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ARTICLE

Evaluation of the Cardiac Safety of Long-Acting Endectocide Moxidectin in a Randomized Concentration-QT Study

Sally A. Kinrade[1,*], Jay W. Mason[2], Carlos R. Sanabria[3], Craig R. Rayner[4], Julie M. Bullock[4], Stephanie H. Stanworth[2] and Mark T. Sullivan[1]

Potential effects on cardiac repolarization of single doses of moxidectin, a potent long-acting macrocyclic lactone endectocide, were assessed in a concentration-QT (c-QT; exposure-response) study. This double-blind, placebo-controlled, parallel-group study in healthy male volunteers (*n* = 60) randomized subjects to a single oral dose of moxidectin (4 mg, 8 mg, 16 mg, 24 mg, or 36 mg) or matching placebo. Serial plasma samples for pharmacokinetic (PK) analysis and concurrent triplicate electrocardiogram measurements were taken at baseline and 14 prespecified time points over 72 hours, yielding 900 QT interval-plasma concentration time-matched pairs. Moxidectin had no statistically significant or clinically relevant impact on QT interval at any dose level. The primary mixed effects model analysis revealed no treatment-related impact on the Fridericia-corrected QT interval-plasma concentration gradient (–0.0077, 90% confidence interval (CI) –0.0255 to +0.0101).
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Concentration-QTc response modeling has been assessed as a potential method to replace the traditional thorough QT study. Results from an Innovation and Quality in Pharmaceutical Development-Cardiac Safety Research Consortium study[1] has provided evidence for the predictive accuracy of this method. It is recommended that similar study designs be adopted to provide further evidence for this approach.[2]

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The cardiac safety of moxidectin administered as a single dose up to 36 mg was assessed using a concentration-QT study design in order to verify the lack of cardiac effect observed in previous nonclinical and clinical studies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study demonstrated the safety of single dose moxidectin at a C_{max} 4.4-fold higher that of the planned therapeutic dose. The study design is appropriate for a long half-life, single administration treatment with a sufficiently wide therapeutic index.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our data support the exposure-response study design as a robust assessment methodology for definitive QT assessment. Implementation of a population-PK model *a priori* can assist in decision making.

Moxidectin is a broadly active macrocyclic lactone endectocide of the milbemycin class. It is a semisynthetic methoxime derivative of LL-F29249α (F-alpha), a fermentation product of *Streptomyces cyanogriseus*. The primary mode of action is selective binding to glutamate-gated chloride channels present in the neurons and muscle cells of many ectoparasites and nematodes.[3–5] It is currently in late-stage development for the treatment of the neglected tropical disease onchocerciasis (river blindness), where it was shown to be superior to the current standard of care, ivermectin.[6,7] Moxidectin is also being evaluated as a new treatment for scabies, strongyloidiasis, lymphatic filariasis, and soil-transmitted helminthiasis.

Nonclinical and clinical data reported to date were not suggestive of moxidectin having a QT liability. In a NovaScreen assay,[8] there was no binding to ion channels, including calcium type L and type N, ATP-sensitive potassium, Ca-activated V1 potassium, IKr (human ether-à-go-go [hERG]) potassium, and site 2 sodium channels. The hERG potassium current inhibition showed minimal effect in HEK293 cells at ~100-fold higher concentrations than achieved in adult patients. Due to solubility limitations, the

[1]Medicines Development for Global Health, Melbourne, Australia; [2]Mason Cardiac Safety Consulting, Reno, Nevada, USA; [3]Spaulding Clinical Research, LLC, West Bend, Wisconsin, USA; [4]Certara Strategic Consulting, Melbourne, Australia. ***Correspondence:** Sally Kinrade (sally.kinrade@medicinesdevelopment.com)
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highest concentration of moxidectin that could be tested was 10 μM. This concentration produced <20% inhibition of the hERG ion channel current and, thus, the concentration of half inhibition was >10 μM (6.4 μg/mL). An *in vivo* cardiovascular safety pharmacology study showed no adverse effects (AEs) of moxidectin on the cardiovascular system in the dog at up to 1 mg/kg[6]. No identifiable pro-arrhythmic risk was identified through routine electrocardiogram (ECG) safety assessment of 1,105 patients with onchocerciasis and 244 healthy volunteers who received single oral doses of moxidectin up to 36 mg in phase I to III clinical trials.[6,7,9–13]

Onchocerciasis is endemic in the most remote and resource-poor settings of sub-Saharan Africa and treatment with ivermectin is currently through mass drug administration programs involving whole communities (excluding young children and pregnant women) with limited medical supervision or follow-up. Moxidectin is likely to have a similar usage, providing a rationale for conducting a definitive human QT prolongation risk-assessment to confirm earlier findings.

As moxidectin has a mean terminal half-life in healthy volunteers of more than 30 days, a standard crossover thorough QT (TQT) study[14] was impractical. The International Conference on Harmonisation (ICH) E14 recommends a parallel-group study for drugs with a long half-life where a crossover design is not feasible.[14] A dedicated dose-ranging time-matched collection of pharmacokinetic (PK) and ECG data using a concentration-QT (c-QT) analysis approach was considered an appropriate alternative method[1,2,15,16] for a rigorous assessment of the cardiac safety profile of moxidectin to support the proposed posology of moxidectin, a single oral dose of 8 mg. The primary objective of the study was to analyze the effect of a single oral dose of moxidectin of between 4 mg and 36 mg on the QT interval associated with moxidectin plasma concentrations. The number of subjects selected at each dose level was similar to early-phase dose-escalation studies implementing a c-QT assessment and modeling approach for determination of cardiac safety liability. A population-PK model was implemented *a priori* to simulate exposures following an 8 mg therapeutic dose when co-administered with food. This scenario was considered a worst-case based on extrinsic factors impacting moxidectin PK and the exposures were compared with those anticipated with the 36 mg dose arm in the study. Based on US Food and Drug Administration (FDA) guidance, the anticipated exposure margins were considered sufficient to dismiss inclusion of a study arm with a QT positive control, such as moxifloxacin. Experience with exposure response (ER) analyses of ECG data has increased over the last decade and ER analyses have become an integral part of FDA Interdisciplinary Review Team data review from QT assessment studies.[16] The ER analyses allow for a wide range of plasma concentrations to be analyzed, an alternative effective method for detecting and excluding small QT effects.[2,17]

METHODS

This study was conducted according to ICH principles. Before implementation, the protocol and all materials viewed by participants were approved by an appropriately constituted institutional review board. The principal investigator conducted all aspects of the study in accordance with FDA regulations, the ICH E6 (R1) guidelines for Good Clinical Practice, and applicable local, state, and federal laws. The study was initiated with the first subject screened on January 23, 2017. Completion of the study for primary analysis was achieved on March 14, 2017, and safety follow-up was completed on May 22, 2017, the date of the last subject's last contact.

ECG and pharmacokinetic data collection

Healthy men, aged 18–50 years with a body mass index of 18–30 kg/m^4 were eligible for inclusion in the study. After providing written informed consent, subjects were screened for eligibility up to 28 days before randomization. Subjects who met all of the inclusion and none of the exclusion criteria were admitted to the phase I clinical research unit on day –1. Subjects remained in the clinical research unit for at least 72 hours and were asked to return on days 8, 15, and 22, and at week 12. At week 8, subjects were contacted for assessment of AEs and concomitant medication use. To manage the intensity of assessments during the initial 72-hour period, subjects were enrolled in two cohorts of 30 subjects, ~1 week apart.

The random code was generated by the clinical packaging group and blinded study drug was provided to the site prepacked in individual sequentially numbered containers according to a random code allocating treatments 1:1:1:1:1:1 (block size 6). All site and sponsor staff were blinded to treatment allocation. Only clinical packaging and laboratory staff conducting PK analyses were unblinded during the trial.

On study day 1, after an overnight fast of at least 10 hours, each eligible subject was randomized to treatment in sequential order, each receiving a single dose of 18 tablets (moxidectin 2 mg and/or placebo tablets) with 240 mL of water. No food was allowed for 4 hours after dosing.

Subject assessments were conducted at protocol specified intervals. When multiple procedures were scheduled at the same time point, the vital signs measurements were obtained first, followed by the 12-lead ECG, blood collections, and last by physical examinations.

During confinement, subjects were not allowed to engage in strenuous exercise or to sleep during ECG extractions. The subject's body position was controlled to maintain supine positioning before and during the ECG extractions.

Five subjects discontinued study participation after day 15, none for safety reasons

Unblinding of the study to enable primary ECG and safety analyses occurred after all subjects had completed day 22. The clinical staff was responsible for ongoing subject assessment and all subjects remained blinded to study treatment during the additional 9-week safety follow-up period.

Assessment of ECGs

Pharmacodynamics were assessed via ECGs obtained using a Mortara continuous 12-lead digital ECG recorder, and reviewed and analyzed by a central ECG laboratory. The device remained connected to the subject during

confinement. The ECG data were transmitted wirelessly to the Surveyor system, which extracted triplicate 10-second ECG recordings (~1 minute apart) before dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours after dosing.

The ECG core laboratory staff was blinded to treatment, time, and study day identifiers. Digital ECGs were transmitted using a validated data management system. The cardiologists responsible for interpretation were blinded to all study drug identifiers and collection times. Lead II was the lead of choice for the over-reads and the baseline and on-treatment ECGs were based on the same lead. All ECGs from a particular subject were read by a single reader.

Assessment for hysteresis

Before modeling, the concentration-ΔΔQTcF relationship was explored graphically to determine the presence of hysteresis. Hysteresis was to be assumed if there were at least 3 time points with ΔΔQTcF >5 msec and the time to maximum observed plasma concentration (T_{max}) and the time of maximal ΔΔQTcF (U_{max}) differed by 30 minutes or more and the 1-sided, 1-sample Wilcoxon test for the difference between ΔΔQTcF at T_{max} and at U_{max} was significant at the 1% level.

Model selection

The relationship among time-matched, ΔQTcF, and moxidectin concentrations was investigated by linear mixed-effects modeling. Prespecified alternative models were identified for the analysis in the presence of hysteresis (population PK model with an effects compartment) or of nonlinearity in the analysis results (log linear and/or maximum effect or other model). Quadratic models were found to have a higher Akaike Information Criterion than the linear models, indicating a better fit of the linear model. The quadratic parameter estimate was found to be insignificant ($P = 0.8212$). All analyses were conducted with SAS version 9.4.

Exposure response analyses

The primary end point of the study was the mean ΔQTcF by time point estimated from the mixed concentration effects model. The primary analysis was conducted for the ECG population, defined as all subjects who received a dose of moxidectin and had at least one pair of ECG and PK time-matched pairs. In accordance with the FDA recommendation, ΔQTcF was identified as the dependent variable and treatment, time point, and treatment by time point interaction as the independent variables, with baseline QTcF as a covariate and time-matched observed concentrations of moxidectin as covariate with random effects of intercept and slope for each subject. Concentrations of zero were used for placebo. A spatial power law covariance structure (time-dependent first-order autoregressive covariance designed for unequally-spaced time points) was used. The model was used for predicting population average and 90% 2-sided bootstrapped confidence interval (CI) of the baseline-adjusted difference (ΔΔQTcF) between active and placebo at each time point. The bootstrap method was based on percentile CI using the 5th and 95th percentiles in the resampling distribution using 1,000 iterations.

The criterion for negative QT assessment was the upper bound of the 2-sided 90% bootstrapped CI for ΔΔQTcF being below 10 msec in the primary analysis. The significance and magnitude of parameter estimates of the treatment covariate (active vs. placebo) was considered. The estimated ΔQTcF values from the primary analysis were compared by calculating the differences overall and at each time point between active and placebo, resulting in estimates of ΔΔQTcF. A secondary analysis, referred to as the traditional c-QT analysis, with ΔΔQTcF as the dependent variable was also performed to assess correlation and overall profile of ΔΔQTcF and plasma concentrations, using an unstructured covariance structure with a random intercept and slope subject effect.

Pharmacokinetic sample collection and analysis

To determine moxidectin PKs, blood samples were collected to coincide with ECG extraction time points predose, over the 72-hour confinement and days 8, 15, and 22. Additional samples were collected at 4, 12, 24, 36, and 60 hours postdose for analysis of moxidectin metabolites. In addition, urine and feces were collected from each subject predose and over 72 hours postdose and pooled for each period of 24 hours. Samples were stored frozen at –70°C before shipping to a specialized laboratory for analysis.

Plasma samples were analyzed by a validated liquid chromatography tandem mass spectrometry method. Four milliliters of blood was collected from subjects in potassium (K_2) EDTA vacutainer tubes. After a 10-minute centrifugation at 2,000 *g* at 4°C, dual aliquots of plasma were collected in cryovials and stored at –70°C until sample analysis. Moxidectin and internal standard, deuterated (d3)-moxidectin, were extracted from 150 μL of human plasma via solid phase extraction. The lower limit of quantitation of the assay was 0.1 ng/mL.

For the subset of subjects who received an 8 mg dose, concentration of moxidectin metabolite as hydroxylated isomers M655a, M655b, and M655c in plasma and urine and moxidectin concentrations in urine and feces were also analyzed. Moxidectin metabolite concentrations in plasma and urine and moxidectin in feces were analyzed using qualified liquid chromatography tandem mass spectrometry methods. The lower limit of quantitation was determined to be 1.0 ng/mL for all matrices.

RESULTS

Sixty healthy adult male subjects aged 18–50 years were enrolled and randomized double-blind to moxidectin 4 mg, 8 mg, 16 mg, 24 mg, 36 mg, or matched placebo ($n = 10$ per treatment group; **Table 1**). All subjects were included in the ECG and PK analyses through the 72-hour analysis period. The sample size of 60 subjects was considered adequate, because it was designed to yield a data set consisting of 900 QT interval-plasma concentration time-matched pairs collected at baseline and over 14 prespecified time points during the 72-hour postdose period for all subjects. Additional ECG, PK, safety, and metabolism analyses were also conducted in the study.

Table 1 Demography and disposition of subjects included in the moxidectin concentration-QT study

Characteristic	Treatment group						
	Mox 4 mg (*n* = 10)[a]	Mox 8 mg (*n* = 10)	Mox 16 mg (*n* = 10)	Mox 24 mg (*n* = 10)	Mox 36 mg (*n* = 10)	Placebo (*n* = 10)	Total (*n* = 60)
Age, years							
Mean (±SD)	37.1 (±7.8)	30.4 (±8.73)	30.9 (±8.3)	31.2 (±8.3)	30.2 (±8.9)	32.3 (±6.7)	32.0 (±8.1)
Gender							
Female	0	0	0	0	0	0	0
Male	10	10	10	10	10	10	60
Race, *n* (%)							
White	7 (70.0)	3 (30.0)	5 (50.0)	4 (40.0)	3 (30.0)	5 (50.0)	27 (45.0)
Black	3 (30.0)	7 (70.0)	4 (40.0)	5 (50.0)	5 (50.0)	5 (50.0)	29 (48.3)
Other	-	-	1 (10.0)	1 (10.0)	2 (20.0)	-	4 (6.7)
Weight, kg							
Mean (±SD)	82.2 (±12.6)	75.7 (±11.5)	78.3 (±11.7)	77.5 (±12.4)	83.7 (±11.9)	82.4 (±11.3)	79.9 (±11.8)
Height, m							
Mean (±SD)	1.77 (±0.05)	1.74 (±0.09)	1.74 (±0.06)	1.75 (±0.08)	1.77 (±0.09)	1.78 (±0.06)	1.76 (±0.07)
Body mass index, kg/m^2							
Mean (±SD)	26.2 (±3.7)	24.9 (±3.3)	25.8 (±3.7)	25.1 (±3.0)	26.7 (±3.1)	26.1 (±3.1)	25.8 (±3.3)

Mox, moxidectin.
[a]One additional subject was enrolled but not dosed (not included).

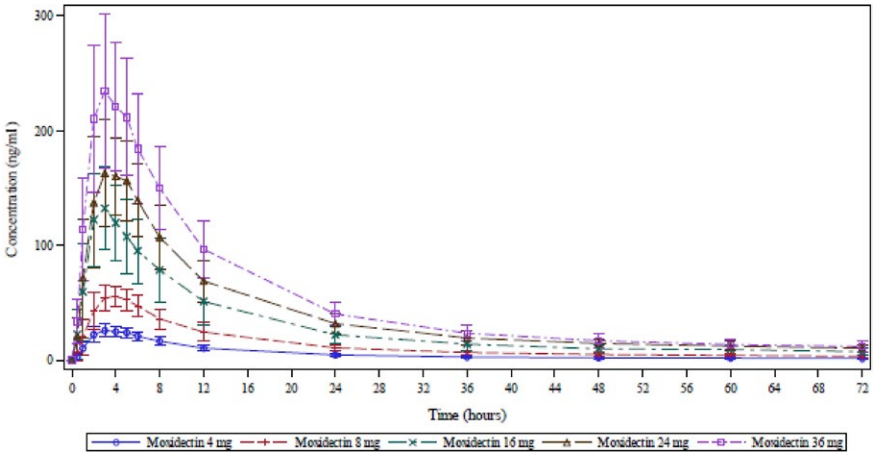

Figure 1 Mean ± SD moxidectin plasma concentration (ng/mL) vs. time (linear scale).

Moxidectin plasma concentrations

The mean plasma moxidectin concentrations by treatment and time point for all subjects are presented in **Figure 1**. Geometric mean maximum plasma concentrations (C_{max}) increased with dose in an approximately linear fashion, varying from 27.2 ng/mL in the 4 mg dose group to 247 ng/mL in the 36 mg dose group. Geometric mean time of maximum plasma concentration (T_{max}) ranged from 2.71 (16 mg dose group) to 3.69 (8 mg dose group) hours. The maximum geometric mean C_{max} achieved (247 ng/mL) was 4.4-fold that of the proposed onchocerciasis dose of 8 mg observed in this study (56.7 ng/mL). This also exceeded, by at least twofold, simulations in a population-PK model of "worst case scenarios" of exposure margins that would result from co-administration with food.

QT interval-plasma concentration assessment

The mean gradient of the regression slope for QTcF vs. RR interval for the entire population was 0.0294 (**Figure 2**) the prespecified criterion for adequate Fridericia heart rate correction was 0.045.

The relationship between time-matched, baseline-adjusted Fridericia-corrected QT interval (ΔQTcF) and moxidectin concentrations was investigated by linear mixed-effects modeling (**Table 2**). The baseline corrected and placebo subtracted QTcF (ΔΔQTcF) value was calculated as the placebo-corrected ΔQTcF estimated from the model, as described in the Methods section.

Because there was only a single ΔΔQTcF value that exceeded 5 msec, pre-established criteria for further hysteresis assessment were not met.

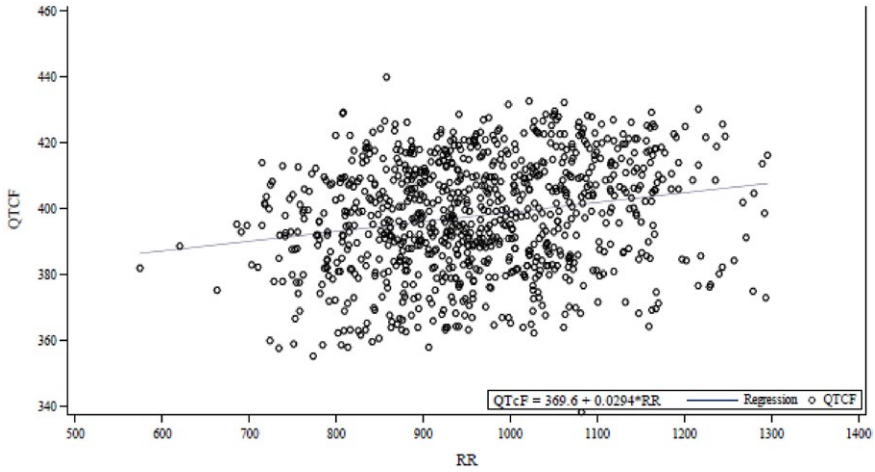

Figure 2 Scatterplot and linear regression for QTcF interval vs. the RR interval is the time between QRS complexes, a measure of heart rate.

Table 2 ΔQTcF model parameters

	Type 3 F-statistic	Type 3 *P* value	Estimate (SE)	90% CI	*P* value
QTcF (msec)					
Base	18.89	< 0.0001	–	–	–
Treatment	0.07	0.7884	–	–	–
Timepoint	5.37	< 0.0001	–	–	–
Treatment*timepoint interaction	0.55	0.8909	–	–	–
Moxidectin	0.52	0.4727	–	–	–
Slope			−0.0077 (0.01062)	−0.0255, 0.0101	0.4727

Parameter values of type 3 tests and *P* values as well as estimates of slope and intercept are obtained from the linear mixed effects model as ΔECG = baseline + treatment + postdose timepoint + treatment*time point interaction + plasma moxidectin concentration (covariates with random intercept and slope). A spatial power law covariance structure is used as the covariance structure for the repeated timepoint effect. Primary analysis is provided for the primary parameter, QTcF, and repeated for the other exploratory parameters.
CI, confidence interval.

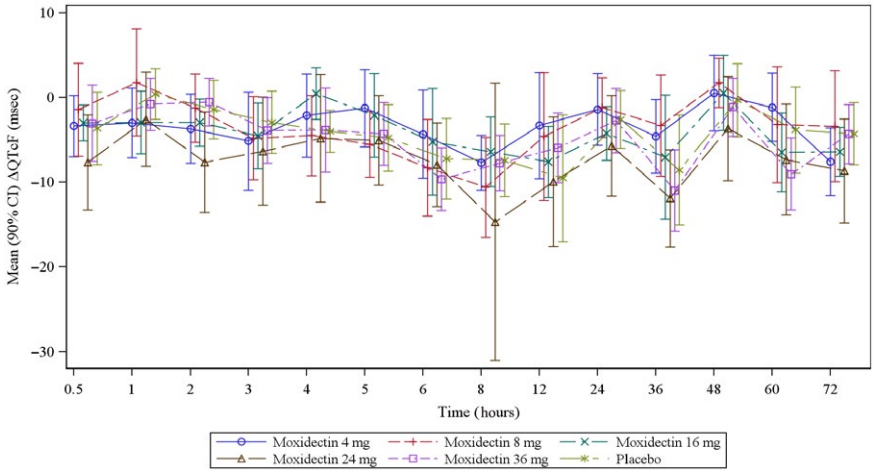

Figure 3 The ΔQTcF interval vs. time by dose of moxidectin (mean and two-sided 90% confidence interval (CI).

The change from baseline in QTcF (ΔQTcF) for each dose cohort is shown in **Figure 3**. Mean ΔQTcF was generally modestly negative in all cohorts, including placebo. The primary mixed effects model revealed a nearly flat ΔQTcF – plasma concentration gradient (–0.0077, 90% CI –0.0255 to +0.0101, *P* = 0.4727).

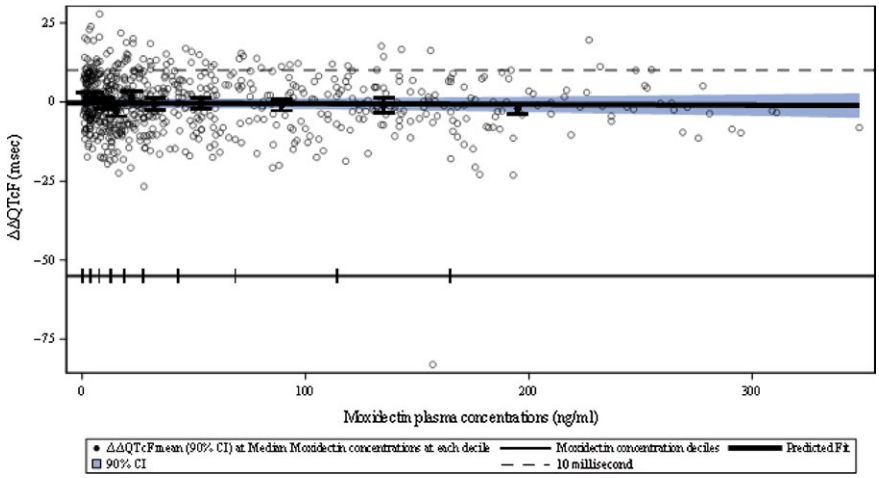

Figure 4 Linear regression model of ΔΔQTcF (in milliseconds) vs. moxidectin concentrations derived from all concentration-QTcF pairs and showing observed median-decile plasma moxidectin concentrations and associated mean ΔΔQTcF with 90% confidence interval (CI).

The primary criterion for negative QT assessment was to be the upper boundary of the 2-sided 90% bootstrapped CI for ΔΔQTcF being below 10 msec at the largest geometric mean C_{max} value. As ΔQTcF was used as the dependent variable in this analysis at the request of the FDA, the 10 msec criterion was drawn from the pre-established criterion for the more traditional analysis using ΔΔQTcF as the dependent variable (**Table 3**). This was exceeded at a single time point (hour 12) but the change was not statistically significant (difference 4.2 msec, 90% CI –2.20 to +11.10, $P = 0.1436$), occurring after T_{max} and surrounded by small negative and positive changes. This by-time-point estimate represents effects at the average plasma concentration at the given time point.

Table 3 Summary of the primary analysis mixed effects model predicted ΔΔQTcF by timepoint with 90% CIs

	Active - placebo		
Time point	**Predicted difference (ΔΔQTcF, msec)**	**Bootstrapped 90% CI**	***P* value**
Over all timepoints	0.5	–2.6, 3.8	0.7884
0.5 hour	0.6	–2.8, 4.9	0.8394
1 hour	–1.2	–4.4, 2.3	0.6872
2 hours	–0.7	–4.7, 3.2	0.8012
3 hours	–0.9	–5.7, 4.3	0.7743
4 hours	2.2	–2.2, 6.6	0.4661
5 hours	2.4	–2.3, 7.2	0.4259
6 hours	1.4	–3.4, 6.5	0.6405
8 hours	–0.8	–5.3, 4.1	0.7734
12 hours	4.2	–2.2, 11.1	0.1436
24 hours	0.2	–2.9, 3.6	0.9316
36 hours	1.7	–3.7, 7.5	0.5537
48 hours	0.6	–3.5, 4.9	0.8424
60 hours	–1.0	–4.8, 2.9	0.7317
72 hours	–1.2	–5.1, 2.9	0.6778

Predicted ΔΔQTcF values and confidence bounds were obtained using a linear mixed effects model as ΔECG = baseline + treatment + post-dose time point + treatment * time point interaction + plasma moxidectin concentration (covariates with random intercept and slope). A spatial power law covariance structure was used as the covariance structure for the repeated timepoint effect.

A ΔΔQTcF-plasma concentration linear regression model drawn from all concentration-QTcF pairs from the five moxidectin groups is shown in **Figure 4**, with ΔΔQTcF at the median moxidectin concentration in each decile also presented and referred to as the traditional c-QT analysis. The fit line was nearly flat (–0.0023, 90% CI –0.0136 to +0.0089) with no visible difference among the groups and median values of each decile ΔΔQTcF also falling on or very close to the fit line.

The ΔΔQTcF-plasma concentration mixed effects model predicted ΔΔQTcF at the highest geometric mean C_{max} observed (247 ng/mL at the 36 mg dose) to be –0.8678 (90% CI –3.8122 to +2.0766), and at the highest observed concentration (348 ng/mL) to be –1.1010 (90% CI –5.0659 to +2.8640).

A single extreme outlier reading in a single patient with a ΔΔQTcF value of –83 msec was found to be spurious. On review of the subject's tracings, it was clear that due to a flat T-wave in lead II, the QT duration in an hour 8 ECG was measured incorrectly at 315 msec. The correct measurement was 410 msec. When re-analyzed without the outlier, the new fit line was again flat with little difference from the original analysis (0.0020, CI –0.0059 to +0.0099).

These results indicate that moxidectin did not have an effect on the electrocardiographic QT interval.

Heart rate, PR interval, QRS duration, and changes in ECG status

There was a modest increase in the heart rate (HR) in all five moxidectin cohorts and the placebo cohort in the hours after waking, consistent with expected diurnal variability. All moxidectin groups were similar to the placebo group. Baseline and placebo corrected HR (ΔΔHR) fluctuated around zero throughout the 72-hour post-treatment period with no evidence of a dose response effect.

Few standard categorical absolute changes in QTcF (≤30 msec, >30–60 msec, or >60 msec) or binary categorical changes (>450 msec, >480 msec, or >500 msec) occurred during the ECG assessment period. One subject in the 24-mg dose group had a single reading exceeding 450 msec (473 msec at hour 1) on a single ECG, although the mean value of triplicate readings was 440 msec. Two subjects in the 8-mg dose group and three in the 24-mg dose group had a change in QTcF compared with baseline of >30 msec with none exceeding 60 msec.

HR below 50 beats per minute with at least a 25% decrease from baseline was observed in one subject in the 36-mg dose group at hours 2 and 3. No other low HR outliers were observed. HR above 100 beats per minute with at least a 25% increase over baseline was observed in one subject in the 8-mg dose group at hour 1.

There was no evidence of a dose response in change in the PR interval from baseline (ΔPR) and there were minimal fluctuations in QRS interval in all six cohorts. Placebo corrected QRS was generally slightly negative at more timepoints than the active treatment groups. A dose-response pattern was not discernable and there were no outliers for PR and QRS intervals observed.

A total of 10 distinct diagnostic abnormalities were observed in this study. Nine treatment emergent diagnoses were reported and considered clinically significant in two subjects. One subject receiving placebo had a nonspecific T-wave abnormality on all of his tracings, including three baseline ECGs. A second subject receiving moxidectin, 16 mg, had premature ventricular contractions on two of three ECGs at hour 6. Treatment emergent abnormalities were most frequent in the placebo group (n = 5) when compared with active treatment groups. Abnormalities were distributed with no discernible dose or chronological pattern identified.

Safety

Moxidectin was well tolerated at all doses with a safety profile similar to placebo. There was no identifiable treatment-related AE, with no pattern of increasing incidence or severity of AE with increasing dose. Eleven of 60 subjects reported 14 AEs during 12 weeks of follow-up. No AE was reported by more than one subject. A total of four subjects reported five AEs that were considered by the investigator to possibly be related to the study drug: diarrhea (4 mg), headache (8 mg), nasal congestion (8 mg), and dizziness and abdominal discomfort (placebo). Three single laboratory events in three subjects were reported as AEs: increased aspartate aminotransferase (16 mg), increased cholesterol (4 mg), and increased bilirubin (36 mg). All AEs were grade 1 in severity, except for a single event of grade 2 arthralgia (4 mg).

Metabolism and excretion

An assessment of moxidectin and hydroxylated metabolites concentrations in plasma and urine and moxidectin concentration in feces was conducted for all 10 subjects dosed with 8 mg of moxidectin, as described in the Methods section. Moxidectin concentrations in urine were below the limit of quantitation 1.0 ng/mL for 9 of 10 subjects and 1.27 ng/mL in a single subject in the first 24 hours after dosing. Metabolite concentrations in plasma and urine were below the limit of quantitation with only trace amounts detected in plasma samples from 5 of 10 subjects. The mean (± SE) quantity of moxidectin excreted in feces over 72 hours was 0.165 mg (±0.065), which was ~2% of the 8 mg oral dose.

DISCUSSION

Previous experience has shown that, with few exceptions, the degree of impact on the QT interval of drugs or their metabolites is directly correlated with concentrations in plasma.[17–19] Hence, an ER study design in which simultaneous electrocardiographic and plasma concentration measurements are collected provides an appropriate methodology for assessment of these potential effects for a drug that can be safely administered at a sufficiently high dose.

As overall safety of a single dose of moxidectin up to 36 mg in healthy volunteers had already been established, the study was optimized by implementing a randomized parallel-group, placebo-controlled design. Single doses administered in the study ranged from 4 mg (half the proposed dose of 8 mg for treatment of onchocerciasis) to 36 mg (4.5-fold higher). Population-PK modeling indicated that 36 mg would deliver at least two times the worst-case exposure scenario for an 8 mg therapeutic dose when co-administered with food,[20] thus diminishing the risk of obtaining a false-negative result in the absence of inclusion of a positive control.[1] In addition, a complete set of PK-ECG timepoints across all doses was successfully collected for the analysis, providing more than sufficient ER data on which to base an assessment of the QT effect of moxidectin. The c-QT design as an alternative to a parallel group TQT required a similar number of subjects to a crossover TQT study and ~fourfold fewer subjects than would have been required for a parallel-group design, the relevant alternative for drugs with prolonged half-life, such as moxidectin. After placebo and baseline subtraction, there were 700 time matched, placebo-corrected, baseline adjusted QTc (ΔΔQTc)-plasma concentration pairs, which favorably compares with the International Consortium for Innovation and Quality in Pharmaceutical Development-Cardiac Safety Research Consortium study, which yielded 315 QTc-plasma concentration pairs and 189 ΔΔQTc-plasma concentration pairs per drug. Thus, the c-QT design enabled a smaller more efficient study with faster study completion and data analysis turnaround.

The prespecified criterion for negative QT assessment was the upper bound of the 2-sided 90% bootstrapped CI for ΔΔQTcF being below 10 msec in the primary analysis. The ΔQTcF was the dependent variable in this analysis, with inclusion of several covariates, as specifically requested by the FDA. The 10 msec criterion was drawn from the preestablished criterion of the more common analysis using ΔΔQTcF rather than ΔQTcF as the dependent variable. However, there is no generally accepted criterion for a model using ΔQTcF in which ΔΔQTcF CI is estimated by bootstrapping. In the more typical analysis, with a continuous confidence band about the fit line, in a negative study, the upper

boundary should not exceed 10 msec, except perhaps at the extreme right end of the fit line at very high plasma concentration not anticipated with clinical use. In this study, the continuous confidence band was well below 10 msec throughout. The primary analysis established a discreet CI at each timepoint, rather than a continuous band along the fit line. We believe that the single CI exceeding 10 msec does not indicate a positive effect of moxidectin on QT.

A limitation of this study was the inclusion of male subjects only. The rationale for this was to avoid the long-term commitment to contraception that would be required of healthy volunteer women of child-bearing potential. In addition, it provided PK data for comparison with an earlier study that enrolled only men that supported the pivotal phase III trial in patients with onchocerciasis.

In summary, the primary finding in these analyses was that single oral doses of moxidectin 4 mg, 8 mg, 16 mg, 24 mg, and 36 mg had no statistically or clinically significant effect on QT at any dose level, including the maximum dose (36 mg) at which mean C_{max} exceeded that of the clinical dose (8 mg) by 4.4-fold. There was also no clinically significant effect on HR, PR, QRS, or abnormal diagnostic statements. Moxidectin was well tolerated at all doses administered in this study.

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Conflict of Interest. S.A.K. and M.T.S. are employees of Medicines Development for Global Health (MDGH) a nonprofit biotechnology company. C.R.R. and J.M.B. are employees of Certara Strategic Consulting that consults for academic, government, and industry clients. C.R.S. and S.H.S. are employees of Spaulding Clinical, which conducted the study. J.W.M. is a consultant cardiologist and consulting Chief Medical Officer of Spaulding Clinical Research.

Author Contributions. S.A.K., J.W.M., C.R.R., and J.M.B. wrote the manuscript. J.W.M., J.M.B., C.R.R., M.T.S., and S.A.K. designed the research. C.R.S. performed the research. J.W.M. and S.H.S. analyzed the data.

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