact on the PK conclusions and Clinical Pharmacology inferences. Please see the individual study review in Section 4.2.3 on page 33 for the details.

countries for mass treatment (not in the US), or to the "Previous Chewable" tablet, which was an investigational 500 mg mebendazole chewable formulation. The relative bioavailability was assessed between the "Previous Chewable" tablet and Vermox 500 mg solid oral tablet. Given the reported systemic exposure to mebendazole from the "Previous Chewable" tablet formulation (BA study, GAI1001) was similar to the exposure from the "New Chewable" tablet (subsequent food effect study, GAI1002), the relative BA / PK of the "New Chewable" tablet was determined by historical comparison to the PK of the "Previous Chewable" tablet and Vermox solid oral tablet by the Applicant.

The PK parameter estimates resulting from the three different 500 mg mebendazole formulations are compared in Table 3 below. The systemic exposures of mebendazole from both chewable tablet formulations were higher compared to the exposure resulting from the solid oral tablet (Table 3 below). The mean and range of C_{max} were comparable between the "Previous Chewable" and "New Chewable" tablet formulations; while the mean AUC estimate for the "New Chewable" tablet was slightly higher (~30%) than that of the "Previous Chewable" formulation, and the "New Chewable" tablet also showed a higher degree of inter-subject variability as indicated by the range and SD (74% CV vs. 66% CV, respectively).

Table 3: Comparison of Exposure Parameters Derived from Venous Plasma Sampling (Mean (SD), Range) Resulting from the Different Formulations in Adults, Fasted (source: Module 2 7 2 Summary of Clinical Pharmacology Studies Table 19)

PK parameter	VERMOX 500-mg solid tablet[a] n=18	Previous MBZ chewable 500-mg tablet[a] n=18	New MBZ chewable 500-mg tablet[b] n=16
C_{max} (ng/mL)	9.36 (7.74)	14.1 (10.3)	14.0 (9.17)
Range	1.31 – 29.6	3.07 – 37.1	3.95 – 40.6
AUC_{last} (ng.h/mL)	79.9 (59.7)	134 (88.5)	175 (129)
Range	2.01 - 253	32.5 - 388	18.4 – 553

[a] Source Study GAI1001
[b] Source Study GAI1002
MBZ=mebendazole

2.1.4 Food Effect

Systemic exposure to mebendazole from the New 500 mg Chewable tablet was approximately 3- to 4-fold higher when administered with a high fat breakfast compared to when administered under fasted conditions to healthy adult volunteers (Table 4). Please refer to Sections 2.2.1 and 4.2.2 for detailed results.

Table 4: Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Pharmacokinetic Parameters Following Administration of New Chewable formulation (a 500 mg Fast-Disintegrating Chewable Tablet) With and Without Food (source: Clinical Study Report GAI1002, Table 4)

Parameter	Geometric Mean Treatment B: Fed (Test, n=16)	Geometric Mean Treatment A: Fasted (Ref, n=16)	Geometric Mean Ratio (%) (90% CI)	Intra-Subject CV (%)
C_{max} (ng/mL)	48.29	11.69	412.97 (326.65; 522.11)	39.03
AUC_{last} (ng.h/mL)	396.38	136.55	290.28 (244.82; 344.19)	27.87
AUC_{∞} (ng.h/mL)[a]	NR	NR	NR	NR

[a] AUC_{∞} could not be reliably estimated due to unacceptable variability in the terminal phase (r^2adj.<0.90)
CI = confidence intervals, CV = coefficient of variation, NR = Not reported
Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
Test: Mebendazole 500-mg fast-disintegrating chewable tablet administered under fed state
Ref : Mebendazole 500-mg fast-disintegrating chewable tablet administered under fasted state

2.1.5 Comparison of Exposure to Mebendazole Metabolites in Adult Subjects and Pediatric Patients

Two major metabolites of mebendazole are formed, i.e., (1) amino metabolite due to hydrolysis ("hydrolyzed metabolite"), and (2) hydroxylated metabolite due to reduction ("reduced metabolite"). The hydrolyzed metabolite is inactive, whereas, the reduced metabolite has been reported to have limited anthelmintic activity.

In the clinical studies conducted in support of the proposed "New Chewable" mebendazole tablet, the observed metabolite-to-parent ratio (MPR) values were greater than one, in both adults and in pediatric patients. This indicates that systemic exposure to these metabolites is greater than the parent drug mebendazole. In addition, compared to adults, the MPRs for exposure parameters in pediatrics were lower, which suggests that there may be differences in metabolism of mebendazole as a function of age. However, the available data from this study are limited to draw a definitive conclusion. In addition, these differences are of limited clinical relevance due to: (1) the reduced metabolite's limited desired pharmacological activity and, (2) the established safety profile of mebendazole in both adults and pediatrics. In addition, it was noted by the Reviewer that at least some of the samples were analyzed outside of the established stability window that was determined during the bio-analytical method validation.

Considering this information, the reported mebendazole metabolite levels in pediatric patients within this submission are of little value.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The proposed dosing is one single tablet of Vermox Chewable 500 mg (one-time dose). For patients that may have difficulty in chewing the tablet, the proposed alternative administration method is to form a

soft mass – of semi-solid consistency – by placing the chewable tablet on a spoon and adding 2-3 mL of drinking water. The effect of alternative administration methods on the proposed product's BA is not known.

With regard to drug administration and food intake, despite the observed increase in PK exposure (approximately 3- to 4-fold) when Vermox Chewable 500 mg tablet was taken with a high-fat meal vs. fasted, this is deemed to be clinically insignificant since mebendazole has an established wide margin of safety with respect to dose and/or systemic exposure (Medical Review by S. Patel, MD). With regard to safety, higher instances of treatment related GI discomfort/disorders have been observed in clinical trials when given in the fasted state than when given in the fed state. However, the overall rate of GI discomfort/disorders was low (< 4%). Therefore, from a Clinical Pharmacology perspective, Vermox Chewable can be administered without regard to food intake for the proposed indications.

2.2.2 Therapeutic Individualization

Therapeutic individualization is not needed for the proposed Vermox Chewable tablet for the STH indications.

2.3 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling recommendations:

- In ***Dosage and Administration*** section (Section 2), the following should be included:
  VERMOX™ Chewable 500 mg tablet can be taken without regard to food intake

- The ***Clinical Pharmacology*** section (Section 12.3 Pharmacokinetics) is incomplete; therefore, the following recommendations will be forwarded to the Applicant:

  We recommend the following to be included in the PK section of the labeling (12.3):

  (1) Inclusion of PK parameter estimates (i.e, AUC, Cmax, Tmax) from the Clinical Study that was conducted in adults, which assessed the PK of the newer to-be-marketed chewable formulation.

  (2) In particular, provide greater level of PK data / information regarding the food effect that was determined with the newer chewable tablet formulation.

- In ***Specific Populations: Pediatric*** *section* (Section 12.3), the following should be included:
  - ***Based on a limited number of blood samples, the pediatric pharmacokinetic results indicated that children aged 1 to 3 years have higher systemic exposure than in adults.***

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

Following is the collective summary of Clinical Pharmacology relevant information based on: (1) the Applicant provided literature references (2) the report of a clinical study that was conducted utilizing the "Previous Chewable" formulation, and (3) the reports of the clinical studies that were conducted utilizing the proposed final to-be-marketed "New Chewable" tablet formulation.

3.1 Overview of the Product and Regulatory Background

At present, the only approved mebendazole formulation in the US is a 100 mg mebendazole chewable tablet. This formulation was approved by FDA in 1974 for the treatment of *T. trichiura, A. lumbricoides, E. vermicularis,* and *A. duodenale* and *N. americanus* (hookworm) in single or mixed infections. The Applicant also reports that for the same indications, a different 500 mg Vermox solid oral mebendazole tablet formulation is currently used in approximately 60 countries. The Applicant also reports that both the formulations, i.e., 100 mg chewable and 500 mg solid oral tablets, are listed in *"World Health Organization (WHO) Model List of Essential Medicines for Children for the treatment of soil transmitted helminth (STH) infestations"*.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Absorption:

Mebendazole has been reported to have (b) (4) (b) (4) When a tracer dose of [^{3}H]-mebendazole was administered in patients that were previously treated with mebendazole for cystic hydatid disease, both intravenously and orally, relative bioavailability was determined to be 22%[†]. At the therapeutic dose, i.e., 500 mg mebendazole, reported relative bioavailability from the solid oral dosage tablet is <4%. With regard to the food effect on absorption, administration of the New Chewable 500 mg tablet formulation (fast disintegrating tablet) with a high fat breakfast resulted in 2.4- to 4-fold higher systemic exposure to mebendazole compared to administration under fasted conditions. In addition, the observed systemic exposures to mebendazole were higher from the chewable formulations than the reported exposure from the solid oral tablet.

Distribution:

The plasma protein binding of mebendazole is reported to be ≥ 90%. The estimated volume of distribution after intravenous administration is 1.23 L/kg (range: 1 to 2 L/kg).

Metabolism:

The metabolic path for mebendazole metabolism remains unclear. However, in vitro data suggest that mebendazole may induce cytochrome P450 (CYP) enzyme 1A1. In addition, long-term administration of ritonavir, which is a CYP1A2 inducer as well as inhibitor of CYP3A4 and CYP2D6, was found to be associated with a significant decrease in mebendazole AUC_{24} (43%) and C_{max} (41%).

[†] *Dawson M, Braithwaite PA, Roberts MS, Watson TR. The pharmacokinetics and bioavailability of a tracer dose of [3H]-mebendazole in man. Br J Clin Pharmacol. 1985a;19(1):79-86.*

The major proportion of an absorbed dose of mebendazole is metabolized in the liver. The mebendazole metabolites are present in plasma and, reported to be detected as conjugates in urine and bile. The major plasma metabolites are the amide hydrolysis product 2-amino 5(6) benzoylbenzimidazole ("hydrolyzed metabolite") and the product of ketone reduction, methyl-5(6) [α-hydroxybenzyl] benzimidazole carbamate ("reduced metabolite"). Plasma concentrations of both metabolites, i.e., hydrolyzed form and reduced form, are reported to be several-fold higher than the mebendazole concentrations.

In urine, the major unconjugated metabolites are the product of both ketone reduction and hydrolysis, which accounts for 87% of unconjugated material in urine (1.24% of the dose). Low concentrations of these metabolites can also be detected in plasma. Only 0.0049% of the dose is excreted unchanged in urine and, a total of 1.4 % of the dose can be accounted for as unconjugated material in urine. A large proportion of the absorbed dose is excreted in urine as unidentified metabolites.

Elimination:

The mean estimates for mebendazole elimination half-life ranges from 3.6 to 7.4 hours. At a dose level of (b) (4), the average oral clearance was estimated to be (b) (4) in 5 subjects. Mebendazole, the conjugated forms of mebendazole, and its metabolites are believed to undergo some degree of enterohepatic recirculation and are excreted in the urine and bile. The percentage of orally administered mebendazole that is excreted in urine varies at different dose levels, resulting from different extents of oral absorption. Generally, less than (b) (4) is excreted in urine and the remainder in the feces.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No, the provided Clinical Pharmacology information does not provide supportive evidence of effectiveness. For the proposed indication, the intended site of action for mebendazole is the GI tract; therefore, the extent of systemic exposure is not expected to relate directly with the proposed drug product's efficacy.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is one 500 mg Vermox Chewable tablet as a one-time dose in adult and pediatric patients 1 year of age and older, which is appropriate for the general patient population for which the indication is being sought.

3.3.3 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug interaction:

An increase in AUC was observed (~3-fold), when the to-be-marketed Vermox Chewable 500 mg tablet was given with a high-fat meal as compared to fasting conditions. However, this increase was deemed clinically irrelevant; therefore, a management strategy for the food effect is not needed.

Drug-drug interaction:

No new drug interaction studies have been conducted under the development program of the proposed drug product. Nevertheless, given that the proposed dosing regimen is a single one-dose treatment and based on the literature derived information, a management strategy for DDI is not needed.

4. APPENDICES

4.1 Bioanalytical Method Report

In three of the clinical studies that included PK assessments, three distinct analytes were measured, i.e., mebendazole and its two metabolites: hydrolyzed form (JNJ-110695) and reduced form (JNJ-110721). Summary of the bioanalytical methods for mebendazole is provided in Table 1. The reported validation parameter estimates for each bioanalytical method is presented in Table 2 and Table 3, for mebendazole and its metabolites, respectively.

Table 1: Bioanalytical Methods Used in Clinical Studies: Summary

Study GAI1001		
Analyte	Mebendazole	
Matrix	Plasma	
Central Clinical Laboratory	Lambda Therapeutic Research Ltd. Plot No. 38, Opp. Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India.	
Analytical Site	(b) (4)	
Sample collection	19 Apr 2008 – 28 Apr 2008	
Sample receipt	21 May2008 – 21 May2008	
Sample analysis	23 May2008 – 30 May2008	
Within the Stability range	Yes	
Study GAI1002		
Analyte	Mebendazole	
Matrix	Whole blood	
Central Clinical Laboratory	Jan Palfijn, Lange Bremstraat 70, 2170 Merksem, Belgium	
Analytical Site	(b) (4)	
Sample collection (Approx.)	25 Feb 2014 – 26 Mar 2014	
Sample receipt	31 Mar 2014 – 31 Mar 2014	
Sample analysis	03 Apr 2014 – 11 Apr 2014	
Within the Stability range	Yes	
Study GAI3003		
Analyte	Mebendazole and its metabolites (JNJ-110695,JNJ-110721)	
Matrix	Plasma, whole blood	
Central Clinical Laboratory	2 sites in Ethiopia and 1 site in Rwanda.	
Analytical Site	(b) (4)	
Sample collection (Approx.)	Mebendazole in Blood	Mebendazole in Plasma
	29 Dec 2014 – 22 Sep 2015	27 Aug 2015 – 29 Sep 2015
Sample receipt	16 Mar 2015 – 07 Sep 2015	07 Sep 2015 – 07 Sep 2015
Sample analysis	19 Mar 2015 – 24 Sep 2015	29 Sep 2015 – 30 Sep 2015
Within the Stability range	Storage period between collection and analysis	
	267 Days	99 Days

Table 2: Bioanalytical Methods for Mebendazole: Validation Parameters (source: Module 2 7 2 Summary of Clinical Pharmacology Studies Appendix 6)

Method Name	(b) (4) Validation of an LC-MS/MS method for the determination of JNJ-108329 in human EDTA plasma	Janssen R&D BA10485: Validation of an LC-MS/MS method for the determination of JNJ-108329 in human K_2EDTA blood.	Janssen R&D BA10884: Validation of an LC-MS/MS method for the determination of JNJ-108329 in human EDTA plasma
Matrix	EDTA plasma	EDTA blood	EDTA plasma
Validated concentration range	1.00 – 1,000 ng/mL	1.00 – 1,000 ng/mL	1.00 – 1,000 ng/mL
Inter-run accuracy (%)	1.7 – 10.4%	-1.1 – 14.0%	-9.5 - -7.1%
Inter-run precision (%CV)	1.6 – 4.3%	1.7 – 8.7%	1.9 – 8.4%
Intra-run accuracy (%)	1.5 – 10.2%	-1.3 – 6.0%	-9.5 - -3.1%
Intra-run precision (%CV)	1.4 – 3.2%	1.1 – 7.0%	1.7 – 8.5%
Intra-run accuracy (dilution) (%)	9.8%	0.9%	NA
Intra-run precision (dilution) (%CV)	3.0%	1.1%	NA
Selectivity (interference <20% of LLOQ)	6 out of 6 sources of plasma	6 out of 6 sources of plasma	6 out of 6 sources of plasma
Matrix effects	No matrix effect observed	No matrix effect observed	No matrix effect observed
Recovery	91.0 – 97.2%; IS 93.9%	62.9 – 72.1%; IS 77.2%	109.5 – 112.3%; IS 110.6%
Stability in EDTA blood	2h at 4°C 2h at RT 2h at 37°C	Bench top 4h melting ice, 2h RT 6 F/T cycles at -20°C Long term stability 284 days at -20°C and 263 days at -70°C	NA
Stability in EDTA plasma	Bench top 6h at RT 3 F/T cycles at -20°C Long term stability 100 days at -20°C	N/A	Bench top 72h at RT 6 F/T cycles at -20°C Long term stability: 210 days at -20°C and -70°C

Table 3: Bioanalytical Methods for Mebendazole Metabolites: Validation Parameters (source: Module 2 7 2 Summary of Clinical Pharmacology Studies Appendix 6)

Method Name	Janssen R&D BA10781: Qualification of the LC-MS/MS Method for the Quantitation of JNJ-110695 and JNJ-110721 in human blood	Janssen R&D BA10781: Qualification of the LC-MS/MS Method for the Quantitation of JNJ-110695 and JNJ-110721 in human blood
Analyte Name	**JNJ-110695 (H-MBZ)**	**JNJ-110721 (R-MBZ)**
Matrix	EDTA blood	EDTA blood
concentration range	2.00 to 1,000 ng/mL	1.00 to 1,000 ng/mL
Inter-run accuracy (%)	NA	NA
Inter-run precision (%CV)	NA	NA
Intra-run accuracy (%)	± 13.0% at all QC levels	± 9.0% at all QC levels
Intra-run precision (%CV)	≤7.0% at all QC levels	≤5.5% at all QC levels
Intra-run accuracy (dilution) (%)	NA	NA
Intra-run precision (dilution) (%CV)	NA	NA
Selectivity (interference <20% of LLOQ)	Passes	passes
Stability in EDTA blood (in capillaries)	2 hours 37°C, 24 hours RT (light)	2 hours 37°C, 24 hours RT (light)
in blood +2% BSA	146 days in spiked blood in a freezer	146 days in spiked blood in a freezer

Reviewer's assessment:

The quality control samples that were used during the method validation are reported in Table 4.

Table 4: Accuracy and Precision of the Bio-analytical Methods for the determination of Mebendazole - spiked quality control samples

Validation Report	Matrix	QC sample Concentrations	N	%CV	%Bias
(b) (4)	Plasma	2.72 ng/mL, 31.1ng/mL, 777 ng/mL	24	<6%	<6%
BA10485	Blood	3 ng/mL, 40 ng/mL, 800 ng/mL	18	<6%	<4%
BA10884	Plasma	3 ng/mL, 40 ng/mL, 800 ng/mL	2	<3%	<9%

Based on the reported validation parameters in Table 1 and Table 4, bio-analytical methods that were used to quantify mebendazole appear reasonable. However, the following findings pertaining to the bioanalytical methods for mebendazole metabolites were concerning:

(1) The first blood sample collected in study GAI3003 was on 29th December 2014. Based on the date of the quality control sample run, it appears that sample analysis was done 29th September 2015. Therefore, some samples may have been analyzed after more than 270 days after collection, which is outside of the established stability period of 146 days (Table 3).

(2) The information on the inter-run performance of the bioanalytical methods for mebendazole metabolites is missing.

Nevertheless, one of the two key mebendazole metabolites is inactive and the other has limited activity. Therefore, the abovementioned findings do not appear to have any clinical implications, and accordingly, in-depth analysis of abovementioned findings or follow-up with the Applicant was not undertaken.

4.2 Individual Study Review

Out of four studies that were conducted in support of the proposed drug product, the following three studies had Clinical Pharmacology relevant assessments:

Study	Study Type	Formulation used	Test Formulation referred as
GAI1001	Phase 1- Relative BA	Investigational chewable tablet & Solid tablet	Previous chewable tablet
GAI1002	Phase 1- Food effect	Fast disintegrating chewable tablet formulation	New chewable tablet (Final to-be-marketed formulation)
GAI3003	Phase 3- Efficacy		

4.2.1 GAI1001

Title:
An Open-Label, Single-dose, Relative Bioavailability Study in Healthy Adults of A New Chewable Tablet Formulation of VERMOX® Compared to the Currently Marketed Tablet

Rationale/Relevancy:

The Vermox solid oral tablet has established safety and efficacy. In addition, this formulation has been used extensively in pediatrics. This study evaluates the relative BA between Vermox solid oral tablet and of the "Previous Chewable" tablet. The results from this study was utilized to assess the effect of formulation change, i.e., from solid oral dosage form to chewable formulation, on systemic exposure.

Objective:

The primary objective of this study was to determine the relative bioavailability of Previous chewable tablet formulation containing 500 mg mebendazole with respect to VERMOX solid oral tablet, which also contains 500 mg mebendazole. The secondary objective was to assess the safety.

Study Design:

This was an open-label, single-dose, relative bioavailability, randomized, 2-way crossover design study in healthy volunteers. All subjects were randomly assigned to one of the two possible treatment sequences to ensure that they received both of the following treatments with at least a 1 week washout period:

- Treatment A (Reference) - A single 500 mg mebendazole tablet: VERMOX solid oral tablet
- Treatment B (Test) - A single 500 mg mebendazole chewable tablet: Previous chewable tablet

Dosing and PK sampling:

After fasting for at least 10 hours, subjects received a single dose of study drug in each treatment period. A washout period of at least 7 days separated the single dose of study medication in Periods 1 and 2. Blood samples were collected for pharmacokinetic analysis at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 5, 7, 9, 12, 16, 24, 30, 36, and 48 hours after each dosing in each period.

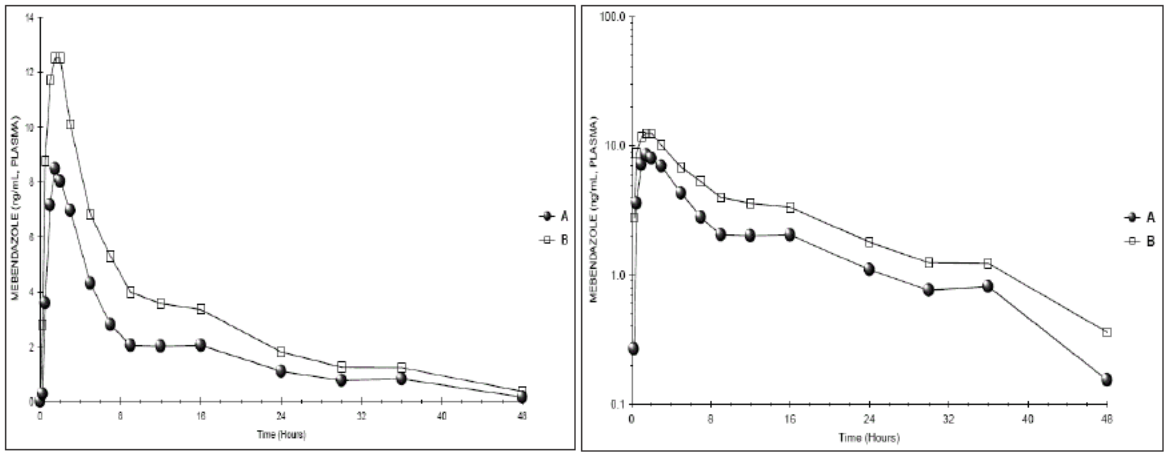
Pharmacokinetic Analysis:

Plasma samples were analyzed to determine concentrations of mebendazole using a validated assay method, with the quantification range of 1 - 1000 ng/mL. The pharmacokinetic parameters C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{½}$ and λ_z were estimated by non-compartmental analysis utilizing WinNonlin (Pharsight Corporation, Version 5.0.1). With regard to the statistical analysis, the primary parameters of interest were the log-transformed estimates of AUC_{last} and C_{max}. A mixed-effect model with treatment, period, and treatment sequence as fixed effects, and subject as a random effect, was used to estimate the least squares means and intrasubject variance. Using this model, estimated least squares means and intrasubject variance, the point estimate and 90% confidence intervals for the difference in means on a log scale between Treatment A and Treatment B were obtained. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratios of the mean AUC_{last} and C_{max} of the test to reference formulation (Treatment B / Treatment A).

Pharmacokinetic Results:

A total of 20 subjects were randomized. Out of which, 19 received treatment and 18 completed the study. All subjects were Asian men (100%) and the overall median age was 25 years (range: 20 to 41 years). One subject withdrew from the study on medical grounds before the planned sampling procedures and one subject did not report for the Period 2 treatment. Consequently, 18 subjects were included in the pharmacokinetic analysis. Mean mebendazole plasma concentration time-curves from both the treatment groups are presented in Figure 1. Descriptive statistics of pharmacokinetic parameter estimates and the means of log-transformed estimates are presented in Table 1 and 2, respectively.

Figure 1: Mean Mebendazole Plasma Concentration-Time Profiles in Linear and Log-linear Scale (source: Clinical Study Report GAI1001, Figure 1)



A: Treatment A-VERMOX (mebendazole) 500-mg tablet (n=18)

B: Treatment B-Mebendazole 500-mg chewable tablet (n=18)

AUC_{∞} was not reported because a valid estimate of the terminal log-linear slope of the PK profile was available for only 3 subjects. The criteria to determine a valid estimate of the terminal log-linear slope was that the coefficient of determination (r^2 adj) of the line that describes the terminal elimination phase should not be less than 0.90 and The value of percentage of AUC_{∞} obtained by extrapolation ($\%AUC_{\infty,ex}$) should not be greater than 20%.

Table 1: Pharmacokinetic Parameter Estimates Following Oral Administration of a Single 500-mg Dose of Mebendazole Reference and Test Tablet (source: Clinical Study Report GAI1001, Table 2)

PK Parameters	Mean (SD)					
	Treatment A			Treatment B		
	n	Mean ± SD	%CV	n	Mean ± SD	%CV
*t_{max}, h	18	1.50 (1.00-5.00)	-	18	1.50 (0.50-3.00)	-
C_{max}, ng/mL	18	9.36 ± 7.74	82.7	18	14.1 ± 10.3	73.2
AUC_{last}, ng·h/mL	18	79.9 ± 59.7	74.7	18	134 ± 88.5	66.0

h-hour(s)
*t_{max} is reported as median (range)
Treatment A: VERMOX (mebendazole) 500-mg tablet
Treatment B: Mebendazole (chewable) 500-mg tablet

Table 2: Geometric Means and 90% Confidence Intervals for the Ratio of the Means Pharmacokinetic Parameters Estimates for Previous Mebendazole Chewable Tablet and VERMOX Solid Oral Tablet (source: Clinical Study Report GAI1001, Table 3)

PK Parameter	N	Geometric LSM		Ratio (%) Treatment B / Treatment A	90% Confidence Intervals	MSE
		Treatment B	Treatment A			
C_{max}	18	11.177	6.875	162.6	135.84-194.54%	0.0952
AUC_{last}	18	111.146	55.122	201.6	149.79-271.42%	0.2608

Treatment A: VERMOX (mebendazole) 500-mg tablet
Treatment B: Mebendazole (chewable) 500-mg tablet
MSE = Mean Squared Error

Safety Results:

No deaths or other serious/significant adverse events were reported during the study. One subject's discontinuation was due to dizziness prior to receiving treatment with study drug.

Applicant's conclusion:

Previous chewable tablet formulation of mebendazole has a greater systemic bioavailability than the VERMOX solid oral tablet. Specifically, the respective C_{max} and AUC values were 1.5 to 2 times higher. However, it is not clear if the greater systemic bioavailability of the chewable formulation is specific to the formulation tested or if it is related to all chewable formulations of this drug substance. In addition, because there are no historical data available on the comparative bioavailability of other chewable formulations relative to tablets meant to be swallowed whole, it is not possible to reconcile the observed difference.

Overall, both formulations of mebendazole were well tolerated by healthy subjects, as a single dose administration and no relevant differences in the safety profiles of the test and reference formulation were observed. No deaths, serious and unexpected adverse events occurred during the course of the trial.

Reviewer's assessment:

Following administration of Previous chewable tablet, geometric mean ratios of C_{max} and AUC estimates are 1.6 and 2 times higher than the estimates obtained following the administration of solid oral tablet. Results from the consequent study: GAI1002, which tested New chewable tablet, exposure parameter estimates were similar to estimates reported in this study for Previous chewable tablet. This indirect comparison indicates that the formulation change, i.e., solid vs. chewable formulation, could be one of the key driving factors for the higher systemic exposure to mebendazole.

4.2.2 GAI1002

Title:
A Single-Dose, Open-Label, Randomized, 2-Way Crossover Study to Assess the Effect of Food on the Bioavailability of Mebendazole from a Fast-Disintegrating Chewable Formulation of Mebendazole in Healthy Subjects

Objectives:

Primary Objective: The primary objective was to evaluate the effect of food on the bioavailability of mebendazole from New chewable tablet that contains 500 mg mebendazole in healthy adult subjects. Safety and tolerability were also assessed.

Exploratory Objectives:

- To evaluate the pharmacokinetic (PK) parameters of mebendazole from whole blood and capillary samples.
- To evaluate the excretion of mebendazole in urine.

Study Design:

This was an open-label, randomized, single-center, single-dose, 2-way crossover study conducted in healthy volunteers. All subjects were randomly assigned to 1 of 2 possible treatment sequences to ensure that they received both of the following treatments with a washout period of at least 7 to 10 days:

- Treatment A (Reference): a single 500 mg dose of mebendazole (as 1 x 500 mg New chewable tablet) given in a fasted condition. No food was allowed for at least 4 hours after dosing.
- Treatment B (Test): a single 500 mg dose of mebendazole (as 1 x 500 mg New chewable tablet) given just after high-fat breakfast. No food was allowed for at least 4 hours after dosing.

Dosing and PK sampling:

Three sets of serial pharmacokinetic blood samples were collected during the study: one set of venous whole blood samples (from both, fed and fasted treatment arms) and two sets of capillary blood samples. One set of capillary samples was collected into a capillary tube (15 µL, fasted treatment only) from the venous sampling before plasma separation and another set of capillary samples (15 µL, fasted treatment only) was taken via a fingerstick at the same time points as the venous samples. Blood samples for pharmacokinetic analysis were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 16, 24, 25, 26, 28, 30, 36, 48, 72, and 96 hours after each dosing in each period.

Pharmacokinetic Analysis:

Plasma samples were analyzed to determine concentrations of mebendazole using a validated assay method, with the quantification range of 1-1000 ng/mL. Based on individual plasma/blood concentration-time data, the following PK parameters were determined for mebendazole: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2\lambda}$, λ_z, and F_{rel}, $AUC_{0\text{-}24h}$, and $AUC_{0\text{-}48h}$.

Exploratory Analyses – Evaluation of Capillary Fingerstick Sampling:

In addition to the assessment of the food effect on mebendazole pharmacokinetics, an exploratory analysis was performed to compare plasma and whole blood concentrations of mebendazole using capillary whole blood samples obtained from Treatment A (fasted). Similarity between the two sets of capillary blood samples, i.e., from the venous whole blood sampling and fingerstick sampling, was assessed.

Pharmacokinetic Results:

Sixteen subjects were enrolled in the study. All 16 subjects completed both treatment periods of the study and were included in the pharmacokinetic analysis. The mean plasma concentration-time profiles of mebendazole after single-dose administration of New chewable tablet under fed and fasting conditions are presented in Figure 1. Both, the rate and the extent of mebendazole exposure were higher under fed conditions (Treatment B) than under fasted conditions. Descriptive statistics of pharmacokinetic parameter estimates and the means of log-transformed estimates is presented in Table 1 and 2, respectively.

Figure 1: Mean Plasma Mebendazole Concentration-Time Profiles Following Administration of New Chewable formulation (a 500 mg Fast-Disintegrating Chewable Tablet) With and Without Food (source: Clinical Study Report GAI1002, Figure 1)

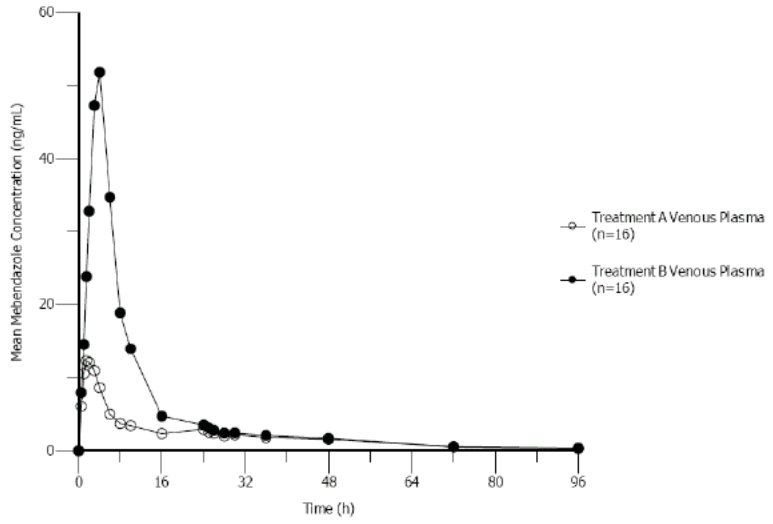


Table 1: Arithmetic Mean (SD) Pharmacokinetic Parameters Following Administration of New Chewable formulation (a 500 mg Fast-Disintegrating Chewable Tablet) With and Without Food

(source: Clinical Study Report GAI1002, Table 3)

Parameter	Treatment B Fed (n=16)	Treatment A Fasted (n=16)
C_{max} (ng/mL)	56.2 (35.8)	14.0 (9.17)
t_{max} (h)[a]	4.00 (2.00 – 6.00)	1.50 (0.50 – 3.00)
AUC_{24} (ng.h/mL)	400 (194)[b]	111 (60.0)[b]
AUC_{48} (ng.h/mL)	425 (187)[c]	176 (93.0)[d]
AUC_{last} (ng.h/mL)	456 (249)	175 (129)
AUC_{∞} (ng.h/mL)[e]	NR	NR
$t_{1/2}$ (h)[e]	NR	NR
$F_{rel, \infty}$ (%)	NR	NA
$F_{rel, 24}$ (%)	386 (130)	NA
$F_{rel, 48}$ (%)	282 (81.2)	NA

h = hour; NR = Not reported; NA = Not applicable, SD = Standard deviation

[a] Median (range)

[b] n=15; AUC_{24} for subject 2754 could not be estimated reliably (t_{last} occurred earlier than 24 h)

[c] n=14;AUC_{48} for subjects 2754 and 3113 could not be estimated reliably (t_{last} occurred earlier than 48 h)

[d] n=11; AUC_{48} for subjects 2754, 3113, 4201, 5315 and 6064 could not be estimated reliably (t_{last} occurred earlier than 48 h)

[e] Could not be estimated due to unacceptable variability in the terminal phase (r^2adj.<0.90)

Table 2: Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Pharmacokinetic Parameters Following Administration of New Chewable formulation (a 500 mg Fast-Disintegrating Chewable Tablet) With and Without Food (source: Clinical Study Report GAI1002, Table 4)

	Geometric Mean			
Parameter	Treatment B: Fed (Test, n=16)	Treatment A: Fasted (Ref, n=16)	Geometric Mean Ratio (%) (90% CI)	Intra-Subject CV (%)
C_{max} (ng/mL)	48.29	11.69	412.97 (326.65; 522.11)	39.03
AUC_{last} (ng.h/mL)	396.38	136.55	290.28 (244.82; 344.19)	27.87
AUC_{∞} (ng.h/mL)[a]	NR	NR	NR	NR

[a] AUC_{∞} could not be reliably estimated due to unacceptable variability in the terminal phase (r^2adj.<0.90)

CI = confidence intervals, CV = coefficient of variation, NR = Not reported

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.

Test: Mebendazole 500-mg fast-disintegrating chewable tablet administered under fed state

Ref : Mebendazole 500-mg fast-disintegrating chewable tablet administered under fasted state

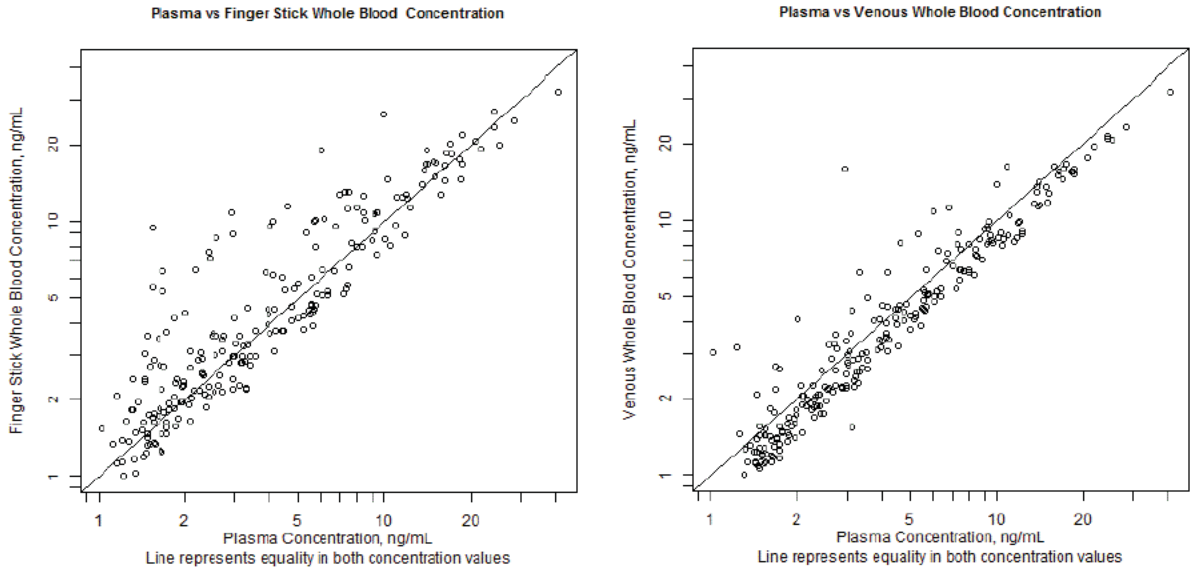
Results from Exploratory Analyses – Evaluation of Capillary Fingerstick Sampling

In the exploratory analysis results, some fingerstick capillary samples had much higher mebendazole concentrations than the corresponding (time-matched) plasma concentrations, which may suggest contamination by site personnel (from dosing of the slurry that was prepared by dissolving the drug product on a spoon) or subjects (from contacting the mouth any time after dosing). In the analyses of these data, an outlier concentration value was defined as a fingerstick whole blood value that both: (1) differed from its time-matched venous whole blood value by a factor of ≥ 2, and (2) had a concentration $\geq$10 ng/mL. A total of 30 concentration values among all subjects' values were identified as outliers and were not included in this analysis. Three subjects (Subjects 2286, 2754, and 5911) had 4 or more outlier

values; PK parameters were calculated for these subjects, but these subjects were not included in the descriptive statistics for these parameters.

As per the Applicant, the results of this exploratory analysis indicated that mebendazole concentrations and PK parameters determined in whole blood obtained by capillary fingerstick sampling correlate well with plasma concentrations and plasma PK parameters of mebendazole. Correlation plots for mebendazole fingerstick whole blood concentrations vs. plasma concentration and venous whole blood concentration vs. plasma concentration are presented in Figure 2.

Figure 2: Comparison of Mebendazole Venous Plasma, Venous Whole Blood, and Fingerstick Whole Blood Concentrations - Following Administration of New Chewable formulation (a 500 mg Fast-Disintegrating Chewable Tablet) Without Food (source: Clinical Study Report GAI1002, Figure 2)



Safety Results:

All 16 subjects were included in the safety analyses. None of the reported adverse events was related to study drug except for single event of nausea, which was assessed as possibly related to the study drug by the investigator. Overall, the study drug was well tolerated and the safety findings were consistent with previously reported data for mebendazole.

Applicant's conclusion:

- Administration of New mebendazole chewable tablet with a high fat breakfast resulted in 3- to 4-fold higher systemic exposure to mebendazole compared to administration under fasted conditions.
- An exploratory analysis showed that concentrations of mebendazole in whole blood and capillary fingerstick whole blood samples correlated well with concentrations in plasma. Therefore, the fingerstick sampling technique would be a useful alternative to traditional venipuncture in identifying differences in systemic exposure in some patient groups (e.g., pediatric patients) or clinical settings in which plasma sampling may not be feasible. However, utilization of this technique will require precautions to avoid contamination of samples.

- New 500 mg mebendazole chewable tablet was well tolerated in healthy subjects after administration under both fasted and fed conditions.

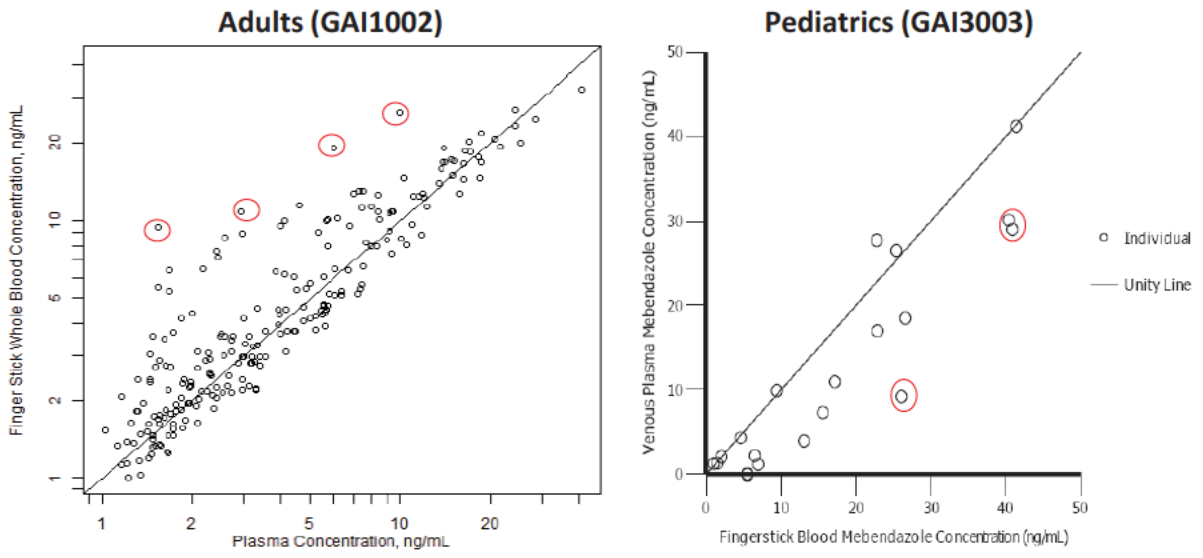
Reviewer's assessments:

The inferences derived by the Applicant with regard to food effect on the systemic exposure to mebendazole from New chewable tablet appear reasonable. However, the Reviewer does not agree with the Applicant's inferences made with regard to the proposed similarity / correlation between concentrations of mebendazole in plasma samples and whole blood capillary fingerstick samples. Following are the concerns with the proposed relationship:

(1) The set outlier criteria is not acceptable. An outlier concentration value was defined as a fingerstick whole blood value that both: 1) differed from its time-matched venous whole blood value by a factor of ≥2, and 2) had a concentration ≥10 ng/mL.

(2) Instances of sporadic and/or inconsistent relationship in some concentration values were observed in both adults (this study) and pediatrics (Study GAI3003). Some of the prominent examples of such incidences are marked Red Circle in Figure 3. However, given that drug concentrations in whole blood capillary fingerstick samples were mostly higher than their respective venous plasma concentrations, it can be approximated that the mebendazole plasma levels will be equal or lower than the levels that are detected in the fingerstick samples. Therefore, the Reviewer agrees with the Applicant's proposed approach of using mebendazole concentrations in whole blood capillary fingerstick samples as "worst case" or "maximum" estimates for the systemic PK exposure to mebendazole.

Figure 3: Sporadic Inconsistencies Between Mebendazole Venous Plasma and Fingerstick Whole Blood Concentrations – Adults (GAI1002) and Pediatrics (GAI3003)



4.2.3 GAI3003

Title:
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 Helminth Infections (Ascaris lumbricoides and Trichuris trichiura) in Pediatric Subjects
Objectives:

Primary Objective: To compare the efficacy and safety of a single dose of 500 mg mebendazole chewable tablet (New Chewable tablet) with placebo in the treatment of *Ascaris lumbricoides* and *Trichuris trichiura* infections in pediatric patients.

Secondary Objectives: To assess mebendazole systemic exposure in pediatrics that is resulting from a single dose of 500 mg mebendazole chewable tablet. The exploratory objective was to compare efficacy and safety.

Study Design:

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted to assess the efficacy and safety of a single dose of 500 mg mebendazole chewable tablet (New Chewable tablet) for the treatment of *A. lumbricoides* and *T. trichiura* infections in children between the ages of 1 and 16 years. Prior to dosing, stool samples were collected from patients to detect presence of infection. The primary efficacy endpoints were cure rates for *A. lumbricoides* and *T. trichiura* infections at the end of the double-blind period for patients with positive corresponding egg counts at baseline. Secondary efficacy endpoints were egg count reductions at the end of the double-blind period.

Dosing and PK sampling:

Patients received a single oral 500 mg mebendazole chewable tablet or matching placebo on Day 1 and 500 mg mebendazole chewable tablet during an open-label phase on Day 19 ± 2. For children 3 to 16 years of age, the study drug was administered as a tablet, which was chewed and swallowed without water. However, prior to administration in children of age 1 to < 3 years, the tablet was formed in to a soft mass – semi-solid consistency – by placing it on a spoon and adding 2-3 mL of drinking water. Most patients received drug with food during open-label phase. For patients enrolled in the PK substudy (N=44), fingerstick capillary blood samples (1 original and 1 backup sample) were collected at predose and at 1, 2, 3, 5, 8, and 24 hours postdose for determination of mebendazole concentrations in blood. Venous blood samples were also collected at the 3 hour and 24 hour time points from patients in the 7 to 16 years of age group. For all patients, concentrations of 2 metabolites (hydrolyzed and reduced forms of mebendazole) were also determined in collected blood samples at all time points.

Pharmacokinetic Analysis:

The PK parameters were determined via noncompartmental analysis with Phoenix™ WinNonlin software. The following PK parameters were determined: C_{max}, t_{max}, AUC_{0-8}, AUC_{last}.

Utilizing metabolite-to-parent ratio (MPR), i.e., the ratio of the parameter value for metabolite to that of parent: mebendazole, the other PK parameters analyzed during this study included – MPR C_{max}, MPR AUC_8, and MPR AUC_{last} were determined for individual patients.

Pharmacokinetic Results:

Of the 792 subjects screened, a total of 295 patients were enrolled and randomly assigned to study treatments (mebendazole or placebo) during the double-blind treatment phase. Age of the enrolled patients ranged from 1 year to 15 years (median = 8 years, mean= 7.8 years). Of these, 278 (94.2%) patients completed the double-blind treatment phase and entered the open-label phase. PK substudy was conducted in 44 children during the open-label phase:

22 children - 1 to < 3 years of age

12 children - 3 to 6 years of age

10 children - 7 to 16 years of age

Mean blood concentration-time profiles, which were derived from fingerstick sampling in different age groups, are compared in Figure 1. Descriptive statistics of reported pharmacokinetic parameter estimates stratified by age group and Helminth Species are provided in Table 1. Mean blood concentration-time profiles showed higher concentrations in the youngest age group (1 to < 3 years of age) and substantial intersubject variability was observed with the higher mebendazole exposure, especially in patients with the lowest body weight and youngest age.

Overall, the data did not indicate a major trend toward a differential exposure to mebendazole as a function of helminth species.

Figure 1: Mean Whole Blood Mebendazole Concentration-Time Profiles in Pediatric Subjects

(source: Clinical Study Report GAI3003, FIGPK5- Figure 4)

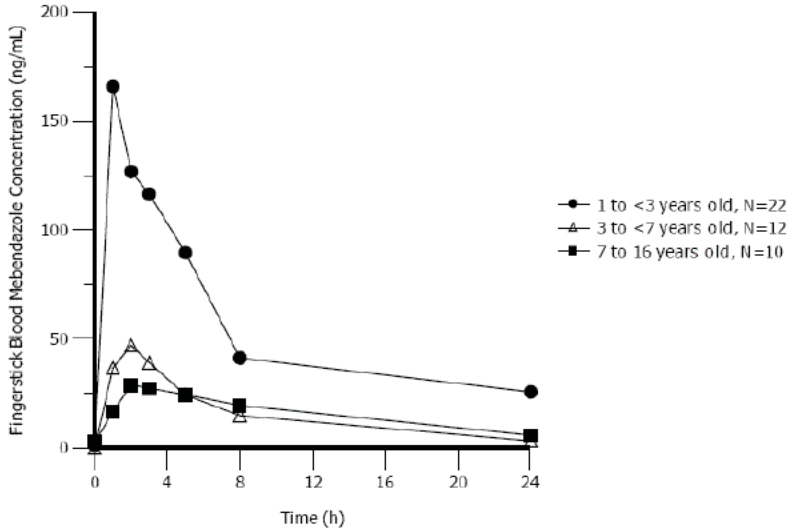


Table 1: Mean (SD) Capillary Whole Blood Mebendazole Pharmacokinetic Parameters by Age Group and Helminth Species (source: Clinical Study Report GAI3003, Table 7)

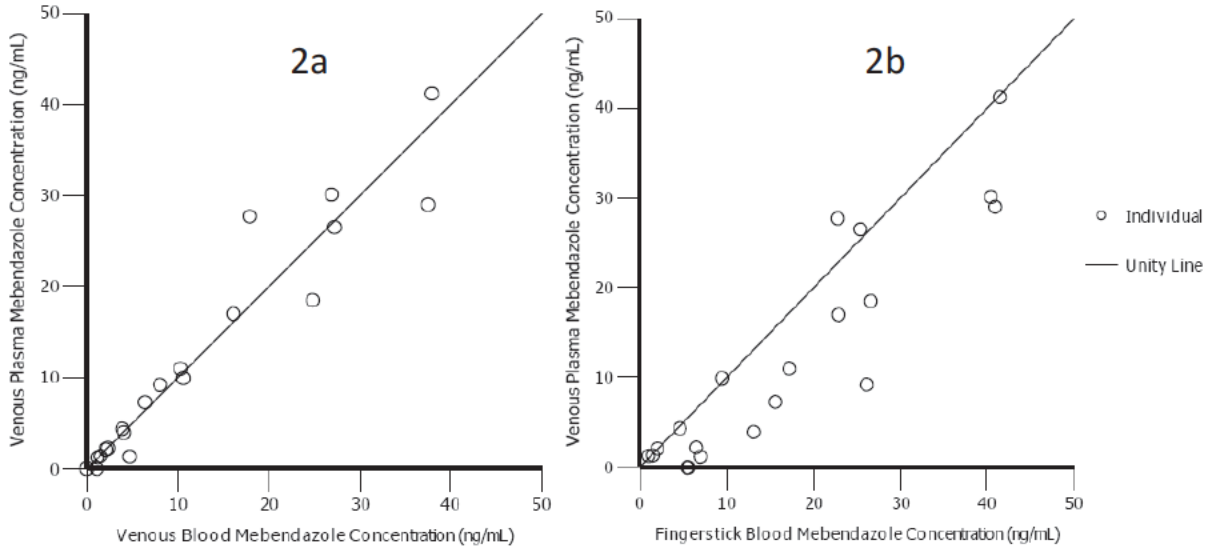
Parameter	1 to <3 years	3 to 6 years	7 to 16 years
All Helminth Species			
N	22	12	10
C_{max} (ng/mL)	210 (212)	49.9 (26.8)	34.2 (13.8)
Range	31.1 - 881	2.26 - 101	15.6 - 52.1
t_{max} (h)[a]	2.50 (1.00 – 8.00)	2.00 (0.98 – 3.00)	3.00 (1.00 – 8.00)
AUC_8 (ng*h/mL)	697 (367)[b]	242 (139)[c]	182 (66.3)
Range	111-1437	102-467	88.0-271
AUC_{last} (ng*h/mL)	1,320 (844)	416 (215)	387 (190)
Range	206 - 4076	161 - 874	116 - 747
Ascaris lumbricoides (large roundworm).			
N	9	3	7
C_{max} (ng/mL)	242 (250)	32.6 (26.3)	31.0 (12.4)
t_{max} (h)[a]	3.00 (1.00 – 5.00)	2.00 (1.78 – 2.60)	3.00 (1.00 – 5.00)
AUC_8 (ng*h/mL)	756 (314)[d]	NR	178 (61.8)
AUC_{last} (ng*h/mL)	1,687 (1,020)	516 (32.7)	376 (141)
Trichuris trichiura (whipworm)			
N	6	8	3
C_{max} (ng/mL)	195 (112)	57.0 (27.3)	41.7 (16.4)
t_{max} (h)[a]	2.50 (1.00 – 5.00)	2.01 (0.98 – 3.00)	3.00 (2.00 – 8.00)
AUC_8 (ng*h/mL)	757 (394)	256 (142)	192 (90.4)
AUC_{last} (ng*h/mL)	1,090 (476)	418 (238)	415 (317)
Ascaris lumbricoides (large roundworm) and *Trichuris trichiura* (whipworm)			
N	7	1	0
C_{max} (ng/mL)	182 (248)	44.5	NR
t_{max} (h)[a]	2.00 (1.00 – 8.00)	2.00	NR
AUC_8 (ng*h/mL)	578 (423)	133	NR
AUC_{last} (ng*h/mL)	1,045 (759)	203	NR

NR = Not reported
[a] Median (range)
[b] n=21
[c] n=9
[d] n=8

Results of correlation analysis between plasma and fingerstick whole blood sampling:

To assess the capillary fingerstick sampling method as an alternate to traditional venous sampling in pediatrics, venous samples were obtained in addition to fingerstick samples at 3 and 24 hours postdose in 10 patients of age 7 to 16 years. The correlation was assessed between concentrations in venous whole blood samples (Figure 2a) and fingerstick whole blood samples (Figure 2b) with concentrations in venous plasma samples. In most cases, the mebendazole concentration estimated by the fingerstick method overestimated the concentration measured in venous plasma (Figure 2b).

Figure 2: Correlation between Venous Plasma and Venous Whole Blood (2a), and between Venous Plasma and Capillary Whole Blood (2b) for the 3- and 24-hour Time Points (source: Clinical Study Report GAI3003, FIGPK5- Figure 6 & 3)



Metabolite Exposure (Unplanned analysis):

Because of the concern of external contamination, in an unplanned analysis, PK substudy samples were analyzed for whole blood concentrations of the hydrolyzed and the reduced metabolites of mebendazole. This analysis was done based on the understanding that the concentrations of metabolites would not be expected to increase in the event of external contamination. Mean blood concentration-time profiles of these metabolites following administration of New 500 mg mebendazole chewable tablet in different age groups are plotted in Figures 3 and 4, for reduced and hydrolyzed metabolite, respectively. The arithmetic means (SD) of PK parameters are presented by age group in Table 2. For both, hydrolyzed and reduced metabolites, exposure parameter estimates (C_{max} and AUC) showed substantial intersubject variability, especially in the youngest age group (1 to < 3 years). The mean metabolite-to-parent ratios indicated that mean exposure to the hydrolyzed and reduced metabolites were up to 2.5-fold higher than mebendazole in the youngest age group and at least 4-fold higher than mebendazole in the older age groups. However, unlike the observed correlation in mebendazole exposure that showed higher exposure to mebendazole in the youngest patients, there was no such correlation between exposure to the

hydrolyzed metabolite concentration and subject age. However, slight correlation was observed between exposure to the reduced metabolite concentration and subject age.

Figure 3: Mean Whole Blood Reduced Mebendazole Metabolite Concentration-Time Profiles in Pediatric Subjects (source: Clinical Study Report GAI3003, FIGPK5- Figure 18)

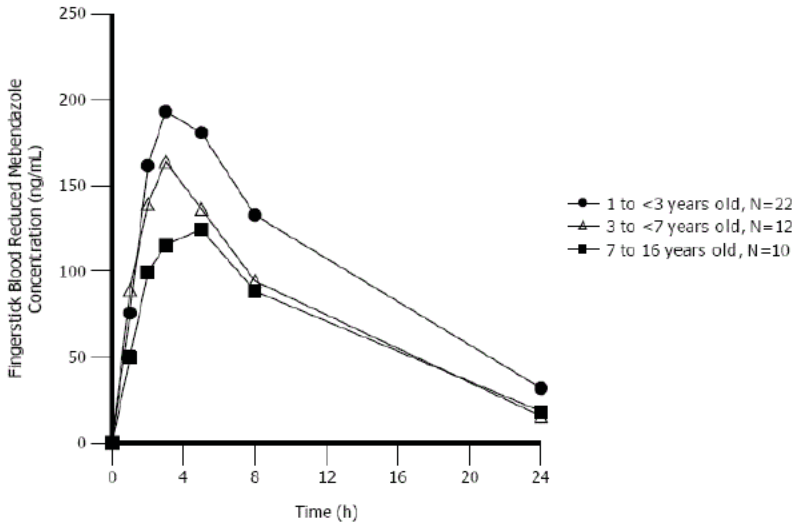


Figure 4: Mean Whole Blood Hydrolized Mebendazole Metabolite Concentration-Time Profiles in Pediatric Subjects (source: Clinical Study Report GAI3003, FIGPK5- Figure 11)

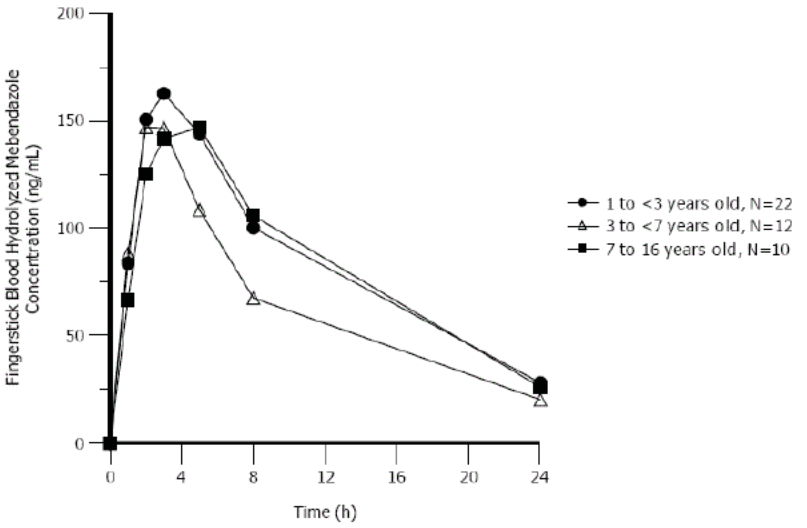


Table 2: Mean (SD) Capillary Whole Blood Mebendazole Metabolites Pharmacokinetic Parameters by Age Group (source: Clinical Study Report GAI3003, Table 8)

Parameter	1 to <3 years	3 to 6 years	7 to 16 years
Mebendazole			
N	22	12	10
C_{max} (ng/mL)	210 (212)	49.9 (26.8)	34.2 (13.8)
Range	31.1 - 881	2.26 - 101	15.6 - 52.1
t_{max} (h)[a]	2.50 (1.00 – 8.00)	2.00 (0.98 – 3.00)	3.00 (1.00 – 8.00)
AUC_8 (ng*h/mL)	697 (367)[b]	242 (139)[c]	182 (66.3)
Range	111-1437	102-467	88.0-271
AUC_{last} (ng*h/mL)	1,320 (844)	416 (215)[d]	387 (190)
Range	206 - 4076	161 - 874	116 - 747
Hydrolyzed Mebendazole			
N	22	12	10
C_{max} (ng/mL)	189 (97.5)	165 (63.0)	165 (71.8)
t_{max} (h)[a]	3.00 (2.00 – 8.00)	2.01 (1.02 – 5.00)	4.00 (2.00 – 8.00)
AUC_8 (ng*h/mL)	981 (597)[b]	809 (366)[c]	936 (429)
AUC_{last} (ng*h/mL)	2,027 (1,560)	1,682 (836)	1,992 (1,200)
$MPRC_{max}$	1.97 (1.62)	7.17 (9.75)	6.15 (2.04)
$MPRAUC_8$	2.27 (1.70)[b]	4.79 (2.25)[c]	6.51 (2.34)
$MPRAUC_{last}$	2.46 (1.98)	5.67 (2.34)[d]	6.58 (2.89)
Reduced Mebendazole			
N	22	12	10
C_{max} (ng/mL)	218 (112)	184 (89.6)	139 (56.5)
t_{max} (h)[a]	3.00 (2.00 – 8.00)	3.00 (1.00 – 8.00)	5.00 (1.00 – 8.00)
AUC_8 (ng*h/mL)	1,201 (646)[b]	1,035 (461)[c]	774 (317)
AUC_{last} (ng*h/mL)	2,466 (1,630)	2,027 (921)[d]	1,630 (917)
$MPRC_{max}$	1.73 (1.13)	3.95 (0.968)	4.12 (1.12)
$MPRAUC_8$	2.10 (1.23)[b]	4.56 (0.793)[c]	4.35 (1.46)
$MPRAUC_{last}$	2.41 (1.67)	4.97 (0.723)[d]	4.28 (1.69)

NR – Not reported
[a] Median (range)
[b] n=21
[c] n=9
[d] n=11

Efficacy Results:

Overall, mebendazole treatment as a single dose was efficacious and showed statistically significant higher cure rates for *A. lumbricoides* and *T. trichiura* infections as compared with placebo treatment (Tables 3 and 4). There was also a statistically significant difference in the egg count reduction at the end of the treatment after mebendazole treatment as compared with placebo treatment for both *A. lumbricoides* and *T. trichiura* infections. (b) (4)

Table 3: Cure Rate of *Ascaris lumbricoides*; Intent-to-treat Subjects With *Ascaris lumbricoides* Infections at Baseline (source: Clinical Study Report GAI3003, Table 9)

	Placebo (N=81)	Mebendazole 500 mg (N=86)
Baseline (eggs/g)		
N	81	86
Mean (SD)	16959.6 (20684.03)	17610.1 (23476.82)
Median	10560.0	9420.0
Range	(36; 90804)	(48; 117384)
Visit 3 (eggs/g)		
N	76	81
Mean (SD)	13706.7 (23168.25)	366.7 (2325.26)
Median	5934.0	0.0
Range	(0; 143040)	(0; 20064)
Cure rate at visit 3		
N (%)	9 (11.1%)	72 (83.7%)
95% CI	(5.2%; 20.1%)	(74.2%; 90.8%)
p-value		<0.001

Note: p-value is based on the Cochran–Mantel–Haenszel (CMH) test, controlling the effect of site.
Note: Subject with missing stool sample at Visit 3 is considered not cured.

Table 4: Egg Count Reduction: *Ascaris lumbricoides*; Intent-to-treat Subjects With *Ascaris lumbricoides* Infections (source: Clinical Study Report GAI3003, Table 10)

	Placebo (N=119)	Mebendazole 500 mg (N=124)
Baseline (eggs/g)		
N	119	124
Mean (SD)	584.5 (930.05)	647.8 (1256.22)
Median	264.0	168.0
Range	(12; 5916)	(12; 8808)
Visit 3 (eggs/g)		
N	112	118
Mean (SD)	523.0 (1020.93)	260.7 (1042.93)
Median	210.0	54.0
Range	(0; 7704)	(0; 10536)
Cure rate at visit 3		
N (%)	9 (7.6%)	42 (33.9%)
95% CI	(3.5%; 13.9%)	(25.6%; 42.9%)
p-value		<0.001

Note: P-value is based on the Cochran–Mantel–Haenszel (CMH) test, controlling the effect of site.
Note: Subject with missing stool sample at visit 3 is considered not cured.

Safety Results:

There were no deaths, serious adverse events, or discontinuations due to treatment-emergent adverse events (TEAEs) reported during the study. Overall, the incidence of TEAEs was low and comparable between the mebendazole and placebo treatment groups. A subgroup analysis for the incidence of TEAEs by age, sex, and the feeding status (fed and fasted) had no specific observable trends during both the double blind and open label phases of the study.

Applicant's conclusion:

- A single dose of New 500 mg mebendazole chewable tablet was found to be generally safe and more effective than placebo in the treatment of *A. lumbricoides* and *T. trichiura* infections in pediatric patients between 1 and 16 years of age.
- Mebendazole concentrations in whole blood samples collected from a subset of patients showed substantial intersubject variability in systemic exposure and highest exposure was seen in the youngest children (1 to 3 years of age) group. Older children had mebendazole systemic exposure that was similar to the exposure reported in adults (Study GAI1002). As expected, exposure to 2 major metabolites of mebendazole exceeded that of mebendazole.
- Overall, New 500 mg mebendazole chewable tablet was well tolerated by children with no reported choking or vomiting with intake.
- Age, sex, feeding status, and systemic exposure to mebendazole had no impact on the safety outcomes of the study.

Reviewer's assessments:

The reported PK parameter estimates for pediatric patients are derived from the capillary fingerstick samples. The mebendazole concentrations in capillary fingerstick samples had spurious and/or inconsistent relationship with the concentrations in time-matched venous plasma samples. Specifically, the drug concentrations in whole blood capillary fingerstick samples were sporadically higher than venous plasma concentrations, in some samples. As noted previously, similar inconsistency was also observed in Study GAI1002 results, which was conducted in adults.

Therefore, given the observed inconstancies, the exposure determined solely based on the capillary fingerstick samples cannot be used for definitive quantitative inferences. However, it can be approximated that the mebendazole plasma levels will be equal or lower than the levels that are detected in the fingerstick samples. Therefore, mebendazole concentrations in whole blood capillary fingerstick samples can be used as "worst case" or "maximum" estimates of the systemic PK exposure to mebendazole. These "worst case" estimates indicate that highest exposure to mebendazole was seen in the youngest children 1 to 3 years of age (~3 to 4 fold higher than that in adults). However, in children >3 and <16 years of age, reported mebendazole systemic exposures were similar to the exposures reported in adults (Study GAI1002); therefore, the relationship between age and mebendazole systemic exposure is not evident in patients >3 years of age. Nonetheless, there was no apparent association between higher mebendazole systemic exposure and safety findings.

In addition, due to the sporadic inconsistences mentioned earlier, the Applicant has analyzed PK substudy samples for mebendazole metabolite concentrations to rule out the role of external contamination in those inconsistences. This was an exploratory analysis and the analytical method validation that was used to quantify these metabolites is incomplete. In addition, it appears that some samples were analyzed after more than 260 days after collection, which is outside of the established stability period of 146 days. However, given that one of the two mebendazole metabolites is inactive and the other has limited activity, the abovementioned findings do not appear to have any clinical implications and accordingly, in-depth analysis of those findings was not undertaken.

The Applicant provided updates with regard to the PK sub-study:GAI3003

During a pre-inspection visit(s) conducted by the Applicant on August 1-2 2016, two major protocol violations were identified in the GAI3003 PK sub-study. Both violations were pertaining to the dosing in the youngest age group (< 3 years of age) and the Applicant has submitted an analysis report on the potential impact of these subjects' PK data on the PK sub-study analysis results. The Applicant concludes that the overall PK conclusions and inferences in the originally submitted clinical study report remain unchanged. Following is the summary of the Applicant provided observation from the pre-inspection visit(s) and its impact on PK results.

Observations:

Subject 251001272, a 1.5 year old child, spit out part of the mebendazole 500 mg chewable tablet administered as a semi-solid mass on a spoon at Visit 3. This subject was given a second dose, part of which was also spit out. Despite of the pre-specified protocol criteria that a patient who spits out the dose or vomits within 4 h after treatment was deemed no longer PK evaluable, this subject was part of PK sub-study. However, no adverse events occurred in this subject during the study.

Subject 251002233, a 1 year old child, spit out part of the mebendazole 500 mg chewable tablet administered as a semi-solid mass on a spoon at Visit 3. Despite of the pre-specified protocol criteria that a patient who spits out the dose or vomits within 4 h after treatment was deemed no longer PK evaluable, this subject was part of PK sub-study. This subject had diarrhea during the open-label period.

Impact on Previously Submitted Results:

The omission of two subjects based on the abovementioned protocol violations has the following impact on PK results from the subgroup of pediatrics from 1 to < 3 years of age:

- Number of children is reduced to 20 from 22
- For the same age group, mean C_{max} reduces to 174 ng/mL from 210 ng/mL (↓17 %)
- Mean AUC_{last} reduces to 1196 ng*h/mL from 1320 ng*h/mL (↓9 %)
- The values for mean AUC_{0-8} were similar, i.e., 694 ng*h/mL vs. the originally reported 697 ng*h/mL as Subject 251001272 did not have values for this parameter due to a missing sample at 8 h post-dose

The Applicant has also provided information on the impact of exclusion of Subjects 251001272 and 251002233 on the mean metabolite exposure, which is of the lesser extent than the impact on parent mebendazole exposure.

Applicant's conclusion:

Exclusion of Subjects 251001272 and 251002233 from the PK analysis does not alter the pharmacokinetic conclusions of Study MEBENDAZOLGAI3003 as described in the CSR:

> *Whole blood concentrations of mebendazole measured in a subset of patients showed substantial intersubject variability in exposure; highest exposure to mebendazole was seen in the youngest children (1 to 3 years of age). Older children had exposure similar to adults in a previous study (Study GAI1002). As expected, exposure to 2 major metabolites of mebendazole exceeded that of mebendazole.*

Reviewer's assessments:

The Reviewer agrees with the Applicant's conclusions that the exclusion of Subjects 251001272 and 251002233 from the PK analysis is not expected to change any PK conclusions and Clinical Pharmacology inferences that were drawn from the initially submitted GAI3003 PK sub-study results. In addition, these changes are updated in the mean estimates that are reported in Section 2.1.2 (Table 2 on page 7) and the respective edits are marked in Red in Table 5, below. These revised values in Table 5- that compared means of capillary whole blood mebendazole PK parameters by age group and comparison with the plasma PK parameter estimates in adults - suggest that the revised PK parameters for the youngest children (1 to 3 years of age) does not affect the conclusions that were drawn from the original submission.

Table 5: Mean Capillary Whole Blood Mebendazole Pharmacokinetic Parameters by Age Group and Comparison with the Plasma Pharmacokinetic Parameter Estimates in Adults

	Reported Estimates				Compared to Adult Estimates (Fold increase)		
	1 to <3 years[#] (N = 20)	≥3 to <7 years[#] (N = 12)	≥7 to 16 years[#] (N = 10)	Adults[$] (N = 16)	1 to <3 years	≥3 to <7 years	≥7 to 16 years
Mean C_{max} (ng/mL)	~~210~~ 174	49.9	34.2	56.2	~~3.7~~ 3.1	0.9	0.6
Maximum C_{max} (ng/mL)	~~881~~ 739	101	52.1	156	~~5.6~~ 4.7	0.6	0.3
Mean AUC_{Last} (ng*h/mL)	~~1320~~ 1196	416	387	456	~~2.9~~ 2.6	0.9	0.8
Maximum AUC_{Last} (ng*h/mL)	~~4076~~ 2373	874	747	986	~~4.1~~ 2.4	0.9	0.8

[$]Adult PK parameter estimates are calculated from plasma samples in fed condition
[#]Pediatric PK parameter estimates are calculated from whole blood capillary fingerstick samples and most administrations were with food

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/s/

ABHAY JOSHI
09/29/2016

PHILIP M COLANGELO
09/29/2016