CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210867Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	210867
Link to EDR	\\CDSESUB1\evsprod\NDA210867\210867.enx
Submission Date	10/13/2017
Submission Type	NME; Priority
Brand Name	TBD
Generic Name	Moxidectin
Dosage Form and Strength	Immediate Release Tablets 2 mg
Route of Administration	Oral
Proposed Indication	Treatment of onchocerciasis due to (b) (4) *Onchocerca volvulus* in (b) (4) patients 12 years of age and older
Applicant	Medicine Development for Global Health
Associated IND	IND 126876
OCP Review Team	Yang He, Ph.D., Clinical Pharmacology Reviewer; Phil Colangelo, Pharm.D., Ph.D., Clinical Pharmacology Team Leader; Simbarashe Zvada, Ph.D., Pharmacometrics Reviewer; Chao Liu, Ph.D., Pharmacometrics Team Leader
OCP Final Signatory	Kellie Reynolds, Pharm.D. DCP IV Deputy Director Office of Clinical Pharmacology (OCP)

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1. EXECUTIVE SUMMARY

Moxidectin is a macrocyclic lactone and is registered worldwide (including the United States) as a veterinary endectocide, but has not been approved for human use in any countries. The proposed indication and dosage regimen is treatment of onchocerciasis due to [redacted] (b) (4) *Onchocerca volvulus* in [redacted] (b) (4) patients 12 years of age and older at a regimen of 8 mg (4 x 2 mg tablets) as a single one-time dose.

The moxidectin clinical development program encompassed eight completed single oral dose trials spanning Phases 1 to 3, including a total of 1904 subjects. The Phase 2 and 3 trials were well controlled trials conducted in male and female patients with onchocerciasis in sub-Saharan Africa (in areas not previously subject to ivermectin control). Adolescents (≥12 years) with onchocerciasis were included in the Phase 3 trial. The clinical pharmacology of moxidectin has been studied in healthy volunteers and in patients with *Onchocerca volvulus* infection.

In terms of efficacy, administration of a single one-time moxidectin dose of 8 mg was significantly superior to ivermectin (comparator) in reduction of skin microfilariae density, the primary efficacy endpoint in both Phase 2 and Phase 3 clinical trials, with a consistent effect in both trials. Moxidectin 8 mg was also significantly superior to ivermectin across all analysis populations, by gender, age, baseline microfilariae densities at all time points, and by mean change from baseline, percentage reduction, absolute reduction, and the number of subjects achieving and sustaining clearance of microfilariae.

1.1 Recommendations

The Clinical Pharmacology information provided by the Applicant in NDA 210867 for Moxidectin 2 mg tablets is acceptable. The Clinical Pharmacology Review team recommends approval of this NDA.

Table 1.1-1: Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The effectiveness of moxidectin in onchocerciasis patients is primarily supported by one Phase 2 trial and one Phase 3 trial. The clinical pharmacology data, including exposure-response relationship for efficacy, provide supportive evidence of effectiveness at the proposed dosage regimen of 8 mg as a single one-time dose.
General dosing instructions	The Clinical Pharmacology Review Team concurs with the Applicant's proposed dosing recommendation, as follows: single dose of 8 mg with or without food in adolescents and adults.

Dosing in patient subgroups (intrinsic and extrinsic factors)	Adolescents (12 to 18 years of age)	a single dose of 8 mg	concur
	Food Effect	given regardless of food	concur
	Patients with Mild or Moderate Renal Impairment	a single dose of 8 mg	concur
Labeling	No major issues. Editorial revisions by the Clinical Pharmacology Review Team will be proposed.		
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed 2 mg moxidectin tablet formulation is the same as the one used in the pivotal clinical trials, but the manufacturing process and manufacturing site changed after the pivotal trials were completed. Based on a between-study comparison of moxidectin PK exposure, the bioavailability of the to-be-marketed tablet is comparable to the tablet used in the pivotal clinical trials.		

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Moxidectin is a macrocyclic lactone of the milbemycin class. The compound is a semisynthetic methoxime derivative [redacted] (b) (4), a fermentation product of *Streptomyces cyanogriseus*. The molecular weight is 639.82 Dalton (Da).

Mechanism of Action:
Moxidectin binds to glutamate-gated chloride channels in the neurons and muscle cells of parasites leading to interference with parasite pharyngeal pumping, reduction in excretion of immunomodulatory proteins, and impacts the fertility of both male and female adult worms. Moxidectin also has activity at the GABA-A receptor complex which is expressed in the ventral nerve cord in helminths and is believed to be important in normal function of somatic muscles in helminths.

Absorption:
Following oral administration of the 2 mg tablet formulation in fasted subjects, moxidectin peak plasma concentrations are observed within 3 to 4 hours.

Administration of moxidectin in a fed state following ingestion of a high-fat meal slows absorption and increases bioavailability, with mean maximum observed plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) increased by 34% and 39%, respectively, and mean time to the maximum observed concentration (T_{max}) delayed by approximately 1.6 hours in fed subjects. Given the relatively wide

margin of safety, the increased absorption of moxidectin with a high-fat meal is not deemed to be clinically relevant by the Clinical Pharmacology Review Team.

Distribution:
Healthy volunteer and patient studies indicate the mean apparent volume of distribution (Vz/F) following oral administration of moxidectin ranges from 2000 to 3000 L. Moxidectin concentrations in breast milk were higher than those in plasma after a single dose of 8 mg moxidectin in healthy women subjects who were in the late stage of lactation, and the ratio (mean ± SD) of moxidectin AUC in breast milk and plasma was 1.77 ± 0.66. The percentage of the 8 mg moxidectin dose excreted into the breast milk of the healthy female volunteers over 28 days was approximately 0.70% (approximately 0.056 mg). In general, female subjects and subjects with larger BMI have enhanced tissue distribution.

Neither the plasma protein binding nor the red blood cell/plasma cell partitioning of moxidectin have been determined.

Metabolism and Excretion:
Moxidectin has a long terminal half-life, ranging from a mean of 485 to 1139 hours (approximately 20 to 47 days) in healthy volunteers and 559 hours (approximately 23 days) in onchocerciasis patients receiving 8 mg moxidectin. The mean apparent clearance (CL/F) of moxidectin from plasma was 2760 to 3506 mL/h in healthy volunteers and 3500 mL/h in patients.

Moxidectin is minimally metabolized by cytochrome P450 (CYP) enzymes into a small number of hydroxylated metabolites. There is no evidence for non-CYP-mediated metabolism of moxidectin, including glucuronidation. Renal elimination of intact drug is negligible. Following a single 8 mg oral dose of moxidectin, 2% of the dose is eliminated unchanged in feces within the first 72 hours.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosage regimen for moxidectin is a single one-time dose of 8 mg (4 x 2 mg tablets) taken orally with or without food.

2.2.2 Therapeutic individualization

Intrinsic factors:
The hepatic metabolism and renal excretion of moxidectin are minimal. The pharmacokinetics of moxidectin were not studied in dedicated PK studies of hepatic or renal impairment because the regimen is a single one-time dose. However, the Clinical Pharmacology Review Team evaluated the totality of moxidectin PK data for patients with creatinine clearance (CrCL) of 47 mL/min and above and we generally agree with the Applicant's proposal that dose adjustment in patients with mild to moderate renal impairment is not needed. Clinical efficacy and safety studies of moxidectin did not

include patients with CrCL less than 47 mL/min, nor any patients with any level of hepatic impairment, in terms of Child-Pugh Class A, B, or C.

Extrinsic factors:
Moxidectin is not a substrate of CYP450 enzymes, uridine 5'-diphospho-glucuronosyltransferases (UGTs), the drug transporter P-glycoprotein (P-gp), and is not an inhibitor of CYP450 *in vitro*. It induced CYP3A4 *in vitro* but there was no *in vivo* drug-drug interaction between moxidectin and the CYP3A4 substrate, midazolam, in healthy subjects. Moxidectin is a substrate of breast cancer resistance protein 1 (BCRP1), but the extent of interaction is not expected to be clinically significant. Thus, moxidectin has low potential as a victim or perpetrator of clinically relevant drug-drug interactions.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

See **Table 2.4-1** for a summary of labeling issues and recommendations.

Table 2.4-1: Summary of Labeling Issue Identification and Recommendations

Section/heading	Acceptable to OCP?			Comment
	A	AWE	NA	
Highlights	☒	☐	☐	Concur
Section 2.1/ Recommended (b) (4)	☒	☐	☐	Concur
(b) (4)	☒	☐	☐	Concur
(b) (4)	☐	☐	☒	Remove, since it is clearly inapplicable.
Section 5 / Warnings and Precautions	☒	☐	☐	Concur
Section 8.5/ Geriatric Use	☐	☒	☐	Add standard labeling language per 21 CFR 201.57(c)(9)(v)(B)(2)
Section 8.6/ Renal Impairment	☐	☐	☒	Remove, no specific dose adjustment recommendation or clinically relevant information
(b) (4)	☐	☐	☒	Remove, no specific dose adjustment recommendation or clinically relevant

				information
Section 10/ Overdosage	☐	☒	☐	Avoid information about an unapproved dosage
Section 12.1/ Mechanism of Action	☐	☒	☐	Move the detailed information to 12.4 Microbiology
Section 12.2/ Pharmacodynamics	☐	☒	☐	Edit to reflect QT results
12.3/Pharmacokinetics	☐	☒	☐	Need to revise the labeling language, add table of PK parameters, and remove unnecessary data.

A = Acceptable; AWE=Acceptable with minor edits; NA=not acceptable/substantive disagreement (must provide comment)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Moxidectin is a macrocyclic lactone endectocide of the milbemycin class, a semisynthetic methoxime derivative [redacted] (b) (4) a fermentation product of *Streptomyces cyanogriseus*. Moxidectin was developed as a veterinary product, and is registered worldwide (including in the United States) for the prevention of canine heartworm and for the treatment of parasites in livestock such as cattle, sheep, and horses. Moxidectin is not registered for human use in any country.

Moxidectin was granted Orphan Drug designation by the FDA on September 29, 2010. Although Medicines Development for Global Health is exempt from the requirements described under the Pediatric Research Equity Act, [redacted] (b) (4) .

3.2 General Pharmacology and Pharmacokinetic Characteristics

Table 3.2-1: Summary of Clinical Pharmacology and Pharmacokinetics

Pharmacology	
Mechanism of Action	Moxidectin binds to glutamate-gated chloride channels in the neurons and muscle cells of parasites leading to interference with parasite pharyngeal pumping, reduction of excretion of immunomodulatory proteins and impacting the fertility of both male and female adult worms. Moxidectin also has activity at the gabba-aminobutyric acid (GABA)-A receptor complex which is expressed in the ventral nerve cord in helminths and is believed to be important in normal function of somatic muscles in helminths.
Active Moieties	Moxidectin
QT Prolongation	Moxidectin had no statistically or clinically significant effect on QT interval following administration of single oral doses between 4 and 36 mg. At the maximum dose of 36 mg, mean Cmax exceeded that of the 8 mg clinical dose by 4.5-fold. There was also no clinically significant effect on HR, PR interval, and QRS interval.
General Information	
Bioanalysis	The HPLC with fluorescence detection and the HPLC/MS methods were validated to determine moxidectin concentrations in human plasma, urine, and feces.

<table>
<tr><td>Healthy vs. Patients</td><td>Patients with onchocerciasis show 30% higher apparent total clearance compared to healthy volunteers.</td></tr>
<tr><td>Drug exposure following the therapeutic dosing regimen (8 mg, single dose)</td><td>
<table>
<tr><td></td><td>Healthy Subjects (Study 1005)</td><td>Patients with onchocerciasis</td></tr>
<tr><td></td><td>Mean ± SD, N=27 (fasting)</td><td>Mean± SD, N=172 (fasting)</td></tr>
<tr><td>AUC_{inf} (ng●hr/mL)</td><td>3387 ± 1328</td><td>2738 ± 1606</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>58.9 ± 12.5</td><td>63.1 ± 20.0</td></tr>
</table>
</td></tr>
<tr><td>Range of effective dose or exposure</td><td>8 mg, single dose</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>36 mg, single dose</td></tr>
<tr><td>Dose Proportionality</td><td>The Cmax and AUC increased in an approximately dose proportional manner over the range of 4 to 36 mg administered to healthy subjects in a fasting state.</td></tr>
<tr><td>Accumulation</td><td>n/a</td></tr>
<tr><td>Variability</td><td>Between-subject variability of apparent clearance and central volume of distribution are 16.9% and 5.4%, respectively.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Bioavailability</td><td>The absolute oral bioavailability of moxidectin has not been determined.</td></tr>
<tr><td>T_{max}</td><td>Median 2-4 hours</td></tr>
<tr><td>Food effect (Fed/fasted) Geometric Mean % [P value]</td><td>
<table>
<tr><th>AUC_{0-inf}</th><th>C_{max}</th><th>T_{max} (mean ± SD)</th></tr>
<tr><td>139% [p=0.0003]</td><td>134% [p=0.001]</td><td>5.3 ± 2.1 hours [fed] vs.3.7 ± 1.5 hours [fasted]</td></tr>
<tr><td colspan="3">The population PK analysis indicated that food increased the relative bioavailability by approximately 1.4-fold.</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of Distribution</td><td>1708 to 3635 L (healthy subjects); 2222 to 2421 L (patients)</td></tr>
<tr><td>Plasma Protein Binding</td><td>Not determined</td></tr>
</table>

Distribution to Breast Milk	AUC_{milk}/AUC_{plasma} was 1.77±0.66. The percentage of moxidectin dose excreted in breast milk was 0.701±0.299% over a period of 28 days.
Substrate transporter systems [*in vitro*]	Moxidectin is not a substrate for P-gp but is a substrate for BCRP1 in vitro.
Elimination	
Terminal Elimination half-life	A mean of 485 to 1139 hours (approximately 20 to 47 days) in healthy volunteers and 559 hours (approximately 23 days) in onchocerciasis patients
Metabolism	
Fraction metabolized (% dose)	<10%
Primary metabolic pathway(s) [*in vitro*]	Minimal hepatic CYP metabolism observed *in vitro.*
Excretion	
Primary excretion pathways (% dose) ±SD	No human mass balance study was conducted due to long half-life. Feces: 2% dose within the first 72 hours after 8 mg dose;
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	Moxidectin was observed to induce CYP3A4 *in vitro*, but no induction was observed in humans (DDI study with midazolam). Moxidectin did not show induction or inhibition against other CYPs or UGT.
Inhibition/Induction of transporter systems	No inhibition/induction of transporters

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology data, including exposure-response relationship for efficacy, provide supportive evidence of effectiveness at the proposed dosage regimen of 8 mg as a single one-time dose.

The Phase 2 study evaluated the effectiveness of moxidectin across 2, 4, and 8 mg in adults with onchocerciasis. Skin microfilariae density over time, percentage reduction, and proportion of subjects undetectable were used as the clinical endpoints. These are presented by the treatment time points of Month 6 and Month 12 (**Table 3.3.1-1**).

Table 3.3.1-1 Phase 2 Endpoint Comparison by Dose at Months 6 and 12 *(Source: Applicant's Summary of Clinical Efficacy, page 19, Table 11)*

Endpoint	Phase II		
	MOX 2 mg (n = 44)	**MOX 4 mg (n = 45)**	**MOX 8 mg (n = 38)**
Month 12 LS Geometric Mean (mITT) [1] **(95% CI)**	1.445 (1.202, 1.736)	1.387 (1.167, 1.647)	1.187 (0.976, 1.445)
Month 12 Ratio of LS Geometric Means [1] **(Moxidectin/Ivermectin) (mITT)**	0.542 (0.42, 0.69)	0.520 (0.41, 0.66)	0.445 (0.35, 0.57)
Mean mf/mg skin [2] (mITT)			
Month 6	0.06	0.03	0.00
Month 12	0.92	0.81	0.42
Adjusted Mean (SE) Reduction from Baseline [2] (mITT)			
Month 6	0.06 (1.04)	0.06 (1.03)	0.06 (1.04)
Month 12	0.09 (1.07)	0.09 (1.07)	0.08 (1.05)
Mean Percentage Reduction from Baseline (%)			
Month 6	99.7%	99.9%	100%
Month 12	96.1%	96.1%	98.2%
Proportion Undetectable (%)			
Month 6	81.0%	91.1%	100%
Month 12	35.7%	40.0%	59.5%
Sustained Undetectable from Month 1 to N (%) (mITT) [4]			
Month 6	31 (70.5%)	39 (86.7%)	36 (94.7%)
Month 12	15 (34.1%)	18 (40.0%)	20 (52.6%)

Based on exposure-response assessments of complete sustained microfilariae response through Month 6, it appears that an 8 mg single dose is approaching maximum effect. Refer to **Appendix 4.2** for more details of exposure-response analyses.

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

Yes, the proposed dosing regimen is a single one-time 8 mg dose of moxidectin for adolescents 12 years to < 18 years of age and adults.

While the efficacy and safety of moxidectin was evaluated in adults and adolescents 12 years and older in the Phase 3 study, the pharmacokinetics of moxidectin has only been evaluated in adults. However, the subpopulation analyses of efficacy and safety are provided in the NDA submission (see also Clinical Review by Dr. Hiwot Hiruy and Statistical Review by Dr. Edward Bein).

Efficacy in adolescents:
In the Phase 3 study, 77 (15.7%) of the study subjects were ⩾12 and <18 years old and 1395 (44.0%) of the subjects were ⩾18 years old. The magnitude of effect and statistical significance of the primary endpoint favoring moxidectin over ivermectin at Month 12 (p

< 0.0001) was consistently observed for the mITT by age group (≥12 and <18) years and ≥18 years) as shown in **Table 3.3.2-1**.

Table 3.3.2-1 Mean *O. volvulus* Skin Microfilariae Density (mf/mg skin) at Month 12 including Treatment-by-Age group (adults and adolescents 12 years and older) Interaction (mITT population)

Parameter	Skin Microfilariae			
	≥ 12 - < 18 years		≥ 18 years	
	MOX (8 mg) n = 53	IVM (150 µg/kg) n = 24	MOX (8 mg) n = 890	IVM (150 µg/kg) n = 455
LS Geometric Mean[1] (95% CI)	1.201 (0.692, 1.864)	6.735 (4.488, 9.903)	0.522 (0.278, 0.811)	4.727 (3.782, 5.859)
Ratio of LS Geometric Means[2] (95% CI)	0.285 (0.199, 0.406)		0.266 (0.244, 0.289)	
p value	< 0.0001		< 0.0001	

[1] LS Geometric Means, CIs, and p-values are obtained from a mixed-effects model on mf/mg skin at Month 12 with baseline mf/mg skin, sex, age group, treatment group and treatment-by-age group interaction as fixed effects and site as a random effect.
[2] Ratio is derived by back-transforming the difference in LS means on the log transformed data to give a ratio of (X+1)/ (Y+1). Therefore, this will not be identical to the ratio of the LS Geometric Means.
Baseline is defined as the last assessment reported prior to test article administration on Day 1.
Data were transformed using ln (y+1) before analysis; LS Geometric Means and CIs have been back-transformed to the original units.
Source: Phase III CSR, Table 14.2.1.9.3

Based on the primary endpoint comparison, adolescents tended to have higher skin microfilariae densities at Month 12, compared to adults. However, moxidectin is still statistically superior to the comparator (ivermectin) in both adolescents and adults.

Safety in adolescents:
Moxidectin treated adolescents experienced treatment associated adverse events more frequently compared with those treated with ivermectin. These included lymph node pain in 24 (45.3%) moxidectin subjects compared with five (20.8%) ivermectin treated subjects, skin disorders (pruritus, rash, facial swelling and urticaria) in 38 (71.7%) moxidectin recipients compared with 12 (50.0%) ivermectin recipients, general disorders (chills, influenza like illness, pain, peripheral swelling and pyrexia) in 36 (67.9%) moxidectin subjects compared with 9 (37.5%) ivermectin subjects and postural tachycardia in 28 (52.8%) and tachycardia 10 (18.9%) moxidectin compared with 4 (16.7%) and 1 (4.2%) ivermectin treated subjects respectively. However, Grade 3 and 4 events occurred in the adolescent subpopulation at similar rates to the overall population (**Table 3.3.2-2**). Please refer to the Clinical Review by Dr. Hiwot Hiruy) for more details of the safety evaluation.

Table 3.3.2-2 Number (%) of Subjects by TEAE Maximum Severity for Adolescents (< 18 years) and Total Study Population in Phase 3 (mITT)

Population	< 18 years		Total	
Severity	MOX (8 mg) n = 53 n (%)	IVM (150 µg/kg) n = 24 n (%)	MOX (8 mg) n = 978 n (%)	IVM (150 µg/kg) n = 494 n (%)
< Grade 3	24 (45.3)	10 (41.7)	338 (34.6)	152 (30.7)
≥ Grade 3	29 (54.7)	13 (54.2)	640 (65.4)	339 (68.6)

Source: Phase III Tables 14.3.1.8 and 14.1.7.1

Taken together, the Clinical Pharmacology Review Team concurs with the Applicant's proposal of a single one-time 8 mg dose of moxidectin in adolescents and adults 12 years of age and older.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No clinically significant differences in the pharmacokinetics of moxidectin were observed based on age (18 to 60 years), sex, weight (42.7 to 107.2 kg), or renal impairment (creatinine clearance (CLcr) 47 to 89 mL/min, estimated by Cockcroft-Gault). Therefore, there is no alternative dosing regimen and/or management strategy needed/required for subpopulations based on intrinsic factors. The influence of hepatic impairment on the pharmacokinetics of moxidectin in patients is unknown.

In general, the Clinical Pharmacology Review Team concurs with the Applicant's proposal that no dose adjustment is needed in patients with mild to moderate renal impairment. The population PK analysis conducted by the applicant has been reviewed and verified (Refer to **Appendix 4.2**). As detailed in the population PK analysis section, there is no significant trend between moxidectin apparent oral clearance (**Figure 3.3.3-1**) and CrCL based on data collected from the Phase 2 study. However, it should be noted that the lowest CrCL value observed in the Phase 2 study was 47 mL/min. Combining Phase 2 with Phase 3 results adequately covered patients with CrCL of 47 mL/min and above, and indicated that there were no apparent safety issues and/or concerns for patients who have this level of renal impairment as shown in **Table 3.3.3-1**.

Figure 3.3.3-1 Illustration of moxidectin clearance versus creatinine clearance using Phase 2 data* (Source: FDA Pharmacometrics analysis, Appendix 4.2)

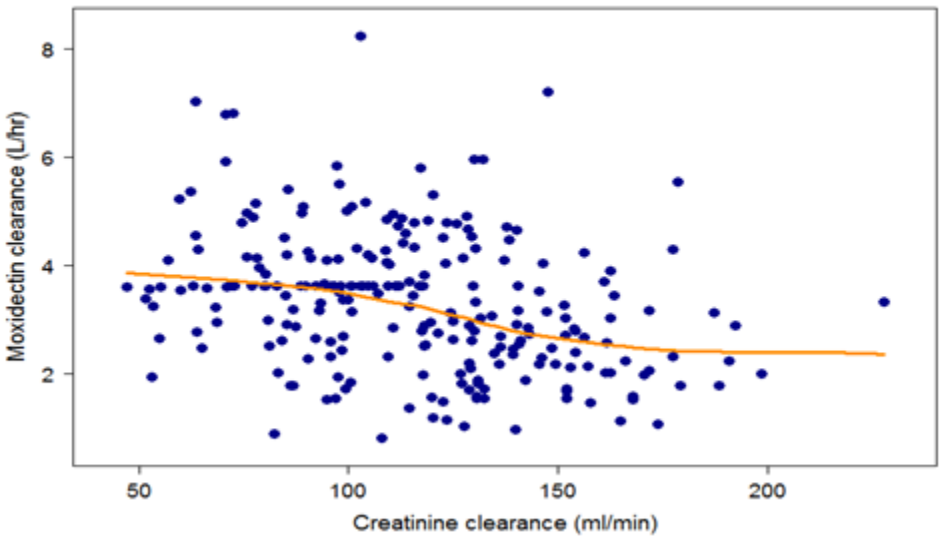


Table 3.3.3-1: Summary of Creatinine Clearance (CrCL) in Moxidectin Recipients in Phase 2 and Phase 3 Studies*

Estimated creatinine clearance	Number of subjects (%)		
	No SAEs n=909	SAE n=69	TOTAL n=978
10 to 29 mL/min	0	1 (1.4)	1 (0.1)
30 to 59 mL/min	116 (12.7)	16 (23.2)	132 (13.5)
60 to 89 mL/min	377 (41.5)	37 (53.6)	414 (42.3)
>90 mL/min	416 (45.7)	15 (21.7)	431 (44.1)

*Lowest observed CrCL estimate for **Figure 3.3.3-1** and **Table 3.3.3-1** was 47 mL/min (Source: Applicant's summary of Clinical Safety, Page 45, Table 21)

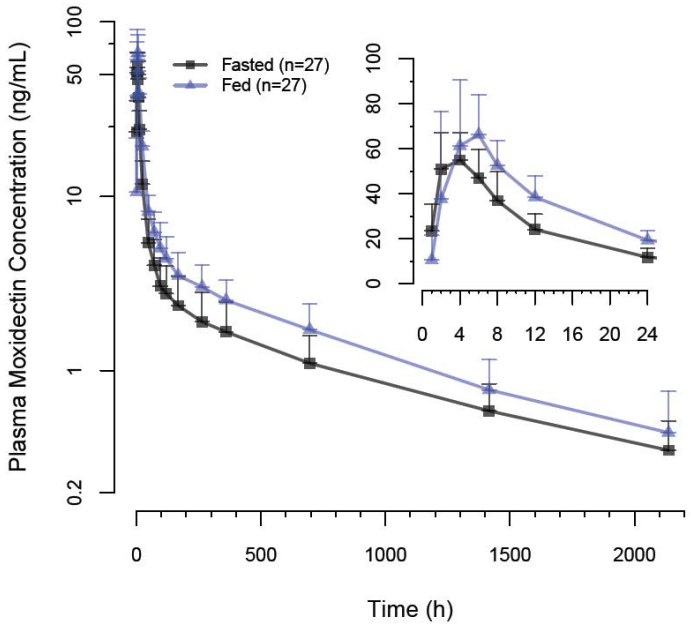
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No, there are no clinically relevant drug-drug interactions based on the results from nonclinical and clinical drug-drug interaction studies (Refer to **Section 2. Summary of Clinical Pharmacology Assessment**). There is no clinically relevant food-drug interaction. The clinical pharmacology and safety data support the conclusion of no clinically relevant impact of food intake on the safety of a single one-time dose of 8 mg moxidectin in the treatment of the proposed indication.

The effect of food on moxidectin pharmacokinetics following a single oral tablet dose of 8 mg was evaluated in Study 1005 and via population pharmacokinetic modelling. Study 1005 was a parallel group design (fed and fasted cohorts), rather than a cross-over design, because of the long half-life of moxidectin. The moxidectin PK profiles following drug

administration in fasting and fed conditions are shown in **Figure 3.3.4-1**. Cmax and AUC were both increased upon administration with food by 34% and 39%, respectively. Both CL/F and Vz/F were observed to be lowered by 35% and 40%, respectively, in the subjects who took moxidectin with food compared with fasting subjects. The terminal half-life remained similar.

Figure 3.3.4-1 Moxidectin Concentrations in Healthy Male Volunteers after an Oral 8 mg Dose While Fed and Fasting (Mean ± SD)



Of the 54 subjects in the safety population from this study, a total of 33 (61.1%) subjects experienced at least one AE. There was no difference in AE profile between the fasted and fed cohorts: 29/33 subjects experienced TEAEs, 15 in the fasted cohort and 14 in the fed cohort.

In addition, the PK and safety of moxidectin doses ranging from 2 mg to 36 mg have been tested in the Phase 1 studies. Given the apparent broad safety margin for moxidectin tested in these clinical trials, the observed increase in bioavailability of moxidectin with a high-fat meal in this study is not considered to be clinically relevant and it is deemed acceptable by the Clinical Pharmacology Review Team that moxidectin can be administered with or without food.

4. APPENDICES

4.1 Summary of Bioanalytical Methods and Validation

The bioanalytical methods used to measure concentrations of moxidectin in human plasma were validated (**Table 4.1-1**). Stability of the analyte was demonstrated during sample processing and long-term storage. The Clinical Pharmacology Review Team considers the bioanalytical methods that were used to determine moxidectin concentration in plasma and other biofluids to be acceptable.

Table 4.1-1: Summary of Bioanalytical Methods

Studies	Study 101	Study 1002 Study 1004 Study 1005 Phase 2	Study 1008
Method	HPLC with fluorescence detection	HPLC with fluorescence detection	Liquid chromatography with tandem mass spectrometry
Lower limit of Quantitation	0.2 ng/mL	0.08 ng/mL	0.1 ng/mL
Validation Range	0.2 – 400 ng/mL	0.08 – 120 ng/mL	0.1 – 100 ng/mL
Inter-day Accuracy (%Bias)	±10.3%	±6.4%	±8.3%
Inter-day Precision (coefficient of variation [%])	11.4%	13.1%	< 8.7 %
Validation Report	RPT-49959	RPT-70109	MDG-R5809

4.2 Pharmacometrics Review

4.2.1 Applicant's Population PK Analyses

Applicant conducted population PK analysis using NONMEM for moxidectin using data from three Phase 1 studies in healthy volunteers (Studies 101, 1005, 1008) and one Phase 2 study (Study 200) in patients with *Onchocerca volvulus*. The PK data from study 1008 were used to update the PK model. This review will be focusing on evaluation of the adequacy of recommended dose and whether the labeling language is supported by the applicant's final population PK based on intrinsic or extrinsic factors.

The objectives of the applicant's population PK analysis were to:

1. Describe the population PK of moxidectin using PK data from healthy volunteers and patients
2. Use individual predictions from the updated population PK model to investigate the relationships between predicted moxidectin exposure and clinically relevant PD outcomes (the Phase 2 study only)
3. Use the findings from the PK-PD modelling to support dosing decisions for ongoing and future studies of moxidectin.

Description of data used in population PK analysis by the applicant

A total of 2827 concentrations (872 from Study 101, 899 from Study 1005 and 1056 from the Phase 2 study) from 210 subjects (58 from Study 101, 54 from Study 1005 and 98 from the Phase 2 study) were included in the population PK analysis.

· Study 101

Study 101 investigated the relative bioavailability of a tablet and a liquid formulation of moxidectin in healthy subjects. This was an open-label, randomized (tablet or liquid formulation), single-dose (10 mg), parallel-design study conducted in 58 healthy male subjects. The demographic characteristics are shown in **Table 4.2.1-1**. Plasma moxidectin concentrations were determined using high-performance liquid chromatography with fluorescence detection. Blood samples (10 mL) for moxidectin plasma analysis were obtained on study day 1 immediately before and 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after administration and on days 6, 8, 21, 24, 30, 90, and 180 after moxidectin administration.

Table 4.2.1-1 Demographic characteristics of healthy male subjects from Study 101 ***(Source: Applicant's population PK report, Table 1, Page 13)***

	Tablet (n= 29) Mean (SD)	Liquid (n= 29) Mean (SD)
Body weight (kg)	82.0 (10.0)	81.8 (11.1)
Body mass index (kg/m^2)	24.7 (2.96)	25.0 (2.67)
Age (years)	33.9 (7.41)	33.5 (5.90)

SD=standard deviation

· Study 1005

Study 1005 investigated the effects of a high-fat meal on the relative bioavailability and pharmacokinetics of a single dose of moxidectin administered orally to healthy subjects. This was a single-dose, randomized (fasted or fed), open-label, parallel-group, inpatient/outpatient study in 54 healthy subjects. The 8 mg doses were administered after an overnight fast of at least 10 hours or after the completion of a standard high-fat breakfast. The demographic characteristics are shown in **Table 4.2.1-2**. Plasma moxidectin concentrations were determined using high-performance liquid chromatography with fluorescence detection. Blood samples (5 mL) for moxidectin plasma analysis were on day 1 immediately before and at 1, 2, 4, 6, 8, 12, 24, and 48, 72, and 96 hours after administration and on days 6, 8, 12, 16, 30, 60, and 90 after moxidectin administration.

Table 4.2.1-2 Demographic characteristics of healthy male subjects from Study 1005 ***(Source: Applicant's population PK report, Table 2, Page 14)***

	Fasted (n= 27) Mean (SD)	Fed (n= 27) Mean (SD)
Body weight (kg)	75.7 (12.0)	70.7 (9.50)
Body mass index (kg/m^2)	23.3 (2.61)	23.1 (2.36)
Age (years)	30.4 (9.52)	30.9 (10.7)

SD=standard deviation, BMI=body mass index

· Study 1008

Study 1008 evaluated the potential effects of a single-oral dose administration of moxidectin on the QT interval in healthy male subjects. This was a randomized, single center, double blind, placebo-controlled, parallel group study in which 60 healthy male subjects were randomized into one of the following groups, with 10 subjects per group: placebo, 4 mg, 8 mg, 16 mg, 24 mg or 36 mg moxidectin. Demographic characteristics of subjects from this study are summarized in **Table 4.2.1-3**. Blood was drawn to determine the pharmacokinetics of moxidectin at the following time points: immediately prior to dosing (baseline), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60 and 72 hours after dosing and 7, 14 and 21 days after moxidectin dosing.

Table 4.2.1-3 Demographic characteristics of healthy male subjects from Study 1008
(Source: Applicant's population PK report, Table 4, Page 17)

	Placebo (N=10) Mean (SD)	4 mg (n= 10) Mean (SD)	8 mg (n= 10) Mean (SD)	16 mg (n= 10) Mean (SD)	24 mg (n= 10) Mean (SD)	36 mg (n= 10) Mean (SD)
Body weight (kg)	82.4 (11.3)	82.2 (12.6)	75.7 (11.5)	78.3 (11.7)	77.5 (12.4)	83.7 (12.0)
Body mass index (kg/m^2)	26.1 (3.11)	26.2 (3.74)	24.9 (3.35)	25.8 (3.71)	25.1 (3.00)	26.7 (3.09)
Age (years)	32.3 (6.72)	37.1 (7.77)	30.4 (8.73)	30.9 (8.32)	31.2 (8.27)	30.2 (8.87)

SD=standard deviation, BMI=body mass index

· Study 200

The Phase 2 study was a randomized, single-ascending-dose, ivermectin-controlled, double-blind, safety, tolerability, pharmacokinetic and efficacy study of orally administered moxidectin in subjects with *Onchocerca volvulus* infection. Demographic characteristics of these subjects are summarized in **Table 4.2.1-4**. Subjects were enrolled in 9 consecutive cohorts:

1. 2 mg: Subjects with >0 and <10 microfilariae (mf)/mg of skin.
2. 2 mg: Subjects with 10-20 mf/mg of skin and the sum of mf in the two eyes were 10.
3. 2 mg: Subjects with >20 mf/mg of skin with or without ocular involvement.
4. 4 mg: Subjects with >0 and <10 mf/mg of skin.
5. 4 mg: Subjects with 10-20 mf/mg of skin and the sum of mf in the two eyes were 10.
6. 4 mg: Subjects with >20 mf/mg of skin with or without ocular involvement.
7. 8 mg: Subjects with >0 and <10 mf/mg of skin.
8. 8 mg: Subjects with 10-20 mf/mg of skin and the sum of mf in the two eyes were 10.
9. 8 mg: Subjects with >20 mf/mg of skin with or without ocular involvement.

Table 4.2.1-4 Demographic characteristics of patients in Study 200 ***(Source: Applicant's population PK report, Table 3, Page 15)***

	2 mg (n= 44) Mean (SD)	4 mg (n= 45) Mean (SD)	8 mg (n= 38) Mean (SD)
Body weight (kg)	59.9 (8.35)	57.6 (6.75)	59.2 (8.76)
Body mass index (kg/m^2)	21.0 (3.0)	21.1 (2.42)	21.1 (3.29)
Age (years)	38.3 (10.9)	37.6 (10.6)	32.1 (13.3)
Females, n (%)	8 (18.2)	14 (31.1)	7 (18.4)

SD=standard deviation, BMI=body mass index

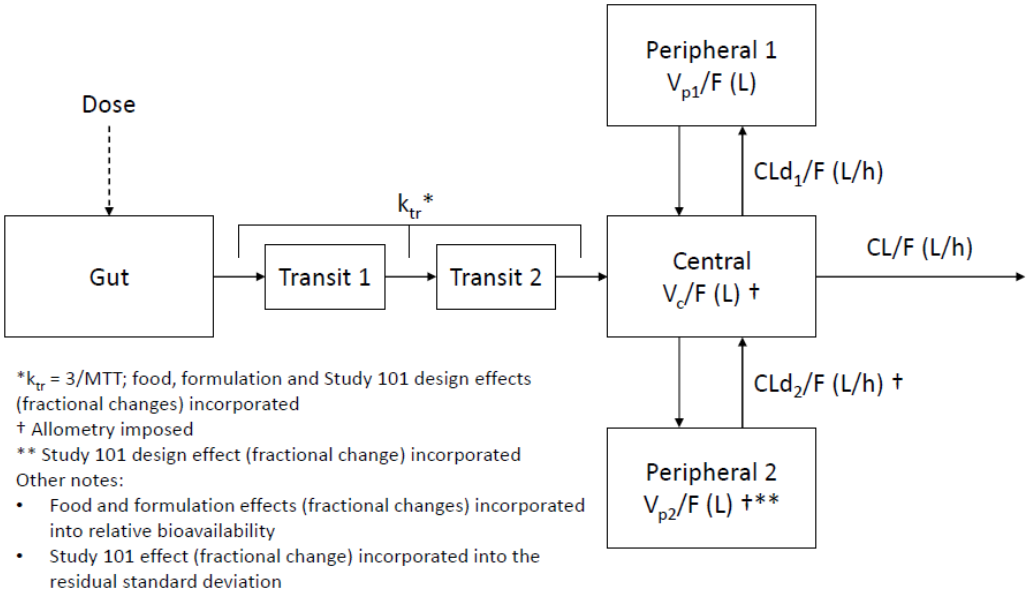
Plasma moxidectin concentrations were determined using high-performance liquid chromatography with fluorescence detection. Blood samples for determination of moxidectin plasma concentrations were scheduled to be collected within 2 hours prior to dosing and at 1, 2, 4, 8, 24, and 72 hours after study drug administration and on study days 8, 13, 18, 1 month (±1 week), 2 months (±1 week), 3 months (±1 week), 6 months (±1 month), and 12 months ±1 month).

· Model building
The population PK analysis was performed in NONMEM 7.3 and Perl Speaks NONMEM (PsN) with post processing of data performed in R. The applicant first built the base and final models using data from Studies 101, 1005 and 200. The final model was then updated with data from Study 1008. PK covariates tested included sex, body weight, body mass index, bilirubin, albumin, creatinine clearance, baseline microfilariae density, age, acetaminophen effect, food, formulation, and healthy status. The applicant excluded all concentrations which were below the lower limit of quantitation (LLOQ), and these constituted approximately 11 % of the PK data used in population PK analysis.

Results

The final population PK parameter estimates are show in **Table 4.2.1-5**. It was a three-compartment model with n-transit absorption (two transit compartments) and first-order elimination as shown in **Figure 4.2.1-1**. The ability of the final model to describe the population PK of moxidectin as evaluated with visual predictive checks as shown in the **Figure 4.2.1-2** to **Figure 4.2.1-5**, and the model was adequately described the population PK of moxidectin. The covariate analysis showed that females had larger values of CL_{d2}/F and V_{p2}/F than males and subjects with a larger BMI had increased V_{p2}/F (stratified by Phase 1 and Phase 2), a finding which can be attributed to lipophilic nature of moxidectin. The impact of food was the main extrinsic factor identified for its potential to impact pharmacokinetics, whereby a high-fat meal increased the relative bioavailability and the mean transit time by approximately 1.4- and 2.1-fold, respectively.

Figure 4.2.1-1 Schematic illustration of the model ***(Source: applicant's population PK report, page 25, Figure 6)***



ktr = transit rate constant, CL/F = apparent clearance, V_c=F apparent volume of distribution of the central compartment, CL_{d1}/F = apparent inter-compartmental clearance between the central and first peripheral compartments, V_{p1}/F = apparent volume of distribution of the first peripheral compartment, CL_{d2}/F = apparent inter-compartmental clearance between the central and second peripheral compartments, V_{p2}/F = apparent volume of distribution of the second peripheral compartment.

Table 4.2.1-5. Parameter estimates from the final population PK model of moxidectin updated with data from Study 1008

Parameter	Estimate	%RSE	BSV	%RSE
MTT (h)	1.70	4.13	0.182	12.1
CL/F (L/h)	3.65	5.81	0.169	10.5
V_c/F (L/70 kg)	127	4.39	0.0541	14.3
CL_{d1}/F (L/h)	5.03	5.05		10.5
V_{p1}/F (L)	216	6.34		
CL_{d2}/F (L/h/70 kg)	3.25	6.15	0.107	12.4
V_{p2}/F (L/70 kg)	1086	5.17	0.164	9.51
Phase 1 effect* on CL/F	0.689	19.6		
Phase 1 effect* on V_c/F	0.800	23.2		
Phase 1 effect* on CL_{d1}/F	0.837	36.3		
Phase 1 effect* on V_{p1}/F	0.515	11.7		
Phase 1 effect* on CL_{d2}/F	1.76	13.4		
Phase 1 effect* on V_{p2}/F	1.27	35.1		
Food effect* on MTT	2.09	10.4		
Food effect* on relative bioavailability	1.36	17.0		
Formulation effect* on MTT (fixed)	0.292	0		
Formulation effect* on relative bioavailability	1.18	14.3		
Sex effect* on CL_{d2}/F	1.48	25.1		
Sex effect* on V_{p2}/F	1.61	21.9		
Phase 1 BMI effect** on V_{p2}/F	1.69	18.3		
Phase 2 BMI effect** on V_{p2}/F	0.586	52.4		
Study 3110A1-101-EU effect* on MTT (fixed)	0.477	0		
Study 3110A1-101-EU effect* on V_{p2}/F	1.19	40.8		
Proportional error (SD; %)	21.5	0.785		
Study 3110A1-101-EU effect* on proportional error	0.900	16.8		

%RSE=Percent relative standard error; BSV=Between-subject variance,
*Fractional change; **Exponent from power function; SD=Standard deviation
Covariance between BSVs for V_c/F and CL/F = 0.0592
Covariance between BSVs for CL_{d2}/F and V_{p2}/F = 0.0908

Figure 4.2.1-2 Visual predictive check for Study 101. The solid blue and red lines represent the medians of the observed and simulated concentrations, respectively. The dashed blue and red lines represent the 10th and 90th percentiles of the observed and simulated concentrations, respectively *(Source: Applicant's population PK report, Page 32 Figure 12)*

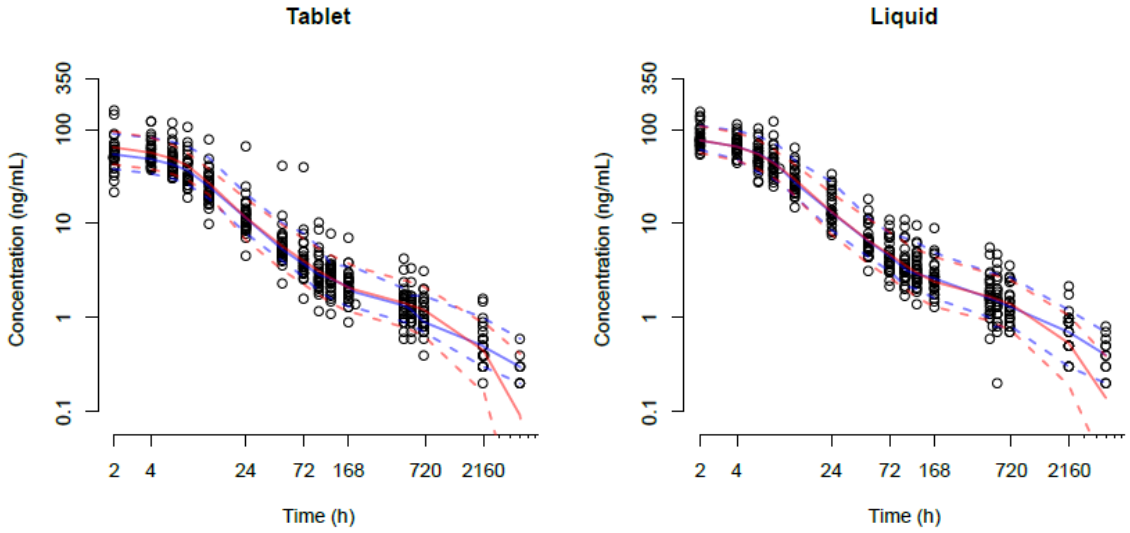


Figure 4.2.1-3 Visual predictive check for Study 1005. The solid blue and red lines represent the medians of the observed and simulated concentrations, respectively. The dashed blue and red lines represent the 10th and 90th percentiles of the observed and simulated concentrations, respectively *(Source: Applicant's population PK report, Page 32 Figure 13)*

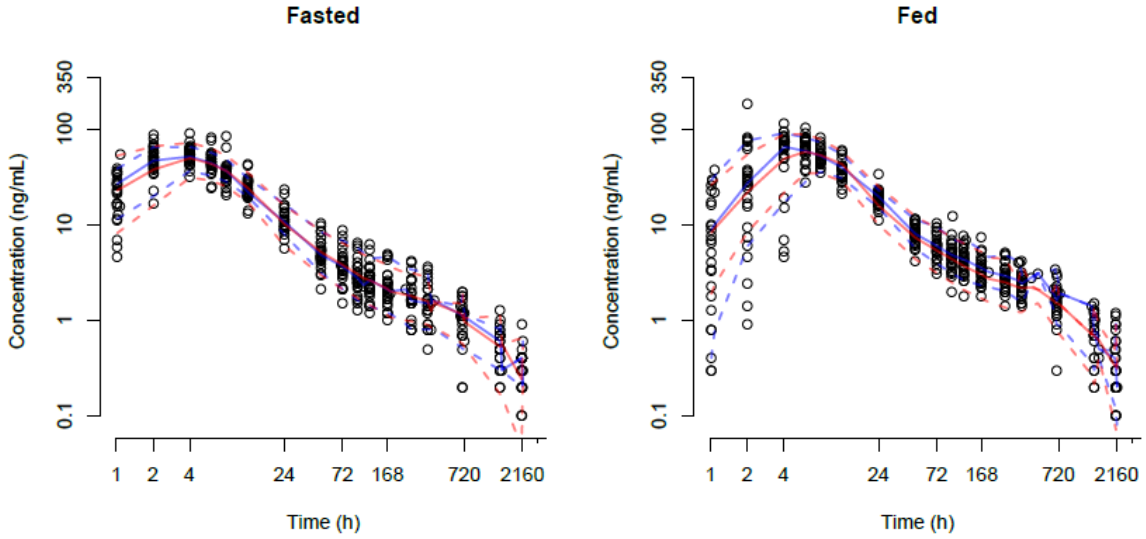


Figure 4.2.1-4 Visual predictive check for Study 200. The solid blue and red lines represent the medians of the observed and simulated concentrations, respectively. The dashed blue and red lines represent the 10th and 90th percentiles of the observed and simulated concentrations, respectively *(Source: Applicant's population PK report, Page 32 Figure 14)*

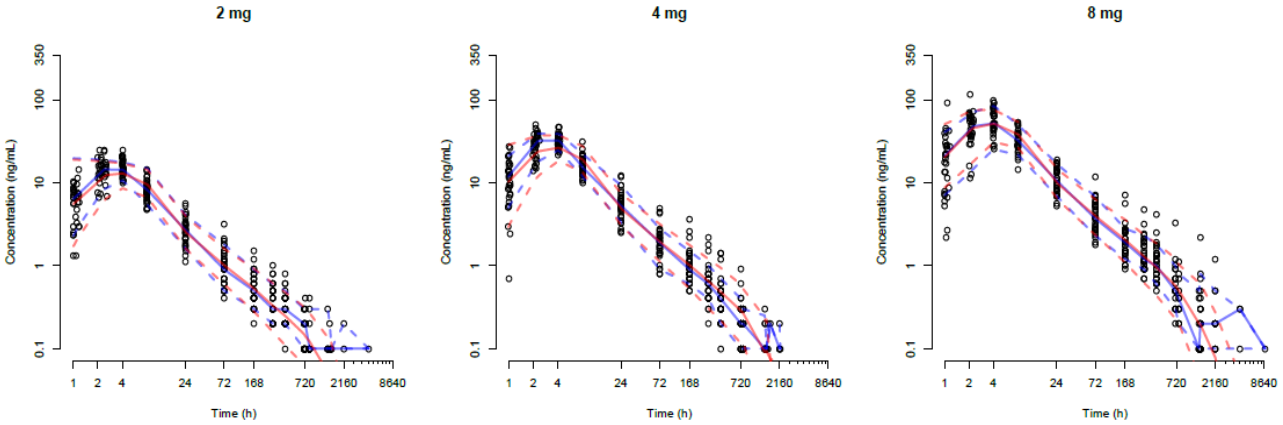
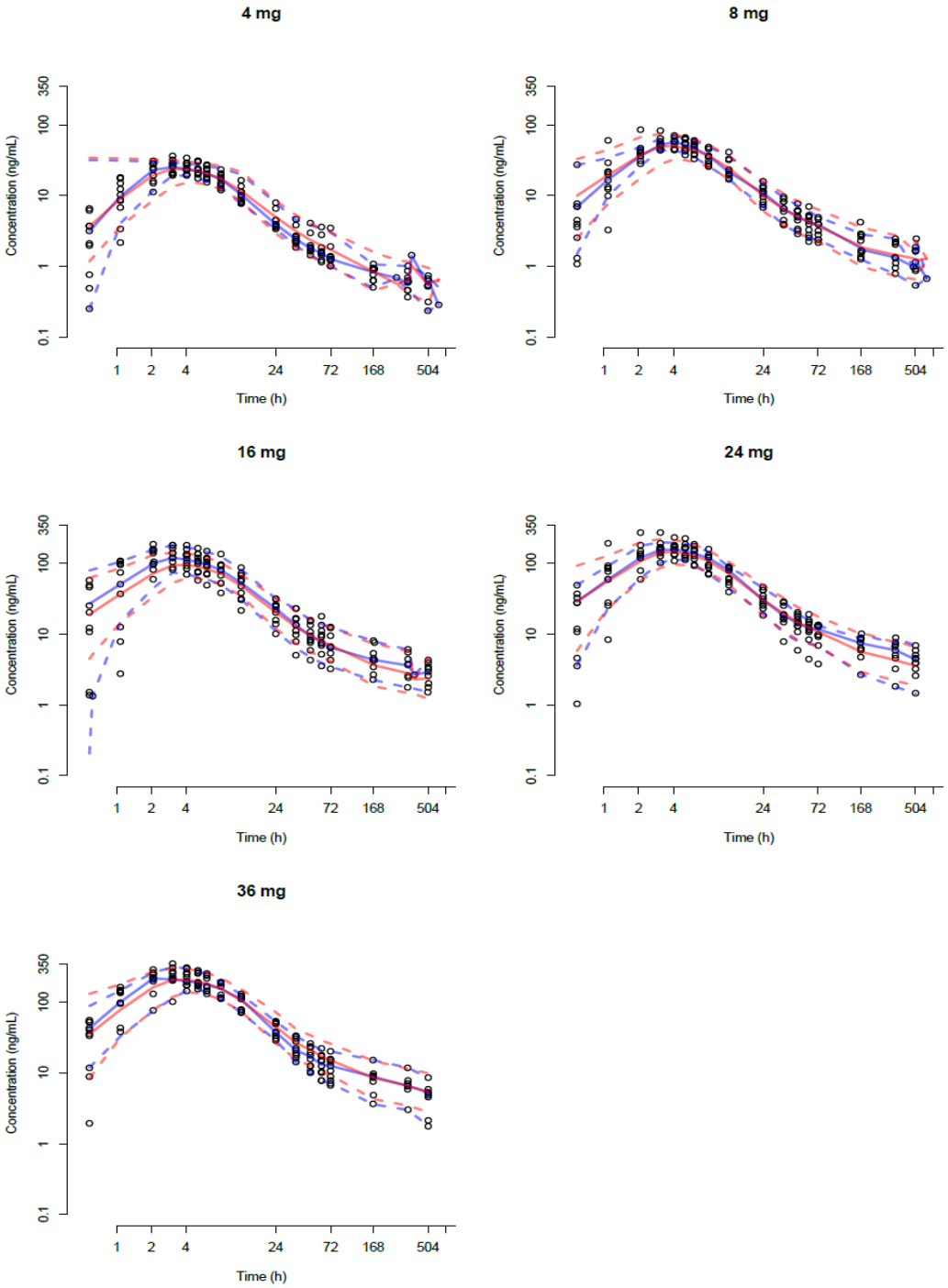
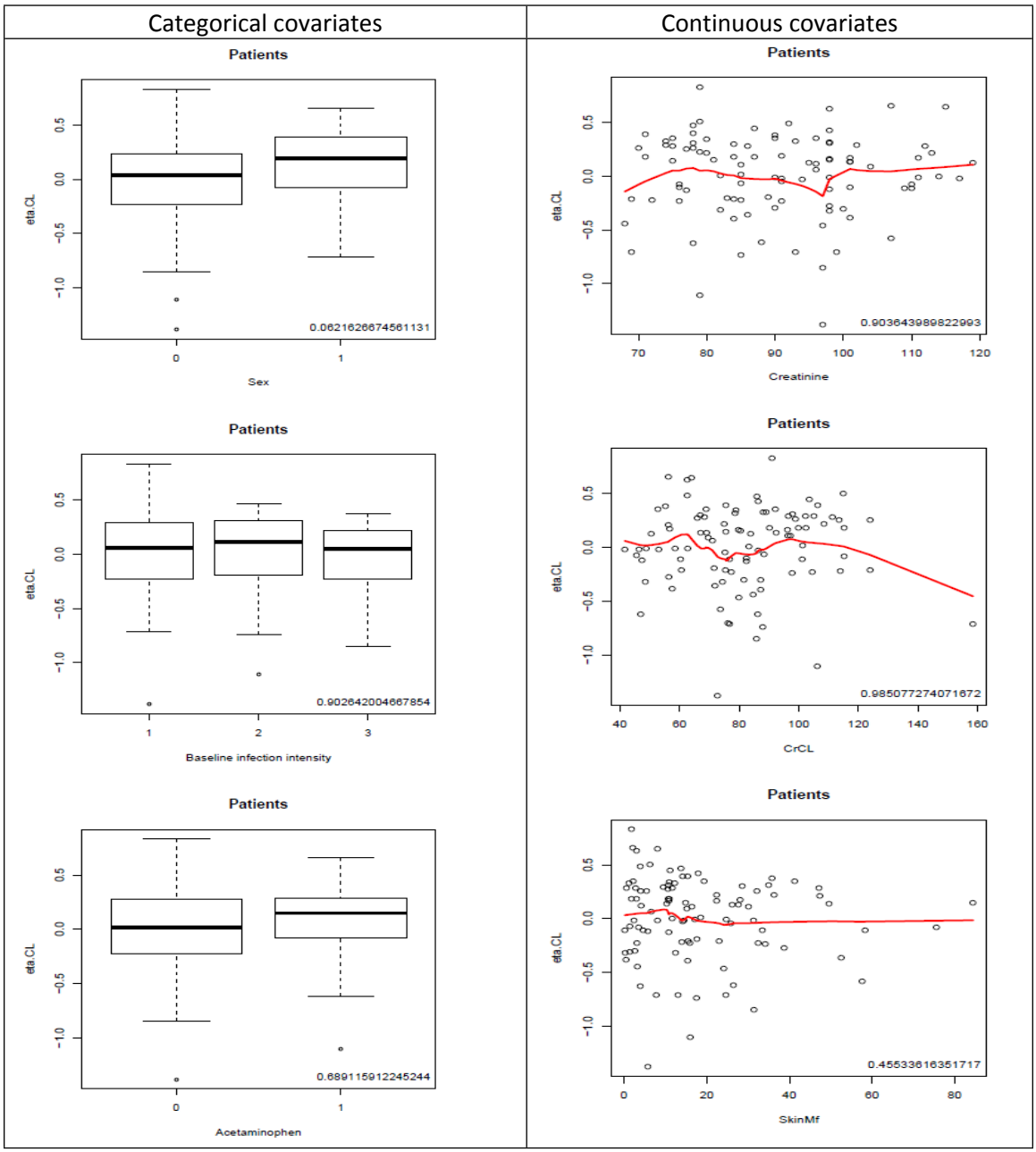


**Figure 4.2.1-5 Visual predictive check for Study 1008 from the final population PK model updated with data from Study 1008. The solid blue and red lines represent the medians of the observed and simulated concentrations, respectively. The dashed blue and red lines represent the 10th and 90th percentiles of the observed and simulated concentrations, respectively. (*(Source: Applicant's population PK report, Page 33 Figure 15)*



The effects of intrinsic or extrinsic factors on PK parameters of moxidectin were evaluated during exploratory analysis. **Figure 4.2.1-6** shows the relationship between random effects on CL against categorical and continuous covariates, respectively.

Figure 4.2.1-6 The relationship between the individual estimated random effects for CL/F (eta.CL) and candidate covariates *(Source: Applicant's population PK report: page 54, Figure 25 and Page 57, Figure 28)*



For sex, 0=male and 1=female. For baseline infection intensity, 1=mild, 2=moderate and 3=severe. For acetaminophen, 0=no and 1=yes, CrCL =creatinine clearance, SkinMf = skin microfilariae density. Within each plot, the p-value from a linear model (with the categorical covariate as a factor) is displayed in the bottom right corner.

Reviewer's comment: Applicant's population PK analysis reasonably described the population of moxidectin. Identified covariates were consistent with what was obtained in final model which excluded Study 1008. However, in terms of leveraging BLQ data, the applicant's model might not be optimized by simply excluding the 11% of LLOQ data. FDA reviewer conducted independent analysis to assess the impact of excluding 11% of LLOQ data from PPK model (Section 4.2.3).

4.2.2 Applicant's Exposure-Response Analyses for Efficacy and Safety

4.2.2.1 Exposure-Efficacy analysis

The exposure-response analysis was performed using data from Phase 2 study because there were no PK data available from Phase 3 study. Data from 98 subjects were available for PKPD analysis, and these patients were those from the Phase 2 study who had PK samples taken; thus, are a subset of the 127 patients who received moxidectin. Exposure data were obtained from final population PK study. The primary endpoint was reduction from baseline (mean change) in the skin microfilariae density at Month 18 between moxidectin treatment groups for Phase 2, while from Phase 3 the endpoint was mean mf density at month 12.

· Dose selection
The 8 mg dose of moxidectin was selected by the applicant for the Phase 3 study and is the proposed therapeutic human dose. The evidence supporting this dose selection includes sufficient exposure safety margin coverage provided by dose-response and exposure-response analyses from PK/PD modeling. The Phase 2 data provided visual and statistical evidence that the increase in moxidectin exposure was associated with decreased probability of microfilariae in the skin at Month 6, increased probability of sustained response in the skin at Month 6 and 12, and slightly decreased microfilariae burden in the skin over 12 months. **Table 4.2.2-1** summarizes the efficacy among different doses.

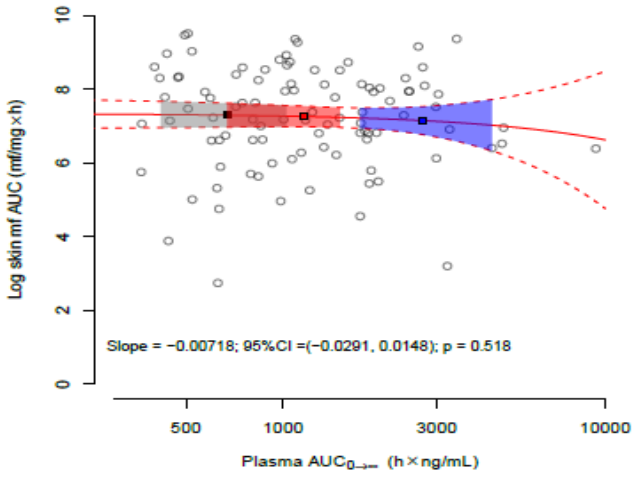
The relationship between moxidectin exposure and skin mf AUC was explored by the applicant. **Figure 4.2.2-1** shows the relationship between predicted AUC to infinity ($AUC_{0-\infty}$) and the log of mf in skin over 12 months ($AUCSK_{0-12}$).

Table 4.2.2-1 Phase 2 Endpoint Comparison by Dose at Months 6 and 12 (Source: Applicant's Summary of Clinical Efficacy, page 19, Table 11)

Endpoint	Phase II		
	MOX (2 mg) n = 44	MOX (4 mg) n = 45	MOX (8 mg) n = 38
Month 12 LS Geometric Mean (mITT)[1] (95% CI)	1.445 (1.202, 1.736)	1.387 (1.167, 1.647)	1.187 (0.976, 1.445)
Month 12 Ratio of LS Geometric Means[1] (Moxidectin/Ivermectin) (mITT)	0.542 (0.42, 0.69)	0.520 (0.41, 0.66)	0.445 (0.35, 0.57)
Mean mf/mg skin[2] (mITT)			
Month 6	0.06	0.03	0.00
Month 12	0.92	0.81	0.42
Adjusted Mean (SE) Reduction from Baseline[2] (mITT)			
Month 6	0.06 (1.04)	0.06 (1.03)	0.06 (1.04)
Month 12	0.09 (1.07)	0.09 (1.07)	0.08 (1.05)
Mean Percentage Reduction from Baseline[3] (%) (mITT)			
Month 6	99.7	99.9	100
Month 12	96.1	96.1	98.2
Proportion Undetectable[4] (mITT) (%)			
Month 6	81.8	91.1	100
Month 12	34.9	40.0	59.5
Sustained Undetectable from Month 1 to Month N (%) (mITT)[5]			
Month 6	31 (70.5)	39 (86.7)	36 (94.7)
Month 12	15 (34.1)	18 (40.0)	20 (52.6)

Source: Phase II Tables [1] MCG_EFF_MXM12_MITT; [2] EFF-MX-MITT; [3] EFFMXMITTC [4] EFFUNMITT; [5] MCG_SR_MITT_TABLE1, TABLE1A, TABLE2

Figure 4.2.2-1 The relationship between predicted AUC to infinity ($AUC_{0-\infty}$) and the log of microfilariae (mf) in skin over 12 months ($AUCSK_{0-12}$) *(Source: Applicant's population PK analysis, page 39, Figure 22)*



Review's comment
The proposed dose of 8 mg showed higher efficacy and it may have reached a plateau because there was no established relationship between change in skin mf density and moxidectin exposure. The effect of 8 mg dose compared with other doses is highly evident

*when the proportion of undetectable mf at either month 6 or 12 is considered as the efficacy endpoint. In addition, FDA reviewer conducted independent analysis for E-R for the primary efficacy endpoints in the phase 3 study (mean skin microfilariae density at month 12), see section 4.2.3 for more details. No clear exposure-response difference between doses when mean reduction from baseline is also used. Meanwhile, when the proportion undetectable mf at month 12 is used as endpoint, the findings showed that the use of 8 mg dose was superior to 2 mg and 4 mg (**Table 4.2.2-1**).*

4.2.2.2 Exposure-safety analysis

The applicant did not perform exposure-safety analysis, but reported that moxidectin at 2, 4 and 8 mg were well tolerated in the Phase 2 study. The nature and severity of adverse events were similar between increasing moxidectin doses (and ivermectin), and reflect the signs and symptoms associated with microfilarial death (also referred to as the Mazzotti reactions). These signs and symptoms included lymph node pain, pruritus, myalgia and rash, along with vital signs changes such as orthostatic hypotension and compensatory tachycardia. The majority of these reactions were mild or moderate, transient and all resolved without treatment. These increases in the number of subjects experiencing signs and symptoms was commensurate with the increased efficacy seen with moxidectin. **Table 4.2.2-2** summarizes the percentage of patients with adverse events in Phase 2 across different dose moxidectin doses and ivermectin 150 µg/kg.

Table 4.2.2-2 ***Percentage of patients reporting adverse events (Source: Applicant's Summary of Clinical Safety, Page 23, Table 12)***

Preferred Term	MOX (2 mg) n=44 n (%)	MOX (4 mg) n=45 n (%)	MOX (8 mg) n=38 n (%)	IVM (150 µg/kg) n=45 n (%)
Any serious adverse event	5 (11.4)	1 (2.2)	2 (5.3)	0
Malaria	0	0	1 (2.6)	0
Pneumonia	1 (2.3)	0	1 (2.6)	0
Typhoid fever	2 (4.5)	0	0	0
Injury	0	1 (2.2)	0	0
Coma	0	1 (2.2)	0	0
Grand mal convulsion	1 (2.3)	0	0	0
Schizophrenia	1 (2.3)	0	0	0
Snake bite	1 (2.3)	0	0	0
Appendicitis	0	0	1 (2.6)	0

4.2.2.3 Applicant's conclusions

- Moxidectin is significantly superior to ivermectin in reduction of skin microfilariae density by the primary efficacy endpoint in Phase 2, based on exposure-response analysis
- In onchocerciasis patients, the nature, incidence and severity of adverse events associated with moxidectin efficacy was similar to ivermectin, and there were no serious adverse events due to efficacy in either moxidectin or ivermectin recipients and no treatment related serious adverse events in any patient.
- Moxidectin 8 mg was acceptable.

4.2.3 Pharmacometrics Reviewer's Analysis

Independent analysis objective

The objective of analysis is to:

- Assess the adequacy of applicant's PPK model to describe the PK data
- Evaluate the effect of moxidectin exposure in mf density at month 12

4.2.3.1. Data sets

The data sets used in the analyses are summarized in **Table 4.2.3-1**

Table 4.2.3-1 Analysis Datasets for FDA Reviewer's Analysis

Study Number	File name	Link to EDR
	mox-pk-all-1008.xpt; expos-skmf-dat.xpt	\\cdsesub1\evsprod\NDA209394\0000\m5\datasets\rd160234\analysis\legacy\datasets

4.2.3.2. Software

NONMEM 7 and R were used for the reviewer's analysis.

4.2.3.3 Method

The FDA reviewer explored the applicant's final population PK model by evaluating the diagnostic plot. Applicant's PPK model was modified for further improvement to describe LLOQ data using M3 method [1,2,3]. In the M3 method, the likelihood for LLOQ observations are maximized with respect to the model parameters, and the likelihood for an observation is taken to be the likelihood that it is indeed below LLOQ. Using applicant's data, the LLOQ was different across different studies, the LLOQ of Study 101 was 0.2 ng/mL but for Study 1008, the LLOQ was 0.1 ng/mL and for Study 1005 and the Phase 2 study, the LLOQ was 0.08 ng/mL. In this analysis, LLOQ values of 0.2 ng/mL for all studies will be used as a more conservative approach.

4.2.3.4 Results

The reviewer conducted population PK analysis with the applicant's models. The results of the applicant's population PK analysis can be repeated. Thereafter, the reviewer updated the applicant's model where M3 method was used. The final PK parameter estimates from the reviewer's model were slightly different when the M3 method was used. The parameter estimates are shown in **Table 4.2.3-2** and diagnostic plots are shown in **Figure 4.2.3-1**. The reviewer's model was better than applicant's model based on diagnostic plots. Using the M3 method, the CL was estimated to be 10.4% higher compared with applicant's model. This difference is not anticipated to have any impact of the conclusions reached by the applicant. The final model developed by the applicant was used to evaluate the effects of renal function on the population PK of moxidectin. Renal function was categorized according to FDA Guidance as shown in **Table 4.2.3-3**. The illustration of effect of CrCL on moxidectin clearance is shown in **Figure 4.2.3-2**. There is no significant effect of renal function on moxidectin clearance down to CrCL of 47

ml/min. Again, it should be noted that no PK information was available in patients whose CrCL was below 47 ml/min.

Table 4.2.3-2 Parameter Estimates for moxidectin final model including data from Study 1008 (Reviewer's model is better than applicant's model)

Description/Acronym	Applicant's model estimate	RSE(%)	Reviewer's model estimate	RSE(%)
MTT (h)	1.7	4.10%	1.86	4.20%
V_c/F (L/ 70 kg)	127	4.40%	96.4	7%
CL/F (L/h)	3.65	5.80%	4.03	5.70%
CL_{d1}/F (L/h)	5.03	5%	7.88	10%
V_{p1}/F (L)	216	6.30%	107	7.40%
CL_{d2}/F (L/h/70 kg)	3.25	6.20%	4.85	5.90%
V_{p2}/F (L)	1090	5.20%	864	5.10%
Food effect on MTT	2.09	10.40%	1.97	11.10%
Formulation effect on MTT	0.292 (fixed)		0.292 (fixed)	
Phase 1 effect on V_c/F	0.800	23.20%	1.00	903.30%
Phase 1 effect on CL/F	0.689	19.60%	0.664	18%
Phase 1 effect on CL_{d1}/F	0.834	36.30%	0.555	20.20%
Phase 1 effect on V_{p1}/F	0.515	11.70%	0.812	51.90%
Phase 1 Effect on CL_{d2}/F	1.758	13.40%	1.232	33.60%
Phase 1 Effect on V_{p2}/F	1.272	35.10%	1.489	19%
Food effect on relative bioavailability	1.36	17%	1.37	16.40%
Formulation effect on relative bioavailability	1.18	14.30%	1.15	21.70%
Proportional error (SD; %)	21.5	0.80%	22.0	0.50%
Study 101 effect on proportional error	0.9	16.80%	1.40	3%
Study 101 effect on MTT	0.477		0.477	
Study 101 effect on V_{p2}/F	1.19	40.60%	1.02	279.20%
Sex effect on CL_{d2}/F	1.48	25.10%	1.39	26.50%
Sex effect on V_{p2}/F	1.61	21.90%	1.70	17.90%
Phase 1 BMI effect on V_{p2}/F	1.69	18.30%	1.68	18.40%
Phase 1 BMI effect on V_{p2}/F	0.586	52.40%	0.641	39.30%
Interindividual variability on parameter reported as variance				
MTT	0.182	12.10%	0.175	12.90%
V_c/F	0.0541	14.30%	0.0695	18.70%
CL/F	0.169	10.50%	0.183	10.50%
CL_{d2}/F	0.107	12.40%	0.068	12.20%
V_{p2}/F	0.164	9.50%	0.107	12.20%

Figure 4.2.3-1: Goodness of fit plots for moxidectin final models. The left panel is for applicant's model while the right panel is for reviewer's model.

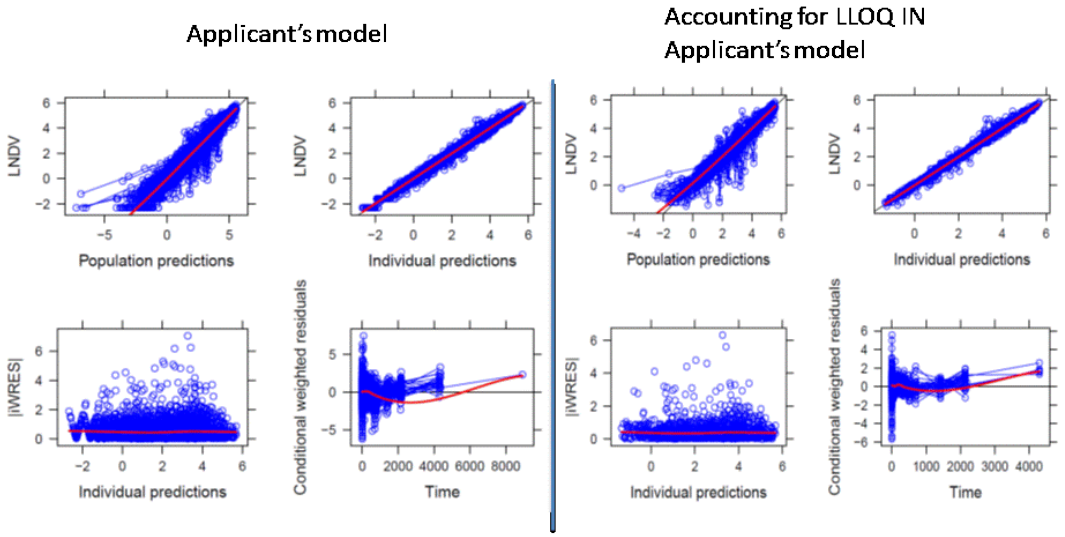


Table 4.2.3-3 Current FDA Guidance on renal function categorization (Source: Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, March 2010, page 8, Table 1)

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

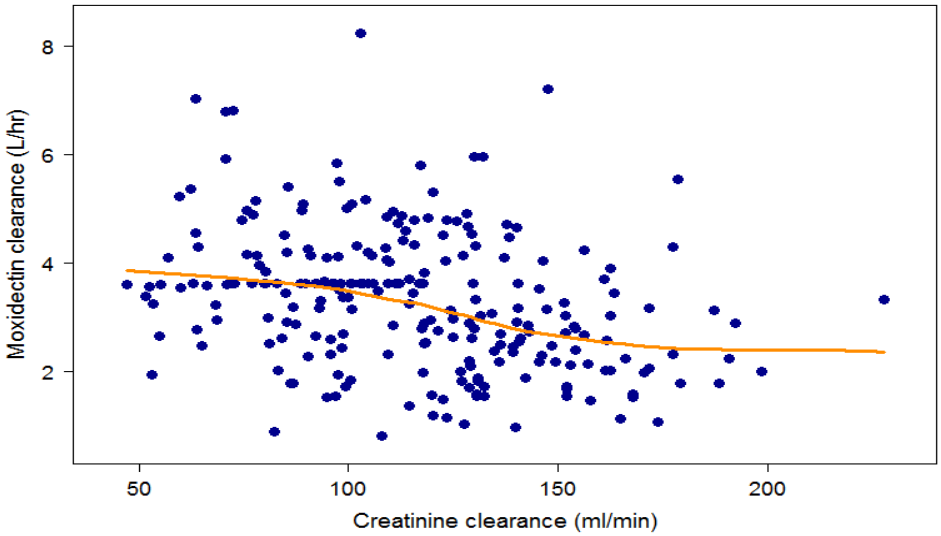
[a] In some situations, collection of 24-hour urine samples for measurement of creatinine clearance, or measurement of clearance of an exogenous filtration marker, may provide better estimates of GFR than the prediction equations. The situations include determination of GFR for patients in the following scenarios: undergoing kidney replacement therapy; acute renal failure; extremes of age, body size, or muscle mass; conditions of severe malnutrition or obesity; disease of skeletal muscle; or on a vegetarian diet.

[b] Stages of renal impairment are based on *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation* in 2002; GFR: glomerular filtration rate;

[c] eGFR: estimate of GFR based on an MDRD equation;

[d] CLcr: estimated creatinine clearance based on the C-G equation.

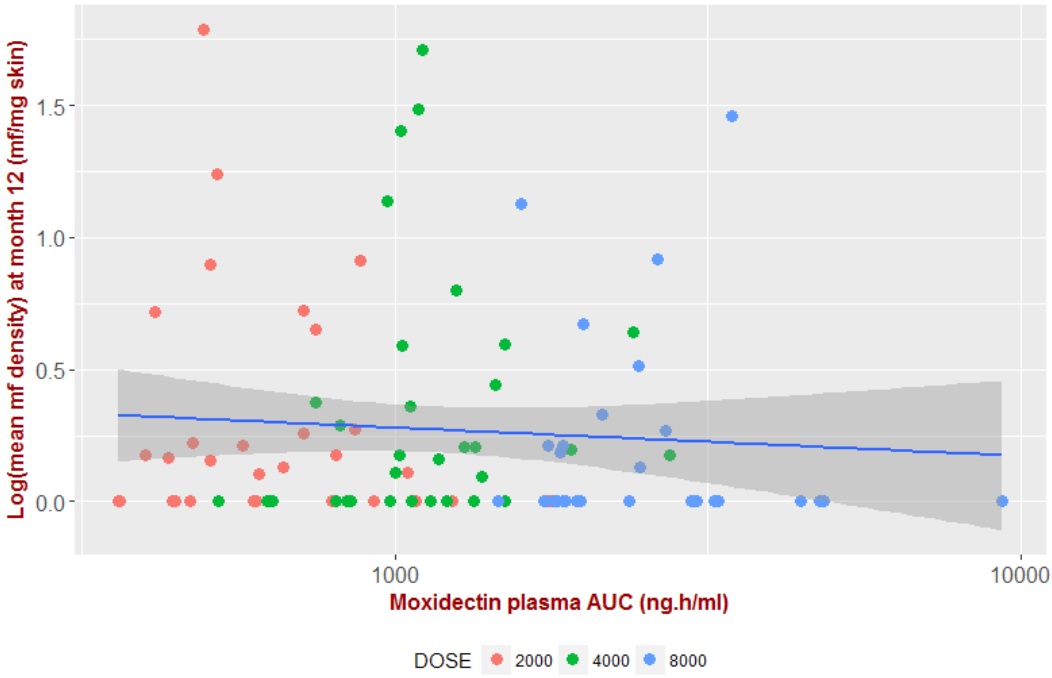
Figure 4.2.3-2: No significant relationship between moxidectin clearance and creatinine clearance



Moxidectin Exposure and mf skin density

The final model with M3 method was used to compute AUC for moxidectin. There is no significant relationship between moxidectin exposure and mean mf density at month 12 as shown in **Figure 4.2.3-3**. The endpoint of month 12 was chosen to match Phase 3 endpoint.

Figure 4.2.3-3: No significant relationship between moxidectin AUC and mean mf density at month 12. The colored dots represent dose in µg.



Reviewer's conclusions
The model developed by the reviewers is better and appropriate for describing the population PK of moxidectin. Even though the model developed by the reviewer was better in describing the PK parameters of moxidectin compared with applicant's model, covariate search gave similar findings as those reached by the applicant. The major findings based on reviewer's analysis are:

- *The M3 method used adequately described the population PK of moxidectin,*
- *Covariates identified by the applicant were similar to those obtained by reviewer, but with different magnitudes of covariate effects,*
- *No dose adjustment in necessary based on renal impairment,*
- *There is no apparent relationship between mean skin mf density with moxidectin plasma exposure at month 12.*

Overall, the reviewer recommends updating the labeling claim based on estimates of clearance and effects of covariates which were obtained from the model where M3 method was incorporated.

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run1010001.mod	Model file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Moxidectin_NDA210867_SPZ\POPPK_Analysis
Run1010001.lst	Output file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Moxidectin_NDA210867_SPZ\POPPK_Analysis
mox_pk_all_1008_BQL_2.csv	popPK dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Moxidectin_NDA210867_SPZ\POPPK_Analysis

4.3 Clinical Pharmacology Review of Individual Study Reports

Individual study reviews included in the integrated review.

Study No.	Study information
1002	Evaluate the extent of moxidectin transfer into breast-milk.
1004	Evaluate potential PK interaction of moxidectin on midazolam.
1005	Assess relative BA and PK following a high-fat meal.
1008	Evaluate potential QT interval changes, preliminary metabolism and excretion of moxidectin (PK ONLY).

4.3.1 Study 1002 Lactation Study

PROTOCOL NO.: 3110A1-1002-EU
Title: An Open-label, Single-dose Study to Evaluate the Excretion of Moxidectin into the Breast Milk of Lactating, Non-Breastfeeding Women

Date(s):	January 2009 - September 2009
Investigator(s):	Phil Bryson Plymouth, PL6 5HH, United Kingdom
Study Center(s):	Veeda Clinical Research, Old Convent of Notre Dame, 119 Looseleigh Lane, Derriford, Plymouth, PL6 5HH, United Kingdom
Analytical Site(s):	(b) (4)

OBJECTIVE(S):
Primary objective:
To evaluate the extent of moxidectin transfer into the breastmilk of non-breastfeeding lactating women following a single oral dose of 8 mg moxidectin.
Secondary objective:
To provide the initial PK and safety profile of moxidectin in lactating women.

METHODS
Study Design: This was a single center, open-label, non-randomized, inpatient/outpatient study of a single 8-mg oral dose of moxidectin administered to lactating women who were not breastfeeding infants at the time of the study. Blood samples (5 mL) for moxidectin plasma analyses were obtained on day 1 before moxidectin administration, at 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after moxidectin administration; on days 6, 8, 14, 30, 60, 90; and on final study evaluation (a total of 17 samples per subject). Breast-milk samples were collected from day -1 to day 13 from all subjects (the inpatient period [day -1 to day 8] was followed by daily home visits for breast-milk and plasma sample collection through day 13). On day 1, samples were collected for the following periods: prior to administration of dose and 0 – 2, 2 – 4, 4 – 6, 6 – 8, 8 – 12, 12 – 24 post-dose. For each sampling interval, the volume was measured. The first 2-week breast-milk collection concluded with an outpatient visit on day 14 for breast-milk and plasma sample collection. The minimum duration of milk collection for study completion was 14 days. From day 15 to day 29 home visits continued for an optional 14-day breast-milk sample collection period, for women who were able to continue expressing breast-milk. Subsequently, 3 outpatient visits occurred on days 30, 60, and 90 to follow-up on the plasma sampling.

Number of subjects: Twelve (12) healthy lactating women participated in this study and all 12 subjects completed the study.

Analytical Methods: Moxidectin concentrations were determined in plasma and breast-milk using a high performance liquid chromatography (HPLC) method with fluorescence detection that was validated over the range of 0.08 ng/mL to 120 ng/mL, using a 500 µL sample. The minimal quantifiable concentrations (MQCs) of moxidectin in plasma and in breast-milk were approximately 0.08 ng/mL. The inter-day accuracy (mean bias) and precision (co-efficient of variation [CV%]) for moxidectin concentrations in plasma were always less than ±2.8% and 12.8%, respectively. The mean recovery of moxidectin from plasma samples measured at the 4

quality control (QC) levels was 84.6%. No potential interference was detected from 6 different lots of plasma.

Pharmacokinetic Assessment: Single-dose PK was derived for each female subject from the plasma and breast-milk concentration versus time using conventional noncompartmental methods, using WinNonlin, Version 5.1.1 (Pharsight).

The midpoint time for milk expression was used as the milk collection time. AUC was calculated for milk in the same way as for plasma and the ratio of AUC for moxidectin in breast milk and AUC for moxidectin in plasma was determined. The amount of moxidectin excreted in milk (Xu) was calculated as the sum of the product of individual milk volumes and concentrations. Moxidectin clearance in milk (CL_{MILK}) was calculated as the ratio of Xu to total AUC. The absolute infant dose, which is equal to Xu, was determined assuming 100% bioavailability of the amount excreted. Each relative infant dose was determined as the ratio of the absolute infant dose (normalized to an infant weight of 5 kg) to the maternal dose of 8 mg moxidectin (normalized by each woman's weight).

RESULTS

The study population consisted of healthy lactating women aged 23 to 38 years, with a mean age of 30.08 years. The post-partum status of the lactating women ranged from 21.0 to 100.3 weeks, with a median of 29.6 weeks postpartum at the time of dosing.

PK sample collection was completed for all the 12 enrolled subjects. The mean (± standard error [SE]) plasma concentration-time profile after administration of a single oral 8 mg doses of moxidectin is presented in **Figure 1** and the mean plasma and breast-milk concentration-time profiles after administration of a single oral 8 mg dose of moxidectin are simultaneously presented in **Figure 2**.

Figure 1: Mean ± SE Moxidectin Plasma Concentrations in Healthy Lactating Women After Single 8-mg Oral Dose with Food (n=12)

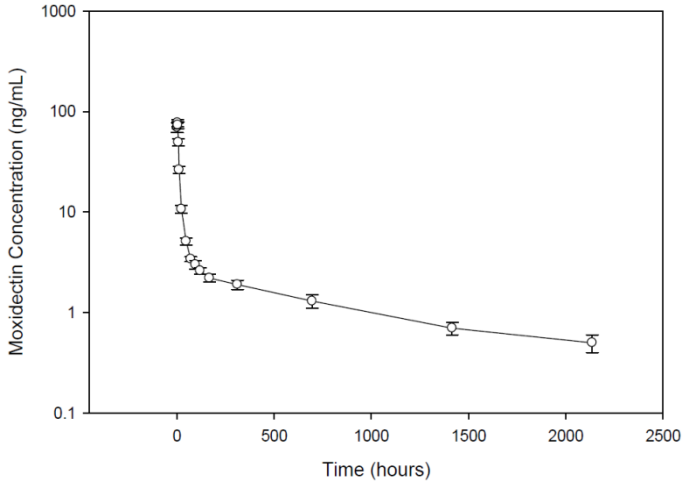
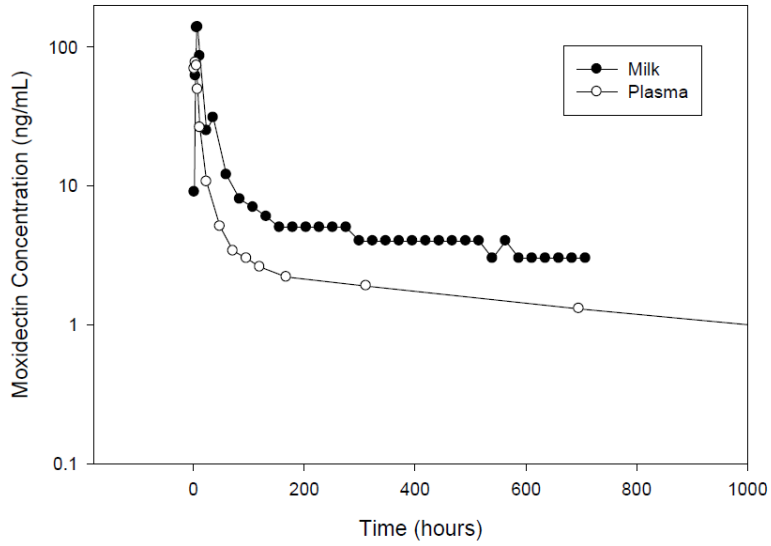


Figure 2: Mean Moxidectin Plasma and Breast-Milk Concentrations in Healthy Lactating Women After an Oral 8-mg Dose with Food (n=12)



Summary statistics for each of the PK parameters shown are listed in **Table 1**. Although the numbers are small, it appears that women who have a lower body weight (**Figure 3**) or smaller BMI (**Figure 4**) have increased amounts of moxidectin excreted in their breast-milk and a higher CL_{MILK} than women with higher weight or larger BMI. There appeared to be no relationship between the length of time post-partum that women were dosed and either the amount of moxidectin excreted in their milk or the CL_{MILK}.

Table 1. Summary statistics for pharmacokinetic parameters in plasma and breast milk

Parameter	Mean ± Standard Deviation (n=12)
Cmax (ng/mL)	87 ± 25
tmax (h)	4.18 ± 1.59
AUC (ng.h/mL)	4046 ± 1796
λz (h-1)	0.00093 ± 0.00029
t½ (h)	832 ± 321
CL/F (L/h)	2.349 ± 1.067
Vz/F (L)	2526 ± 772
% dose excreted in milk	0.701 ± 0.299
amount excreted in milk (mg)	0.056 ± 0.024
CLMILK (L/h)	0.016 ± 0.009
AUC_{milk}/AUC	1.77± 0.66
Absolute infant dose (mg)	0.056 ± 0.024
Relative infant dose (%)	8.73 ± 3.17

Abbreviations: AUC=total area under the concentration time curve, AUC_{milk}=AUC for moxidectin in breast-milk, C_{max}=peak plasma concentration, CL/F=apparent oral dose clearance, CL_{MILK}=clearance in milk, ,t½=terminal-phase elimination half-life, t_{max}=time to C_{max}, V_Z/F=apparent volume of distribution, λ_Z=terminal-phase elimination rate constant.

Figure 3. Subject Weight Versus Moxidectin Clearance and Amount Excreted in Milk in Healthy Lactating Women After Receiving 8 mg Oral Dose with Food (n=12)

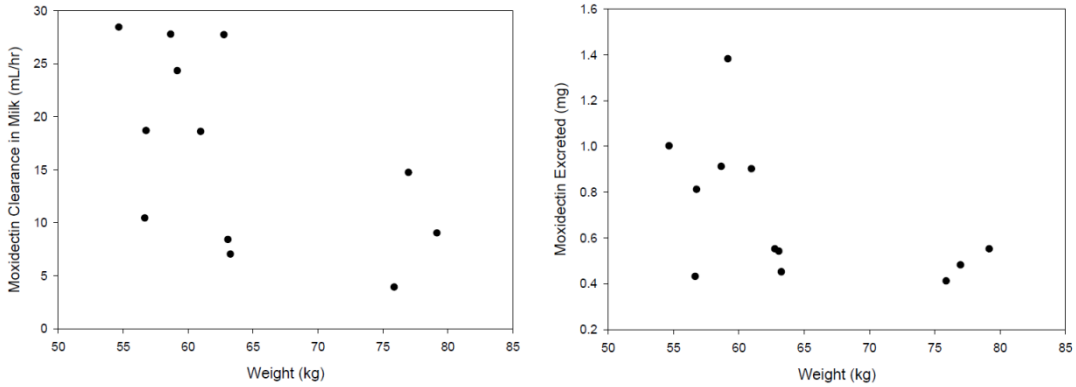
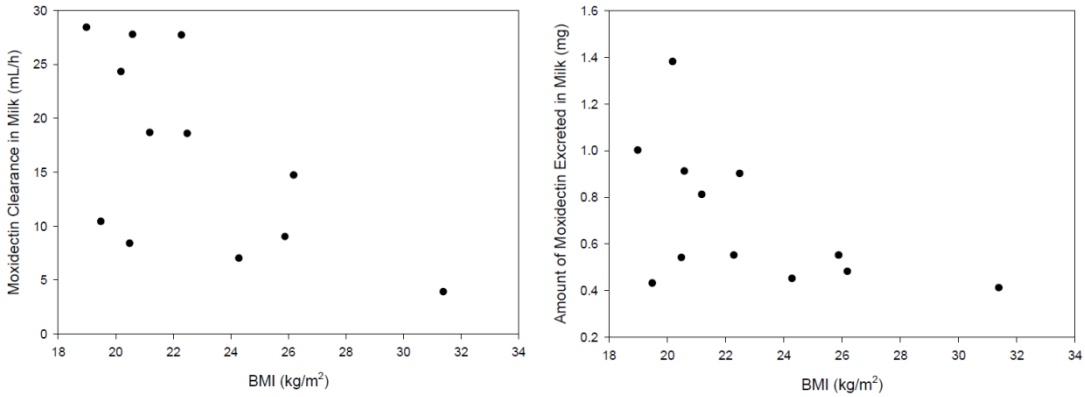


Figure 4. Subject BMI Versus Moxidectin Clearance in Milk in Healthy Lactating Women After Receiving 8 mg Oral Dose with Food (n=12)



SPONSOR'S CONCLUSIONS:

The plasma PK parameters observed in the healthy lactating women enrolled in this study were similar to those observed in healthy young men. Moxidectin is more concentrated in breast-milk as compared with plasma. The milk excretion parameters observed in the women enrolled in this study were qualitatively similar to what was observed in lactating sheep and goats, where 2% to 6% of the administered dose was recovered from the milk in the animals. In addition, it appears that women with higher weight and BMIs had decreased CL_{MILK} compared with women with lower weight and smaller BMI. Moxidectin was safe and well tolerated by lactating women, when administered at a single oral dose of 8-mg.

REVIEWER ASSESSMENT:

The bioanalytical method for determination of moxidectin concentrations was reviewed and deemed acceptable. The reviewer agrees with the Sponsor's conclusion, based on the PK results in plasma and breast-milk from the enrolled women. It is reasonable to postulate that the women with higher BMI tend to have less moxidectin excreted into breast-milk, because the high

lipophilicity of moxidectin may lead to high tissue binding in adipose tissues and low excretion into biofluids, such as breast milk.

4.3.2 Study 1004 Drug Interaction Study

PROTOCOL NO.: 3110A1-1004-EU
Title: An open-label, single-dose, 4-period, sequential study to determine the effect of moxidectin on CYP3A4 activity in healthy subjects using midazolam as a probe substrate

Date(s):	13 May 2009 - 23 Sep 2009
Investigator(s):	Dr. Frank Wagner.
Study Center(s):	Charité Research Organisation GmbH, Berlin, Germany
Analytical Site(s):	(b) (4)

MEMO
The objectives of this study were to evaluate the potential PK interaction of a single oral dose of moxidectin on single oral doses of the CYP3A4 substrate, midazolam, administered 1-week and 3-months later to healthy subjects and to assess the safety of single dose moxidectin and single doses of midazolam when administered 1-week and 3-months later to healthy subjects. A total of 39 subjects were enrolled in the study. Thirty-seven (37) subjects completed the study and were included in the safety and PK analyses.

No difference in midazolam or metabolite PK was noted when single midazolam doses were administered 7 and 90 days after administration of moxidectin. The 90% confidence intervals for combination to monotherapy ratios of the geometric means for Cmax and AUC of midazolam fell within the 80% to 125% window. Therefore, moxidectin does not induce or inhibit CYP3A4 when administered as a single 8 mg oral dose with food. This lack of effect of moxidectin on midazolam PK parameters indicates that other sensitive CYP3A4 substrates are unlikely to be affected by moxidectin.

Reviewer comments:
The bioanalytical method for determination of moxidectin concentrations was validated over the range of 0.08 to 120 ng/ml. The minimal quantifiable concentrations of moxidectin in plasma was approximately 0.08 ng/ml. The reviewer agrees with the Sponsor's conclusion that moxidectin does not affect the PK of midazolam and other CYP3A4 substrates.

4.3.3 Study 1005 Food Effect

PROTOCOL NO.: 3110A1-1005-EU

Title: An open-label, randomized, single-dose, parallel-group study to determine the effect of a high-fat meal on the relative bioavailability and pharmacokinetics of a single dose of moxidectin administered orally to healthy subjects

Date(s):	November 2008 - May 2009
Investigator(s):	Serge Fitoussi, MD, MSc
Study Center(s):	MEDISCIS Poitiers (legal name Larime S.A.) 6, Avenue Mozart, 86000 Poitiers, France
Analytical Site(s):	(b) (4)

OBJECTIVE(S):

Primary objective:

To assess the effect of a high-fat meal (breakfast) on the relative bioavailability (Frel) and PK of a single oral dose of moxidectin in healthy subjects.

Secondary objective:

To obtain additional safety, tolerability, and corrected QT interval (QTc) data concerning moxidectin in healthy subjects.

METHODS

Study Design: This was a single-dose, randomized, open-label, parallel-group, inpatient/outpatient study in healthy subjects conducted at a single investigational site. Moxidectin doses were administered either in a fasting state: after an overnight fast of at least 10 hours; or after consumption of a standard high-fat breakfast. On day 1 of the study, each subject received 1 single dose of 8 mg of moxidectin (4x2-mg tablets) in either fed or fasting conditions, administered with 240 mL of room-temperature water. Subjects were randomly assigned to 1 of the 2 treatments, A or B:

- Treatment A: a single dose of 8 mg of moxidectin (4x2-mg tablets) administered under fasting conditions.
- Treatment B: a single dose of 8 mg of moxidectin (4x2-mg tablets) administered within 5 minutes after completion of a high-fat breakfast.

Administration of moxidectin was preceded by an overnight fast of at least 10 hours in the fasting state or an overnight fast of at least 10 hours followed by a high-fat breakfast in the fed state. Subjects assigned to receive moxidectin in a fed state received moxidectin immediately after completion of the high-fat meal, which was the standard United States FDA-recommended breakfast for food effect studies of 900 calories (with a nutritional distribution of approximately 55% fat, 31% carbohydrates and 14% protein).

Number of subjects: Fifty-four (54) subjects were enrolled in the study, grouped as 27 subjects each in the fasted and fed cohorts.

Reviewer Comment: The long half-life of moxidectin does not allow for a cross-over study design.

Analytical Methods: The concentrations of moxidectin in plasma were determined using a validated high-performance liquid chromatography (HPLC) with fluorescence detection method. The assay was validated using 0.5 mL of plasma across the range of 0.08–120 ng/mL. The inter-day accuracy (mean bias) and precision (% coefficient of variation [CV%]) for concentrations of back-calculated standards were always less than ±2.8% and 12.8%, respectively. The mean recovery of moxidectin was 84.6% and no potential interferences were detected in plasma samples from 6 different lots.

Pharmacokinetic Assessment: The plasma concentration-versus-time data of moxidectin after oral administration were characterized using noncompartmental methods. Consequently, the peak plasma concentration (Cmax) of moxidectin and the time to Cmax (tmax) were determined directly from the concentration-time observations. The area under the concentration-time curve to the last observable concentration (AUC_T) was estimated using the log-linear trapezoidal method. The terminal-phase disposition rate constant (λz) was calculated using regression of the terminal concentration time points. The terminal-phase disposition half-life ($t_{½}$) was also calculated. The area under the concentration-time curve (AUC) was estimated using the formula $AUC=AUC_T+C_T/\lambda z$ (where C_T is the last observable concentration at time T). The apparent oral drug clearance (CL/F) was computed using CL/F=dose/AUC. Apparent volume of distribution (Vz/F) was computed as a ratio of CL/F to λz.

Exploratory PK/PD analyses were performed to investigate potential relationships between moxidectin exposure and change in the corrected Q wave-T wave interval in an ECG (QT interval). The PK/PD relationship of moxidectin and QT interval in ECG was examined graphically using plots showing the time course of moxidectin and Q wave-T wave correction (QTc), based on Fridericia's correction (QTcF) and a population-specific Q wave-T wave correction (QTcN) formula. In addition, hysteresis plots showing concentrations of moxidectin versus QTc observed at the corresponding time points were examined. Models such as linear, log linear, or Emax models (where Emax is the maximum effect attributable to the drug) were used to describe the relationship between QT and plasma concentrations of moxidectin, as appropriate.

RESULTS

Pharmacokinetics (PK)

The study population consisted of 54 healthy male subjects aged 19 to 50 years, with a mean age of 30.65 years. Data from all the subjects were included in the safety analyses. All 54 subjects were to be included in the PK analyses. However, 1 subject (b) (6) from the fed group discontinued participation in the study after the 48-hour blood sample was collected for analyses; this subject was excluded from PK analyses.

The mean (± standard error [SE]) plasma concentration-time profiles after administration of a single oral 8 mg doses of moxidectin under fed and fasted conditions are presented in **Figure 1** and a statistical summary of PK parameters is presented in **Table 1**.

Figure 1: Concentration-Time Profile of Moxidectin After Single Oral Dose of Moxidectin in Healthy Fasting and Fed Subjects

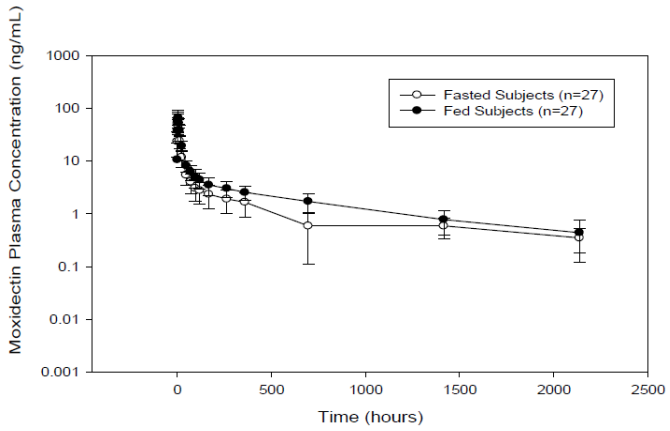


Table 1. Summary statistics for pharmacokinetic parameters

	C_{max}* (ng/mL)	t_{max}* (h)	λ_z (h)	$t_{½}$* (h)	AUC* (ng.h/mL)	CL/F* (L/hr)	Vz/F* (L)
Fasted (n=27)	58.9±12.5	3.7±1.5	0.00107±0.00061	784±347	3387±1328	2.76±1.28	2829±1267
Fed (n=26)	79.1±26.3	5.3±2.1	0.00117±0.000464	700±307	4885±1483	1.78±0.54	1708±724

* Significantly different, $p<0.05$.

Abbreviations: SD=standard deviation, C_{max}=peak plasma concentration, t_{max}=time to C_{max}, λ_z=terminal-phase disposition rate constant, $t_{½}$=terminal phase elimination half-life, AUC=area under concentration-time curve, CL/F=apparent oral dose clearance, V_z/F=apparent volume of distribution.

When moxidectin was administered to subjects in the fed cohort, the mean Cmax increased by 34% (p=0.001), Tmax was delayed by 1.6 hours (43%), mean AUC increased by 39% (p=0.0003), mean CL/F decreased by 35% (p=0.0009) and mean Vz/F decreased by 40% (p=0.0003), as compared with when moxidectin was administered to fasting subjects.

SPONSOR'S CONCLUSIONS: Moxidectin was well tolerated by healthy male subjects at an oral dose of 8 mg in both fasted and fed states. The bioavailability of moxidectin when taken with food appeared to increase. Based on the known safety profile of moxidectin in both healthy volunteers and patients, the clinical impact of administration of moxidectin with food in phase 3 trials should be minimal.

REVIEWER ASSESSMENT:
The bioanalytical method for determination of moxidectin concentrations was validated. The reviewer found the bioanalytical method to be acceptable. The reviewer concurs with the Sponsor's conclusions. The study results showed that Cmax increased by 34% and AUC increased by 39% when moxidectin was administered with high-fat meal, compared with when moxidectin was administered to fasting subjects. Although the food impact on moxidectin PK parameters was statistically significant, the clinical relevance of the increased Cmax and AUC by food should be assessed with the totality of safety data from all clinical trials.

4.3.4 Study 1008 Single Dose and Thorough QT study

PROTOCOL NO.: 3110A1-1002-EU

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

Date(s):	15 February 2017 - 14 March 2017
Investigator(s):	Carlos Sanabria, MD
Study Center(s):	Spaulding Clinical Research, LLC, 525 South Silverbrook Drive, West Bend, WI 53095
Analytical Site(s):	(b) (4)

OBJECTIVES:

Primary objective:

To analyze the effect of a single oral dose of moxidectin on the QT interval associated with moxidectin plasma concentrations.

Secondary Objective:

To assess the safety and pharmacokinetics (PK) of a single oral dose of moxidectin.

Exploratory Objectives:

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

METHODS

Study Design: This was a randomized, single-center, double-blind, placebo-controlled, parallel-group study in which healthy male subjects were randomly assigned to one of the following treatments that used the to-be-marketed 2 mg tablet formulation of moxidectin:

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

Subjects who met all the inclusion criteria and none of the exclusion criteria were admitted to the clinical research unit (CRU) on Day –1 (not less than 12 hours before scheduled dosing).

Number of subjects: A total of 60 healthy subjects were planned and enrolled in the study. All 60 subjects were included in the safety and ECG populations and 50 subjects were included in the PK and PK/PD populations.

Analytical Methods: Plasma and urine samples were analyzed for moxidectin concentrations using validated liquid chromatography tandem mass spectrometry methods. Plasma and urine

samples were analyzed for moxidectin metabolite concentrations and feces samples were analyzed for moxidectin concentrations using liquid chromatography tandem mass spectrometry methods. The method for the detection of moxidectin in human plasma was validated across a linear dynamic range (LDR) of moxidectin concentrations, 0.1 – 100 ng/mL and a lower limit of quantitation (LLOQ) of 0.1 ng/mL was achieved for this assay. The LDR of the assay for moxidectin in urine was 0.1 – 100 ng/mL and the LLOQ was 0.1 ng/mL. The LDR of the bioanalytical assay for moxidectin in feces was 1 - 200 ng/mL, and the LLOQ was 1 ng/mL. The LLOQ was 1 ng/mL for hydroxyl-moxidectin in both plasma and urine during method qualification.

Reviewer Comment: The bioanalytical assays for measurement of moxidectin in plasma, urine and feces have been reviewed and these are deemed acceptable.

Pharmacokinetic Assessment: Blood samples were collected for PK assessments at Baseline (0 hour; within 15 minutes before dosing) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing, and on Days 8, 15, and 22. Blood samples were also collected for planned analysis of moxidectin metabolite concentrations at 4, 12, 24, 36, and 60 hours after dosing.

Urine and feces samples for PK assessments were collected from each subject as follows:

- Urine: Before dosing and for pooled intervals of 0 to 24, 24 to 48, and 48 to 72 hours after dosing (4 samples)
- Feces: Before dosing and each bowel movement during confinement in the CRU. Samples were pooled at the central laboratory for intervals of 0 to 24, 24 to 48, and 48 to 72 hours after dosing (up to 4 samples)

For plasma, the time course of concentrations of moxidectin was presented and summarized using descriptive statistics (number of subjects, mean, SD, percent coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by time point and treatment. The amount of metabolite by collection interval and metabolite-to-parent (molar equivalent) ratios were summarized using descriptive statistics (number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by collection interval and treatment. The PK parameters for plasma moxidectin were determined from the concentration-time profiles for all evaluable subjects.

For urine and feces, the amount of moxidectin excreted by collection interval and dose was presented and summarized using descriptive statistics (number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by time point and treatment.

For urine, the amount of metabolite by collection interval and metabolite-to-parent (molar equivalent) ratios were presented and summarized using descriptive statistics (number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by collection interval and treatment. Descriptive statistics of PK parameters for moxidectin were provided for the PK population by treatment and included number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV% (where applicable).

Pharmacodynamics Assessment: Pharmacodynamics were evaluated by continuous cardiac monitoring. The PD endpoints were calculated from the mean of the triplicate continuous 12-lead ECG data as:
1. dQTcF – baseline-adjusted QT interval corrected by Fridericia's formula (QTcF);
2. ddQTcF – time-matched, placebo-corrected, baseline-adjusted QTcF
The primary study endpoint was the dQTcF matched to the plasma concentration of moxidectin collected at the same time point. The relationship between time-matched dQTcF and moxidectin concentrations was investigated by linear mixed-effects modeling. The ddQTcF value was calculated as the placebo-corrected dQTcF estimated from the model.

Reviewer Comment: The QT interval analyses are reviewed by QT-IRT review team; please refer the QT-IRT review for further details regarding the potential effects of moxidectin on the QT interval.

Safety Assessment: The safety parameters included reported AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements (supine blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and physical examination findings.

RESULTS
Overall, subjects had a mean age of 32.0 years, a mean weight of 79.97 kg, and a mean BMI of 25.8 kg/m2. The majority of subjects were either Black or African American (48.3%) or white (45.0%) and not Hispanic or Latino (90.0%). Per the protocol, all subjects were male (100.0%). Demographic and baseline characteristics were comparable between the treatment groups, with the exception of race and ethnicity, which varied by treatment group.

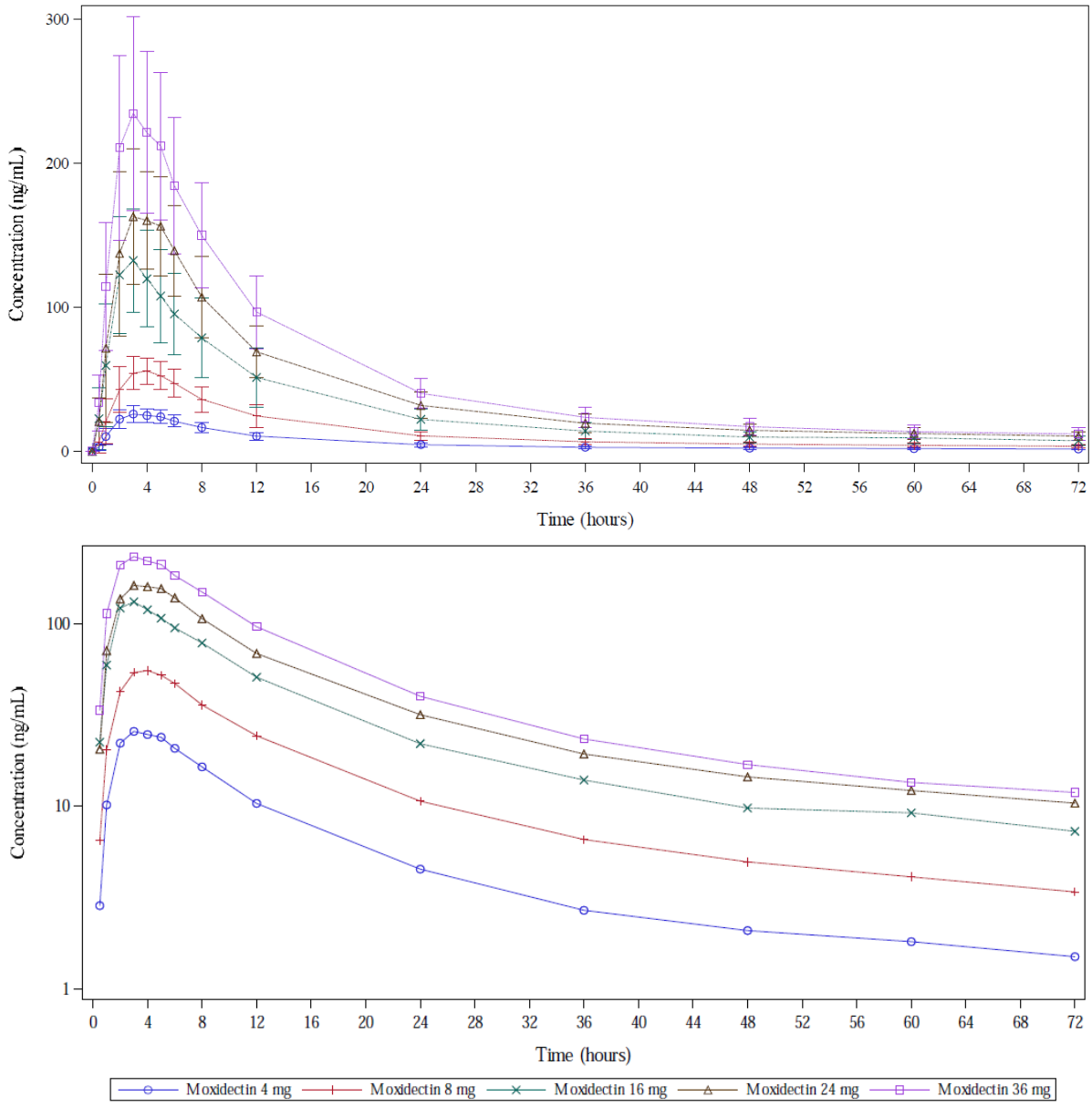
Mean plasma moxidectin concentrations are summarized in **Table 1**. Mean plasma moxidectin plasma concentration-time profiles are presented in **Figure 1**.

Table 1. Summary of Geometric Mean (CV% Geometric Mean) Moxidectin Pharmacokinetic Parameters by Treatment.

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

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

Figure 1: Mean ± SD Plasma Moxidectin Concentration (ng/mL)-Time Profile, Linear Scale (upper panel) and Semi-logarithmic Scale (lower panel)



The Sponsor stated that half-life and half-life-dependent parameters (AUC_{inf}, AUC_{ext}, CL/F, and Vd/F) were not reported because the sampling scheme was not sufficient to calculate half-life estimates.

The Sponsor indicated that moxidectin was not quantifiable in the urine of 9 of 10 subjects and close to the lower limit of quantitation (1.0 ng/milliliter [mL]) in 1 urine sample from 1 subject; therefore, no urine PK parameters are reported. Further, all individual moxidectin metabolite concentrations were BLQ in plasma and urine.

The mean quantity of moxidectin excreted in feces over 72 hours (Ae_{feces}[0-72]) was 0.165 mg (± 0.065), which was approximately 2% of the 8-mg oral dose.

Reviewer Comment:
The Sponsor stated that all PK blood samples collected after dosing had quantifiable concentrations of moxidectin (to 504 hours post dose for most subjects). However, the PK results included only the concentration data up to 72 hours in the clinical study report (CSR). The reviewer further found that the full PK data including those plasma drug concentrations from 72 to 505 hours (rather than 504 hours as stated by the Applicant) were included in the datasets provided in the NDA. Thus, the present CSR is considered acceptable.

Considering the long half-life (485 to 1139 hours in healthy subjects) of moxidectin, the PK sampling time point up to 505 hours is not adequate to capture the entire PK profile.

Safety:
Overall, 10 of 60 subjects (16.7%) reported at least 1 TEAE, with a higher percentage of subjects reporting TEAEs after receiving moxidectin 4 mg or 8 mg (30.0% each) compared with moxidectin 36 mg (20.0%), moxidectin 16 mg or placebo (10.0% each), or moxidectin 24 mg (0%). A total of 4 subjects (6.7%) reported 5 TEAEs that were considered related to study drug. There were no Grade 3 or 4 TEAEs, SAEs, or TEAEs leading to study discontinuation.

SPONSOR'S CONCLUSIONS:

Pharmacokinetics:

- The moxidectin geometric mean estimates for Cmax, AUC_{0-24}, AUC_{0-48}, AUC_{0-72}, AUC_{24-48}, and AUC_{48-72} all increased in an approximate dose-proportional manner as the moxidectin dose increased from 4 to 36 mg.
- Geometric mean estimates for C_{max} and AUC_{0-last} for Group 5 (36 mg) were 247 ng/mL and 5659 h*ng/mL, respectively.
- Exposure was highest for the first 24 hours after dose administration for all groups and decreased during each subsequent 24 hour period, with approximately 50% of the total exposure between 0 and 48 hours after dose administration.

REVIEWER ASSESSMENT:
The present clinical pharmacology review evaluates the PK results from this study. The PD and PK/PD analysis results, including the relationships between QT prolongation and plasma concentration, are reviewed by the QT-IRT group. Please refer to the thorough QT study review for more details regarding the QT prolonging potential of moxidectin.

Although the PK data beyond 72 hours are not presented in the present CSR, the complete moxidectin concentration data are included in the data file provided in the NDA submission. Since the PK sampling time points up to 505 hours were not adequate to characterize the entire moxidectin PK profile and the AUC_{0-inf}, the AUC_{0-last} was used to roughly estimate dose proportionality in terms of AUC. Based on this, it appeared that the increase in AUC_{0-last} was approximately dose proportional up to 24 mg of moxidectin, whereas the increase in AUC_{0-last} was less than dose proportional at 36 mg. Because the limited number of PK time points

precluded adequate estimation of $AUC_{0\text{-inf}}$, the Cmax provides a more meaningful PK parameter to evaluate the dose proportionality of moxidectin for this study. Thus, based upon review of the mean Cmax data, moxidectin Cmax also increased in an approximate dose-proportional manner from 4 to 24 mg, with a slightly less than dose proportional increase at 36 mg. The PK characteristics of moxidectin are further evaluated in the population PK analysis, which is included in the pharmacometric review.

4.4 Summary of Nonclinical Drug-Drug Interaction Studies

In vitro

The metabolite profile was characterized in vitro using human (Study RPT-51895 and Study MDG-R5763) and rat liver microsomes (Study RPT-51895) and using human recombinant cDNA expressed CYP450 enzymes (Study MDG-R5763).

Moxidectin was minimally metabolized in human and rat liver microsomes with intrinsic clearance calculated at ≤ 0.008 mL/min/mg and $t_{1/2}$ at > 60 minutes, suggesting low metabolic turnover in both species. Human recombinant cDNA-expressed CYP450 enzymes, including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5, were evaluated for their potential to metabolize moxidectin. The study results indicated that CYP3A4 and 3A5 appear to be the major CYP450 enzymes responsible for the limited oxidation of moxidectin.

Inhibition of CYP450 enzyme activity by moxidectin was evaluated in human liver microsomes (Study RPT-51894). There was weak inhibition of CYP1A2 and 2C9 activity (IC_{50} values of 459 and 145 µM, respectively). Note that a concentration of 0.1 µM moxidectin corresponds approximately to the plasma C_{max} of 78 ng/mL in healthy volunteers after a single 8 mg oral dose of moxidectin.

The potential of moxidectin to induce CYP3A4 was evaluated in a pilot luciferase reporter gene assay using cultured human hepatocellular carcinoma (HepG2) cells (Study RPT-70409). Moxidectin at the tested concentration of 1.0 µM increased the enzyme activities of CYP2B6 and 3A4 by 2.0-fold and 3.5-fold, respectively.

Moxidectin was determined not to be a P-gp substrate or inhibitor (IC_{50} >100 µM) in studies using Caco-2 cell monolayers (Studies RPT-71499 and RPT-62231). Moxidectin was also reported to be a weak substrate for the transporter protein BCRP in a study using MCDK-II epithelial cell monolayer.

In vivo

The metabolism of moxidectin was assessed in sheep, cattle and rats. In rats, moxidectin was primarily eliminated as the parent compound in feces and most radiolabel was excreted by 2-3 days post-dose. Six metabolites were identified in feces and those accounted for less than 10% of all moxidectin-derived residues. The metabolism of moxidectin in sheep and cattle was similar to that in rats.

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