CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214200Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 15, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 214200
Product Name and Strength:	Cosela (trilaciclib) for injection 300 mg/vial
Applicant/Sponsor Name:	G1 Therapeutics
FDA Received Date:	December 14, 2020
OSE RCM #:	2020-1259-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

G1 Therapeutics submitted a revised container label and carton labeling for Cosela (trilaciclib) on December 14, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review[a] and in an information request[b], as well as in response to recommendations made by the Office of Pharmaceutical Quality (OPQ). We reviewed the revised label and labeling to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

Our review of the revised label and labeling determined that our previous recommendations were implemented. DMEPA concludes the revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] DeGraw, S. Label and Labeling Review for trilaciclib (NDA 214200). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-1259.
[b] DeMar, M. Email: Labeling Information Request for NDA 214200. 2020 NOV 19. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805aec34&_afrRedirect=1181166445523784

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/s/

STEPHANIE L DEGRAW
01/15/2021 05:05:13 PM

HINA S MEHTA
01/20/2021 02:52:08 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214200
Submission Number	002
Submission Date	6/15/2020
Date Consult Received	8/3/2020
Drug Name	Trilaciclib
Indication	(b) (4) chemotherapy-induced myelosuppression in adult small cell lung cancer patients
Therapeutic dose	240 mg/m^2 over 30 min
Clinical Division	DND

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 8/3/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 119254 dated 07/11/2018; 03/28/2019; 02/21/2020 and 02/25/2020 in DARRTS;
- Clinical study report (link), ECG SAP (link), and concentration-QTc analysis report (link) for study G1T28-11 (Submission 0002);
- Proposed label (Submission 0002; link);
- IR responses dated 08/11/2020; 09/14/2020; 09/30/2020; 10/29/2020 and 11/17/2020; and
- Highlights of clinical pharmacology and cardiac safety (Submission 0002; link).

1 SUMMARY

A dose- and concentration-dependent increase in QTc was observed in this QT assessment of IV trilaciclib. There was, however, a time-delay between mean peak trilaciclib concentration and mean maximum increase in QTc. The mechanism for this delay is not known.

The effect of trilaciclib was evaluated in G1T28-11, a double-blind, placebo- and positive-controlled, single ascending dose study of IV trilaciclib in healthy volunteers. The highest dose evaluated was 700 mg/m^2. The data were analyzed using exposure-response analysis (using an effect compartment model to account for the time-delay) as the primary analysis, which did not suggest that trilaciclib is associated with significant QTc prolonging effect at the therapeutic dose (refer to section 4.5) — see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Trilaciclib Cmax (µg/mL)	ΔΔQTcI	90% CI
QTc	Trilaciclib 240 mg/m^2	1.5	4.3	(2.3, 6.4)
QTc	Trilaciclib 360 mg/m^2	2.2	6.5	(3.4, 9.6)
QTc	Trilaciclib 480 mg/m^2	2.9	8.6	(4.5, 12.7)
QTc	Trilaciclib 700 mg/m^2	4.3	12.6	(6.6, 18.6)

For further details on the FDA analysis, please see section 4.

At the time of this review, the high clinical exposure scenario is expected to occur in the Japanese population (40% increase, estimated geometric mean Cmax of 2.2 µg/mL). Under the assumption that trilaciclib is driving the observed QTc effect, a clinically relevant effect can be excluded in Japanese subjects at the therapeutic dose level. The hepatic impairment study is ongoing.

The mechanism of delayed QTc prolongation observed in the clinical study is unknown. Possible mechanisms that are responsible for the delayed QTc prolongation include hERG-active metabolite, increase in the inward current (e.g., late sodium current), and hERG trafficking inhibition. Of note, the clinical pharmacology properties of the major circulating metabolite, M8, are unknown. The sponsor has not evaluated this metabolite in nonclinical safety pharmacology studies.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

See our recommendations for a hERG assay for the major metabolite, M8.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Because trilaciclib showed dose- and concentration-dependent QTc prolongation with a delayed effect and the mechanism for this delayed effect is unknown, the results of the clinical QT assessment cannot be extrapolated to high clinical exposure scenarios if parent drug is not the only moiety driving the QTc effect. Furthermore, the QTc effect was not characterized after repeat dosing of trilaciclib.

If the major metabolite, M8, accumulates significantly with repeat dosing, we recommend that the sponsor conducts an in vitro hERG assay according to best practices (see ICH S7B Q&A 2.1) for M8. This metabolite represents ~25% of plasma total radiocarbon and could potentially contribute to the observed QT effect.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0002 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) as a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

[redacted] BRAND NAME is associated with dose-dependent and delayed increase in the QTc interval. The underlying mechanism of the delayed QT effect is unknown. At the clinical dose of 240 mg/m^2, BRAND NAME did not have ~~a~~n clinically relevant effect on QTc (i.e., >10 msec). QTc prolongation was observed at higher doses.

Reviewer's comment: *We propose to report the observed delayed and dose-dependent effect on QTc interval. We agree with the sponsor's conclusion regarding the therapeutic dose.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Trilaciclib is a kinase inhibitor under clinical development for [redacted] of chemotherapy-induced myelosuppression in adult patients [redacted] a platinum/etoposide-containing regimen or topotecan-containing regimen for small cell lung cancer. The product is provided as lyophilized powder for intravenous infusion after reconstitution and dilution. The proposed dosing regimen is 240 mg/m^2 as a 30-min IV infusion no more than 4 hours prior to chemotherapy on each day chemotherapy is administered.

The IRT reviewed the QT assessment proposal and draft report previously under IND 119254 (DARRTS 03/28/2019 and 02/21/2020). The dedicated QT study, G1T28-11, is a randomized, double-blind, double-dummy, placebo- and positive-controlled, single-dose, single-period, dose-escalation study of IV trilaciclib in healthy volunteers. At the time of initial protocol review, the sponsor proposed to use concentration-QTcF analysis as the primary analysis for the evaluation of drug effect and assay sensitivity. The IRT recommended an increase in the number of patients receiving moxifloxacin treatment, considerations for potential heart rate effect, and the analysis and reporting according to [redacted] (DARRTS 03/28/2019). Upon review of the sponsor's draft study report, which suggests heart rate increase and delay between PK and QTc changes, the IRT recommended the submission of QT evaluation report along with any datasets to support the additional population PK/PD analysis (DARRTS 03/28/2019). It was also noted that trilaciclib has a major circulating metabolite (M8, a mono-oxidation of trilaciclib) that has a Tmax around 2-hour postdose and an expected accumulation ratio ranging from 1.4–1.7.

The sponsor provided the final study report in the current submission. While the primary analysis remains the same (concentration-QTc analysis of QTcF), the sponsor also presented results for QTcI. In addition, the sponsor conducted nonlinear mixed effect

modeling on QTcF. For assay sensitivity, the primary analysis method was changed to the by-time central tendency analysis.

Highlight of clinical pharmacology:

Trilaciclib shows minimal accumulation upon repeated dosing of 30-min IV infusion. A population PK model predicted the mean Cmax at 240 mg/m^2 of 1430 ng/mL for females and 1390 ng/mL for males. Majority (79%) of the administrated dose was excreted in feces and 14% in urine (1.9% as unchanged drug). Population PK analysis does not suggest a clinical relevant effect by sex, race, renal impairment, or mild hepatic impairment on maximum trilaciclib exposure, and no significant interaction was found with itraconazole and rifampin. A hepatic impairment study is ongoing. According to the sponsor, the high clinical exposure will occur in the Japanese population. In the Japanese PK bridging study, Cmax in Japanese subjects was found to be 140% higher than a typical patient (GeoMean Cmax: 2210 ng/mL). Clinical pharmacology properties of the major metabolite remain largely unknown.

3.1.2 Nonclinical Safety Pharmacology Assessments

The potential for trilaciclib to adversely affect cardiovascular system function was evaluated in an in vitro hERG assay, a dedicated GLP IV cardiovascular safety pharmacology study in surgically instrumented dogs monitored by telemetry, and by ECGs recorded as part of a GLP 7-day repeat-dose IV toxicity study in dogs. Although trilaciclib did inhibit hERG current in vitro with an IC20 of 2.5 μg/mL and IC50 of 9.07 μg/mL (as a reference, unbound Cmax for trilaciclib at 240 mg/m2 dose was approximately 0.4 μg/mL), there was no effect on heart rhythm or corrected QT interval in dogs given single IV doses up to 45 mg/kg or daily IV doses for 7 days at up to 15 mg/kg. Single IV doses of trilaciclib at 15 or 45 mg/kg increased heart rate in dogs, but the increase was dose-related, relatively mild (30 to 60 beats per minute [bpm]), and short-lived, resolving within 1.5 hours at 15 mg/kg and within 3.5 hours at 45 mg/kg.

Reviewer's assessment: *The sponsor evaluated the effects of trilaciclib (G1T28-1) on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report (link) describes the potential effects of trilaciclib on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (35-36^{o}C), using a step-step voltage protocol(a 2 s depolarized pulse to +40 mV from a holding potential of -80 mV, followed by a repolarizing pulse to -50 mV for 1.5 s) that is different from the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (47 ng/mL cispride) inhibited hERG potassium current by (Mean ± SEM; n = 4) 79.6 ± 1.9%. This result confirms the sensitivity of the test system to hERG inhibition. Samples of the test article formulation solutions collected from stocks were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of trilaciclib at all test concentrations were within ± 10.0% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.*

Trilaciclib produced a concentration dependent inhibition of hERG current with a calculated IC50 value of 9.07 μg/mL. The safety margin of trilaciclib against hERG is provided in the following table:

Table 2: Safety Margin of Trilaciclib on hERG Current

	Cmax(ng/mL)	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50(µg/mL)*	*Safety Margin(Ratio)*
Trilaciclib	*1500*	*70%*	*450*	*9.07*	*20x*

The in vivo cardiovascular pharmacology study (link) assessed effects of intravenous infusion (30 min) of Trilaciclib on ECG parameters and cardiovascular hemodynamic in 6 telemetered dogs (3/sex). Each animal received one of the four dosages (0, 5, 15 and 45 mg/kg) using a modified Latin square design, with doses separated by at least 7 days. No PK data was available in this study. In another in vivo study(link), the mean Cmax at 45 mg/kg was 4610 ng/mL which is ~3x of therapeutic exposure in humans (Cmax: 1500 ng/mL). Trilaciclib caused an increase in heart rate of 30 bpm at 15 mg/mL and 45 to 60 bpm at 45 mg/kg. Trilaciclib had no effects on QTc interval. No positive control drug was used in the study.

In another in vivo toxicology study (link), the sponsor evaluated the potential toxicity of trilaciclib in dogs given daily intravenous doses for7-days by a 30-minute infusion at 1, 5, or 15 mg/kg/day and observed for two weeks after the last dose. The system exposures are provided in the following table:

Table 3: Mean system exposure of trilaciclib in dogs

	Males			Females		
Dose (mg/kg/day) =	**1**	**5**	**15**	**1**	**5**	**15**
C_{max} (ng/mL)						
Day 1	134	784	1640	137	660	1460
Day 7	158	646	2060	174	639	1620

The IV administration of trilaciclib at 15 mg/kg resulted in a mean Cmax that is close to human's therapeutic exposure (Cmax was 1500 ng/mL) at day 1 and a mean Cmax that is higher than human's therapeutic exposure at Day 7. Electrocardiograms were recorded on all animals on Days 1 and 7 at a target time of 15 minutes after the completion of infusion. The QTc changes after each dose on Day 1 and Day 7 are summarized in the following table:

Table 4: Effects of trilaciclib on QTc intervals in dogs

	Males				Females			
G1T28-1 Dose (mg/kg) =	**0**	**1**	**5**	**15**	**0**	**1**	**5**	**15**
QTc interval (msec)								
Pretest^	227	229	229	226	230	225	228	225
Study Day 1	223	233	228	229	227	223	227	230
Study Day 7	231	228	227	233	220	230	227	234
Study Day 1 Delta	-4	4	-1	3	-3	-2	-1	5
Study Day 7 Delta	4	-1	-2	7	-10	5	-1	9

Although there were QTc prolongations on Day 1 and Day 7 at dose level of 15 mg/kg, the sponsor concluded that there were no statistically significant differences between groups for QTc interval. No positive control drug was used in the study.

In summary, results from experiments that conducted by sponsor suggest that trilaciclib may acutely interact with hERG channels at the therapeutic exposure level. However, trilaciclib caused no significant QTc prolongations in telemetered dogs given single IV doses up to 45 mg/kg or daily IV doses for 7 days at up to 15 mg/kg. One possibility is

that trilaciclib is a mixed ion channel blocker (e.g. block both hERG and sodium channel). The mechanism of delayed QTc prolongation in clinical study is unknown. However, possible mechanisms that are responsible for the delayed QTc prolongation include metabolite, increase of inward current (e.g., late sodium current) and hERG trafficking inhibition.

3.2 SPONSOR'S RESULTS

3.2.1 QT/RR Correction Method

(b) (4)

[redacted]

.

Reviewer's comment: (b) (4)

[redacted]

As a result, the evaluation of QTc correction methods is invalid.

(b) (4) [redacted] The correction was performed as follows:

(b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

Reviewer's comment: *The method used for correcting the RR interval for hysteresis is based on* (b) (4)

(b) (4)

Of note, the QT and RR values used to derive the hysteresis-corrected QTcI were from (b) (4)

3.2.2 By Time Analysis

The primary analysis for trilaciclib was based on exposure-response analysis. Please see section 3.2.4 for additional details.

Reviewer's comment: *FDA reviewer presented non-parametric descriptive statistics for all intervals (QTc, HR, PR and QRS). By-time analysis results are not interpretable due to small sample size.*

3.2.2.1 Assay Sensitivity

Sponsor's report shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *The sponsor used by-time as the primary analysis for assay sensitivity. By-time analyses of both sponsor and FDA reviewers show that assay sensitivity was established.*

3.2.2.1.1 QT Bias Assessment

Not applicable.

3.2.3 Categorical Analysis

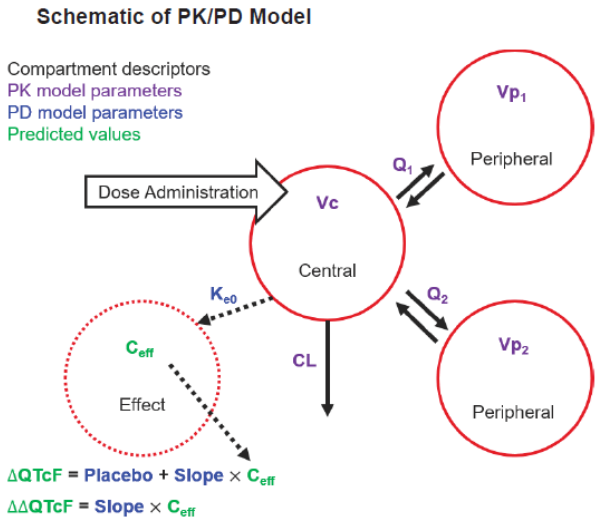
There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results. There were 2 subjects who experienced HR greater than 100 beats/min trilaciclib 440 mg/m^2 dose group. Please see section 4.4 for additional details.*

3.2.4 Exposure-Response Analysis

In the primary analysis, the sponsor conducted linear mixed effect modeling on QTcF. Despite of substantial concentration-QTc hysteresis, the sponsor's analysis suggested a statistically significant positive slope. The model predicted ΔΔQTcF was 5.5 msec (upper 90% CI 9.0 msec) at the highest group Cmax (3928 ng/mL at 700 mg/m^2). The analysis with QTcI also showed PK/PD hysteresis and a positive slope. The model with QTcI predicted an increase of 6 msec (upper 90% CI = 9.7 msec) at the lowest group Cmax (940 ng/mL at a dose of 200 mg/m^2) and 8.1 msec (upper 90% CI = 12.3 msec) at the highest group Cmax (3928 ng/mL at 700 mg/m^2).

In the nonlinear mixed effect modeling, a 3-compartment population PK model was applied to the PK data from this study to derived individual PK parameters of the trilaciclib and an effect compartment was included to describe the QTc changes. The individual ΔQTcF was a function of the placebo response and a linear drug effect based on the effect compartment value (Ceff). The placebo response used a nonparametric model based on nominal time after dose, and sex. An additive inter-individual variability (IIV) term was included on the drug effect slope parameter. An additive residual error model was employed in the PK/PD model. The PD parameters from this QT study was then incorporated in the sponsor's full population PK model (based on multiple studies including this QT study) to simulate QT effect in a typical patient (63.2 years of age, albumin concentration of 39.8 g/L, and BSA of 1.85 m^2). Simulation results suggest that a typical male or female patient receiving a single 30-minute intravenous (IV) dose of 240 or 500 mg/m^2 trilaciclib will likely experience a maximum ΔΔQTcF approximately 4.5 hours after the start of a 30 minute infusion, which is ≤7.7 msec. The upper bound of the 90% confidence interval for the maximum ΔΔQTcF around the mean effect, calculated by considering drug effect model uncertainty only, is 4.7 msec (240 mg/m^2 dose) or 9.8 msec (500 mg/m^2 dose) for a typical male patient, and 5.5 msec (240 mg/m^2 dose) or 11.5 msec (500 mg/m^2 dose) for a typical female patient.



Source: Page 970 of the sponsor's concentration-QTc analysis report (link)

Reviewer's comment:

- *The reviewer agreed with the sponsor that the population PK model adequately described the parent drug exposure in this QT study.*
- *The Pharmacometrics reviewer from the clinical pharmacology review team conducted a separate review and concluded that the sponsor's full population PK model was acceptable.*
- *The reviewer conducted nonlinear mixed effect modeling of QTcI derived from universal correction using the same structure model and different linear model in the effect compartment. Same as that in the sponsor's analysis, the estimate of CI for the predicted ΔΔQTc was calculated based on the 90% CI for the parameter estimate of drug effect slope only. The reviewer's analysis supports the sponsor's conclusion for a lack of clinically relevant effect at the therapeutic dose level. Refer to section 4.5 for details about the reviewer's analysis.*

3.2.5 Safety Analysis

No deaths or SAEs were reported. No TEAEs leading to study discontinuation were reported.

No abnormal individual safety 12-lead ECG results were determined to be clinically significant by the investigator. No ECG results after study drug administration were reported as a TEAE.

Reviewer's comment*: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 Evaluation of the QT/RR Correction Method

The sponsor reported results for both QTcF and hysteresis-corrected QTcI, because an (b) (4) . The reviewer's analysis is based on hysteresis-corrected QTcI using the proposed universal correction for QT/RR Marek et al.[3] and the gamma model ($QTcI = QT + (\beta/\gamma) * (1 - RR^{\gamma})$).[4] For a comparison of the two hysteresis-correction methods, please see Appendix 5.1.

4.2 ECG assessments

4.2.1 Overall

Overall ECG acquisition and interpretation of ECGs extracted in triplicate from Holter recordings in this study appears acceptable.

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[3] Marek et al. *Universal Correction for QT/RR Hysteresis.* Drug Saf 2016;39(6)
[4] Marek et al. *QT/RR curvatures in healthy subjects: sex differences and covariates.* Am J Physiol Heart Circ Physiol 2013;305(12)

4.2.2 QT Bias Assessment

Not applicable.

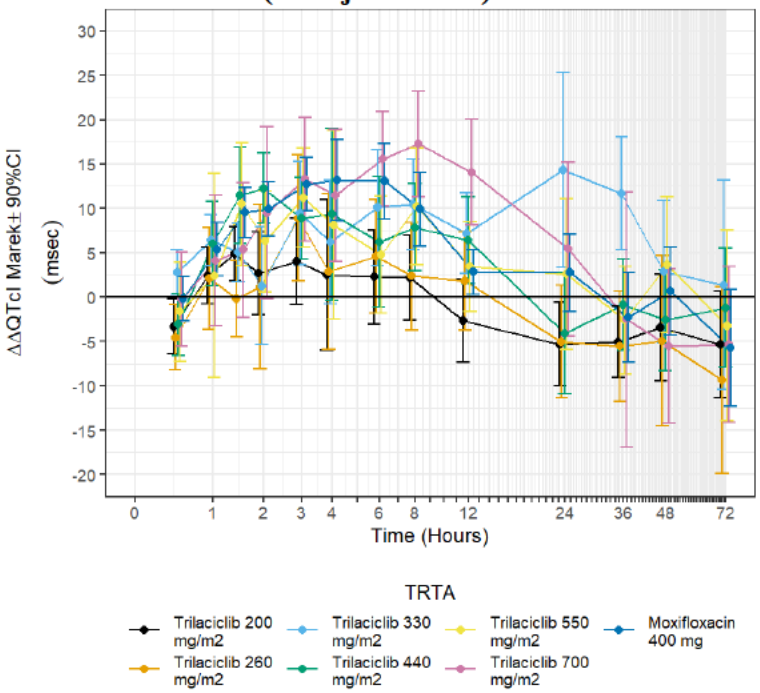
4.3 By Time Analysis

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer evaluated the ΔQTcI, ΔHR, ΔPR and ΔQRS effect using nonparametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcI for different treatment groups.

Figure 1: Median (Treatment), Mean (Moxi) and 90% CI of ΔΔQTcI Time Course (unadjusted CIs).



4.3.1.1 Assay sensitivity

The statistical reviewer used linear mixed model to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcI, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes an unstructured covariance matrix to explain the associated between repeated measures within treatment.

The time-course ΔΔQTcI is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 5).

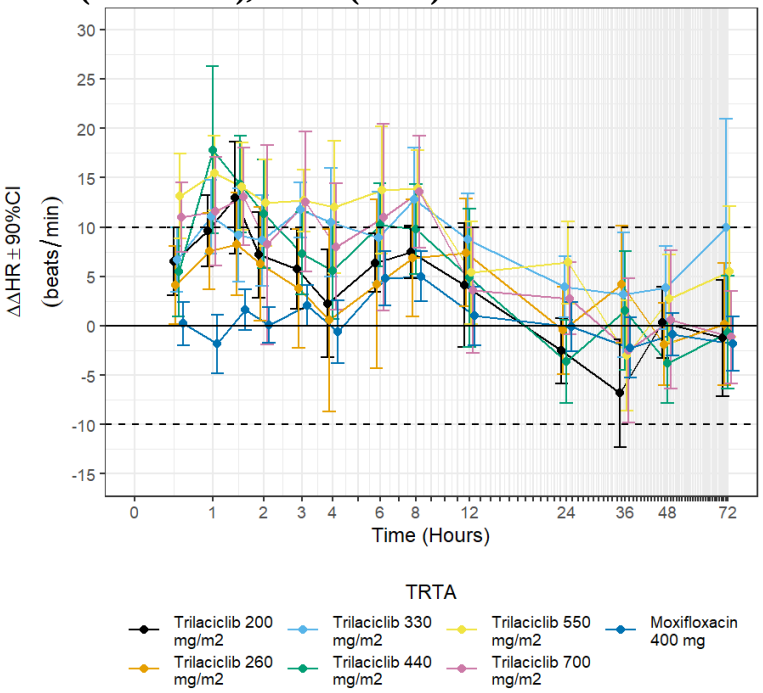
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcI

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCI (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	24 / 18	3.0	12.8	(9.2 to 16.4)	(7.8 to 17.8)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

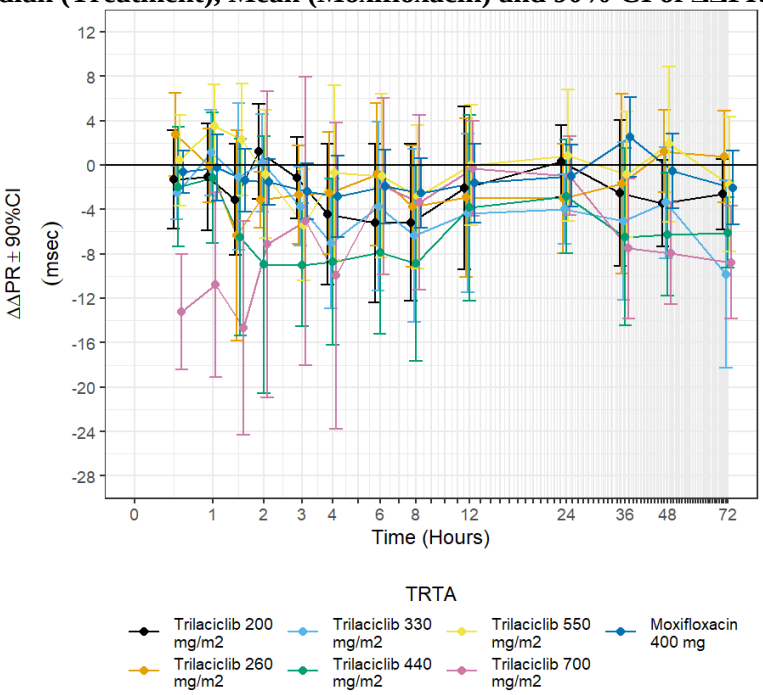
Figure 2: Median (Treatment), Mean (Moxi) and 90% CI of ΔΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

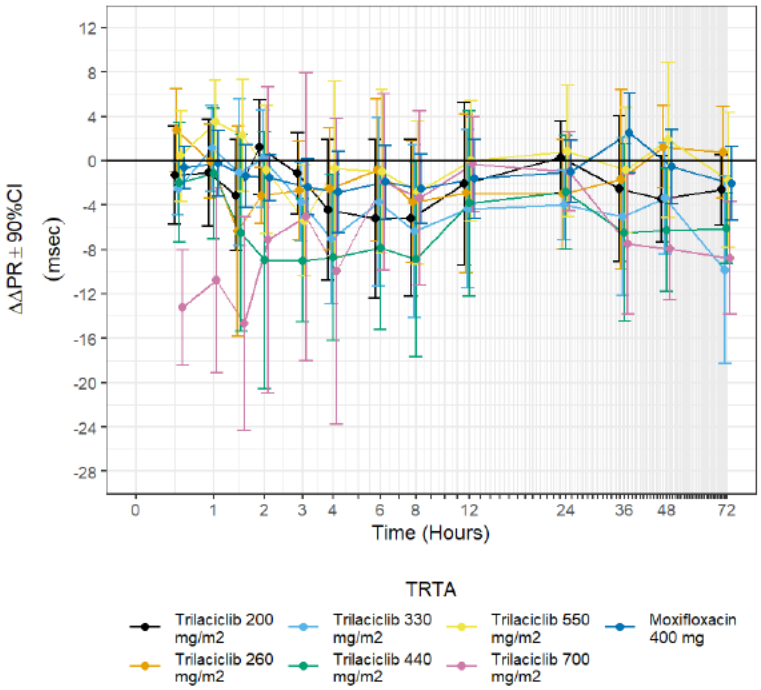
Figure 3: Median (Treatment), Mean (Moxifloxacin) and 90% CI of ΔΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median (Treatment), Mean (Moxifloxacin) and 90% CI of ΔΔQRS Time Course



4.4 Categorical Analysis

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcI greater than 480 msec and/or none of the subjects experienced ΔQTcI greater than 60 msec in any of the trilaciclib dose groups.

4.4.2 HR

Table 6 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were two subjects who experienced HR greater than 100 beats/min in trilaciclib 440 mg/m^2 group.

Table 6: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Trilaciclib 200 mg/m2	6	78	6 (100.0%)	78 (100.0%)	0 (0%)	0 (0%)
Trilaciclib 260 mg/m2	6	78	6 (100.0%)	78 (100.0%)	0 (0%)	0 (0%)

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Trilaciclib 330 mg/m2	6	78	6 (100.0%)	78 (100.0%)	0 (0%)	0 (0%)
Trilaciclib 440 mg/m2	6	78	4 (66.7%)	76 (97.4%)	2 (33.3%)	2 (2.6%)
Trilaciclib 550 mg/m2	6	78	6 (100.0%)	78 (100.0%)	0 (0%)	0 (0%)
Trilaciclib 700 mg/m2	6	72	6 (100.0%)	72 (100.0%)	0 (0%)	0 (0%)
Placebo	18	234	18 (100.0%)	234 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

None of the subjects experienced PR above 220 msec with and without 25% increase over baseline in any of the trilaciclib dose groups.

4.4.4 QRS

None of the subjects experienced QRS above 120 msec with and without 25% increase over baseline in any of the trilaciclib dose groups.

4.5 Exposure-Response Analysis

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTcI using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔΔQTc; and 3) presence of non-linear relationship.

- Figure 2 shows the time-course of ΔΔHR and suggests significant ΔΔHR changes. Therefore, the reviewers used hysteresis-corrected QTcI as the primary endpoint (see section 4.1 of this review).
- Figure 5 evaluates the time-course of drug-concentration and ΔΔQTcI, which shows a delay between peak plasma concentration and changes in ΔΔQTcI. The delay was further quantified by comparing the difference between Tmax and Umax as well as the exposure-normalized Glomb-Ring Index (enGRI)[5] (Table 7), which confirms that a significant delay between peak plasma concentration and changes in ΔΔQTcI. The figure also suggests a trend for dose-dependent increase in QTc and a delay between trilaciclib concentration and heart rate changes.

[5] Ferber et al. Detection and impact of hysteresis when evaluating a drug's QTc effect using concentration-QTc analysis. J Pharmacokinet Pharmacodyn 2020

Figure 5: Time course of drug concentration (top), QTcI (Middle), and HR (bottom)

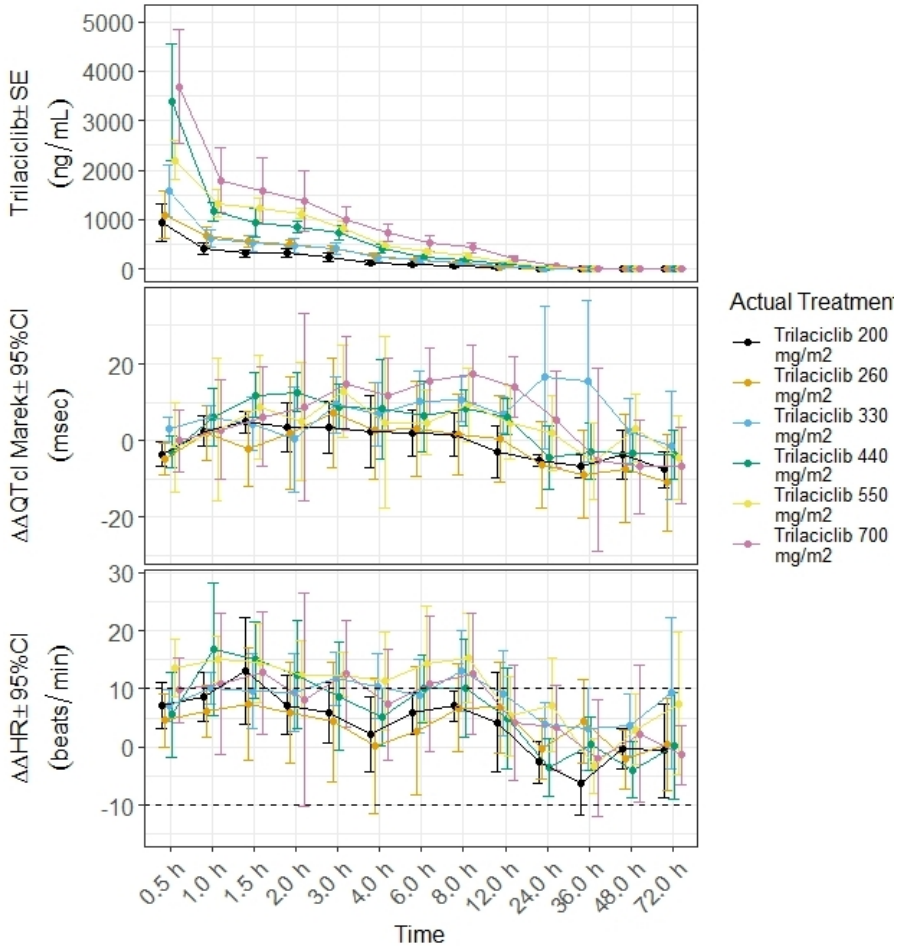


Table 7: Quantitative evaluation of delay

Dose (mg/m^2)	Time-points with mean > 5 ms	Median Tmax (h)	Median Umax[a] (h)	Median difference (h)[b]	enGRI[c] (ms)
200	0	0.5	3.5	3*	2.5
260	1	0.5	2.5	2*	3.3
330	8	0.5	15	14.5*	4.3
440	8	0.5	2	1.5	5.4
550	4	0.5	6	5.5*	5.4
700	8	0.5	9	8.5*	6.1

[a]: Derived from ΔΔQTcI; [b]: One-sided Wilcox test for difference of Tmax and Umax greater than 1 h; [c]: Beginning and end fixed to 0; *P<0.05

Because of the significant, delayed effect between trilaciclib exposure and changes in QTcI interval, linearity check between trilaciclib exposure and ΔQTcI was not proceeded.

The reviewer conducted nonlinear mixed effect modeling based on the dosing information and individual estimates of PK parameters derived from the sponsor's population PK model. An effect compartment model and a direct effect linear model were applied with ΔQTcI as the dependent variable, concentration in the effect compartment model, nominal time point after dose, treatment intercepts (fixed to 0 for Placebo), and centered baseline QTcI as the fixed effect covariates, additive inter-individual variability

on intercept and concentration slope, and additive residual variability. The volume of distribution of the effect compartment is set to be the same as that of the central compartment. In the final model, treatment intercept was fixed to 0 for both placebo and trilaciclib group as the parameter was not estimated with good precision and the removal does not impact overall fitting or the objective function value. In the simulation, QTcI prolonging effect in a typical patient was simulated by multiplying the model predicted concentration in the effect compartment and the slope.

The model fitting and simulation were conducted in NONMEN 7.3. Automation of NONMEM runs and processing were carried out with PsN 6.4, Pinara 2.9.0, Xpose package and R version 3.5.1.

Goodness-of-fit plot and visual predictive check for the model are shown in Figure 6 and Figure 7. Key parameter estimates are shown in Table 8 and the predicted ΔΔQTc in a typical male patient is shown in Table 1. Here are some discussion points about the PK/PD model:

- Because the PK/PD model was constructed based on the assumption of linear PK across all study doses and the assumption that the observed QTcI effect was determined by effect compartment concentration only, the predicted QTcI effect will increase linear with the study dose.
- Under the assumptions for the effect compartment model, plasma concentration of trilaciclib is not a good predictor of drug effect. For example, when the PD parameters are incorporated with the PK model derived from this QT study, the predicted QT values in a typical subject on trilaciclib treatment in this QT study are higher than that in a typical patient despite of lower trilaciclib concentration in plasma (Table 9 vs. Table 1).
- In sensitivity analysis with key PK parameters sampled from prespecified ranges considering extreme covariate effect, the predicted upper bound of 90% CI of maximum QTcI increase is consistently below 10 msec at the 240 mg/m^2 dose level. The conclusion does not hold true at higher dose levels. Under the assumption that trilaciclib is driving the observed QTc effect, the model suggests that a clinically relevant effect can be excluded in the highest exposure scenario known at this stage (geomean Cmax 2210 ng/mL in Japanese subjects).
- The mechanism to the observed delayed effect in QTcI prolongation is not known. Therefore, the prediction of QTc effect in different subject populations should be reviewed with caution. The current modeling practice assumes that parent drug is driving the observed QTc effect and the kinetics of the delayed effect (Ke0) remain constant in different patient populations. However, if the observed effect is driven by the formation of a QT prolonging metabolite and the formation of metabolite is affected by hepatic impairment or DDI, then the rate of clearance into the effect compartment could be different in these populations.

Figure 6: Goodness-of-fit plot for QTcI

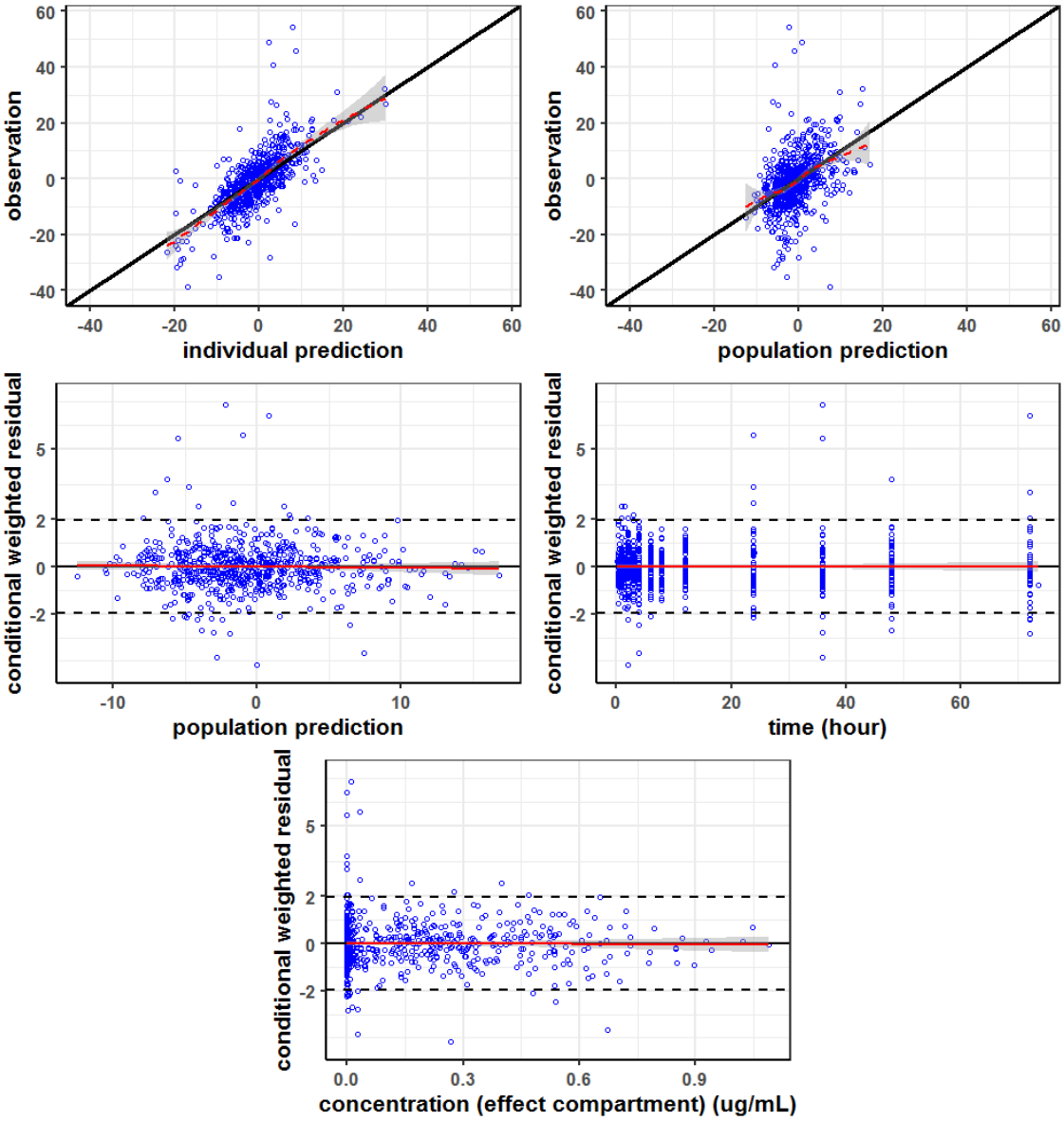


Figure 7: Prediction corrected Visual Predictive Check for QTcI. PBO==1: placebo treatment; PBO==0: drug treatment.

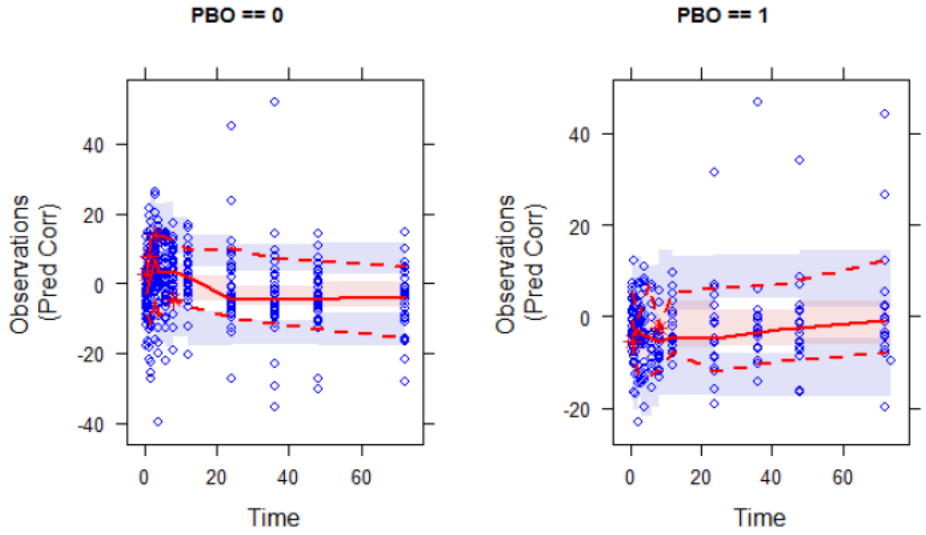


Table 8: Estimate of key parameters from the concentration-QTc model.

	Parameter Estimate	%RSE
Concentration-slope [msec/(ug/mL)]	20.6	29%
Ke0 (hr^{-1})	0.229	24%
IIV on intercept ($msec^2$)	21.7	34%
IIV on slope [$msec^2$/(ug/mL)^2]	288	31%
Residual variability (msec)	7.32	9%

Figure 8: PK/PD profiles in a typical subject.

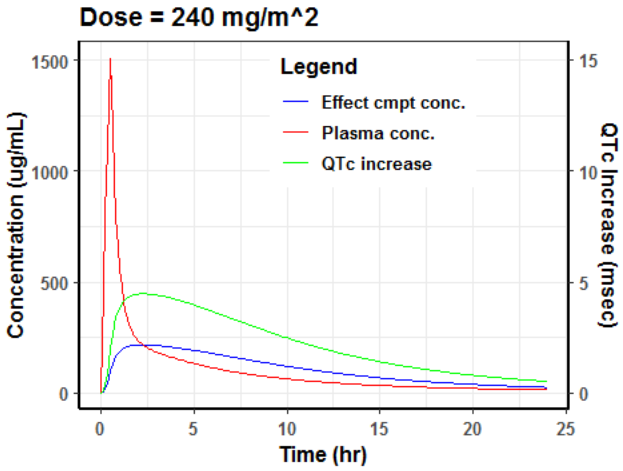


Table 9: Predicted QTcI increases in a typical subject on trilaciclib treatment in this QT study.

ECG parameter	Treatment	Trilaciclib Cmax (ug/mL)	ΔΔQTcI	90% CI
QTc	Trilaciclib 240 mg/m^2	1.3	5.4	(2.8, 8.0)

4.5.1.1 Assay sensitivity

Assay sensitivity was established in the by-timepoint analysis (section 4.3.1.1 of this review) and supported by the concentration-QTc analysis. The time course of QTcI effect in the moxifloxacin treatment arm is shown in Figure 9, the goodness-of-fit plot for moxifloxacin is shown in Figure 10, and the predicted QTcI at the geometric mean Cmax is listed in Table 10.

Figure 9: Time course of moxifloxacin concentration (top) and QTcI (bottom)

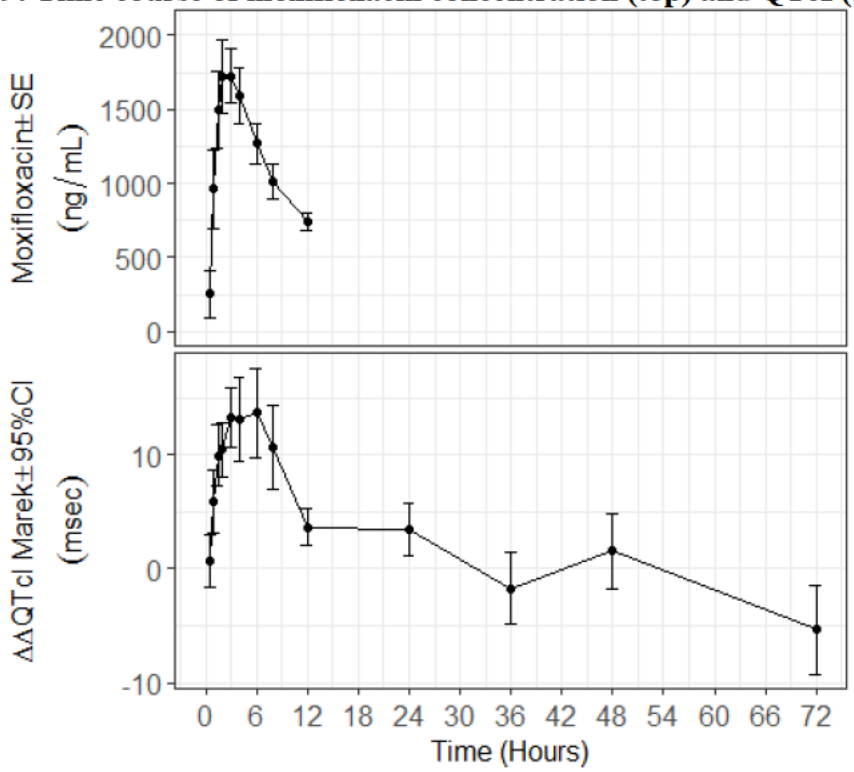


Figure 10: Linearity plot and goodness-of-fit plot for moxifloxacin

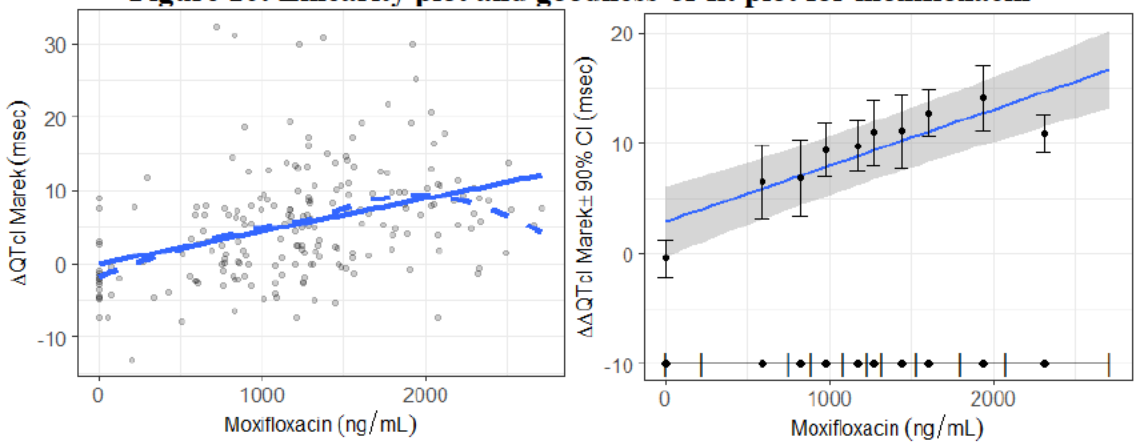


Table 10: Predictions from concentration-QTc model for moxifloxacin

Actual Treatment	Moxifloxacin (ng/mL)	ΔΔQTCI (msec)	90.0% CI (msec)
Moxifloxacin 400mg	1,904.7	1,904.7	1,904.7

4.5.2 HR

A trend for dose-dependent and delayed effect was also observed in the exploratory analysis with HR. The median time to maximum DDHR ranged between 1 (440 mg/m^2) - 10 (330 mg/m^2) hours across different dose groups (2.5 hours in the overall treated population). The plot of ΔHR vs. trilaciclib concentration suggests deviation from linearity in the high concentration ranges.

Linear mixed effect modeling and nonlinear mixed effect modeling were conducted as exploratory analysis. When the default linear mixed effect model (b) (4) was applied to the data, the intercept and concentration slope were statistically significant intercept and the predicted mean effect at the therapeutic dose (Cmax=1430 ng/mL in female subject) was 9.1 bpm (90% CI: 6.8-11.4 bpm). In population PK/PD analysis using a similar structural model for QTcI, the simulated mean increase in HR was 6.9 bpm (upper bound of 90% CI: 8.9 bpm) at the 240 mg/m^2 dose and the time to maximum HR increase occurred at approximately 2-hour postdose in a typical female subject.

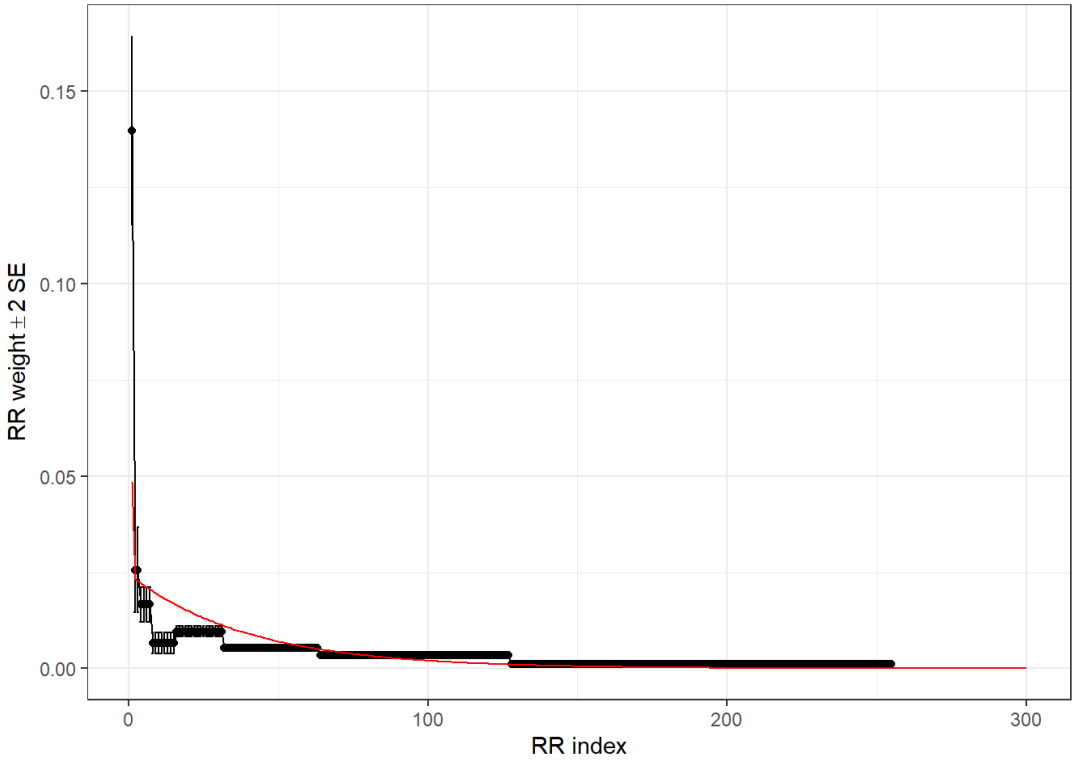
The mechanism behind the observed HR effect is not clear.

5 APPENDIX

5.1 COMPARISON OF COMPUTATION METHODS FOR HYSTERESIS-CORRECTED QTCI

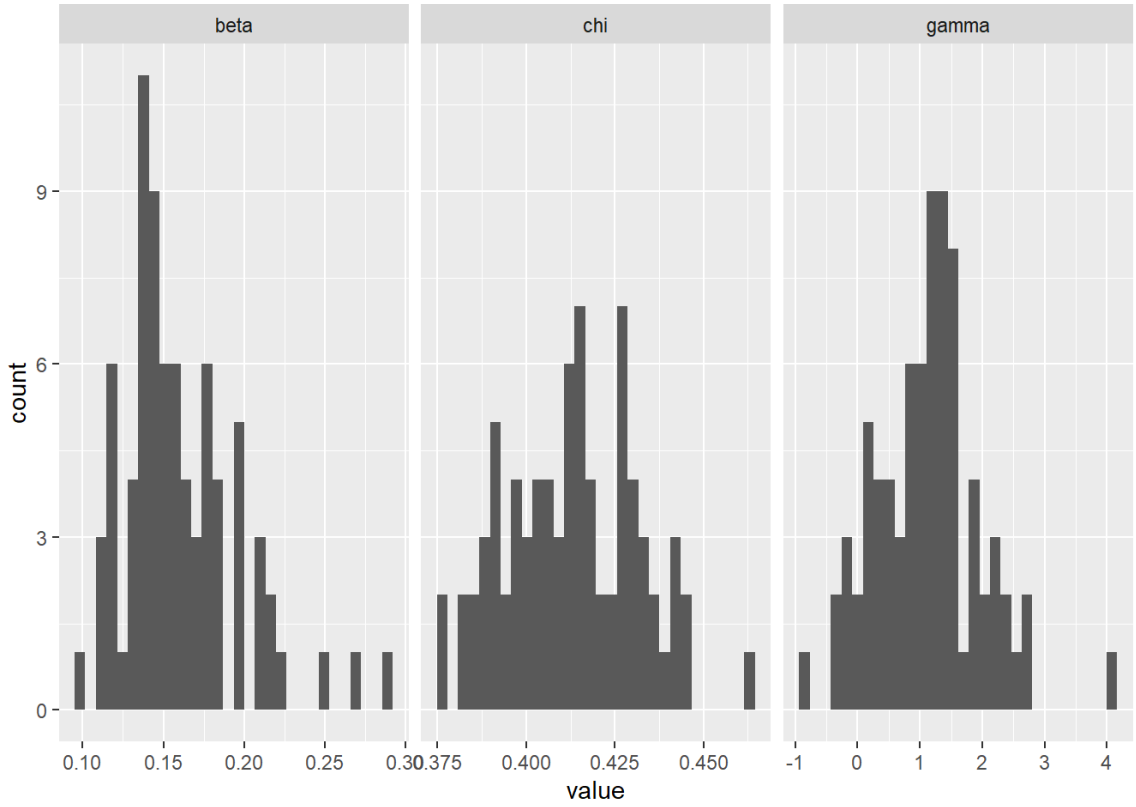
The figure below shows a comparison of the individual RR weight for the method used by the sponsor and Marek's universal QT/RR hysteresis method (by-time weights). The individual weights provided by the sponsor for each RR bin were converted to individual weights by expanding the group and assigning a group weight of bin weight divided by group width. Subsequently, the mean ± 2 SE was calculated per RR index and plotted against RR index (black) compared to the universal QT/RR weights proposed by Marek (in red). This comparison shows that two methods for computing the hysteresis-corrected RR are similar.

Figure 11: Comparison of individual RR weights



The hysteresis-corrected QTcI derived by methodology employed by the sponsor included [redacted] (b) (4) For comparison the figure below shows the parameters of the gamma model ($QTc = QT + \beta/\gamma * (1 - RRc^{\gamma})$) for the hysteresis-corrected RRc obtained via the universal QT/RR hysteresis correction proposed by Marek et al. The distribution of values for the QT/RR curvature (γ) was centered around 1, indicating that the subjects tended to have a linear QT/RR relationship.

Figure 12: Distribution of baseline parameters of QT/RR relationship



5.2 DIAGNOSTIC PLOTS FOR THE EXPOSURE-RESPONSE ANALYSIS FOR HR.

Figure 13: Linearity plot and goodness-of-fit plot ([redacted] (b) (4)) for HR

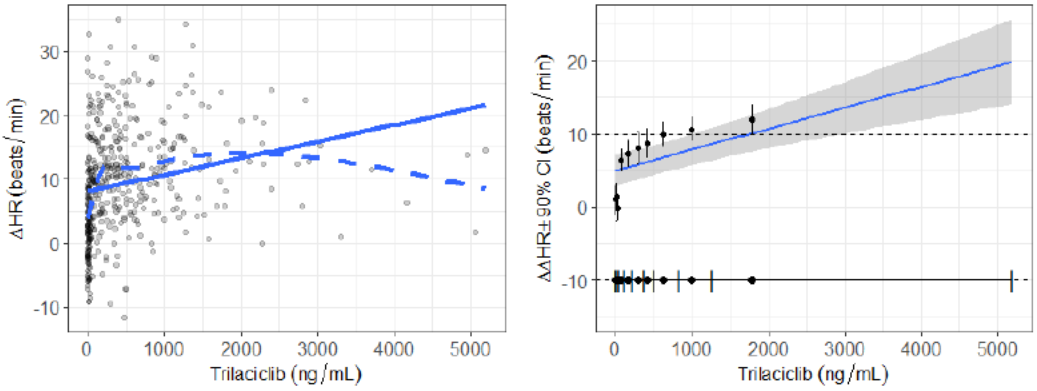


Figure 14: Goodness-of-fit plot (population PK/PD model) for HR

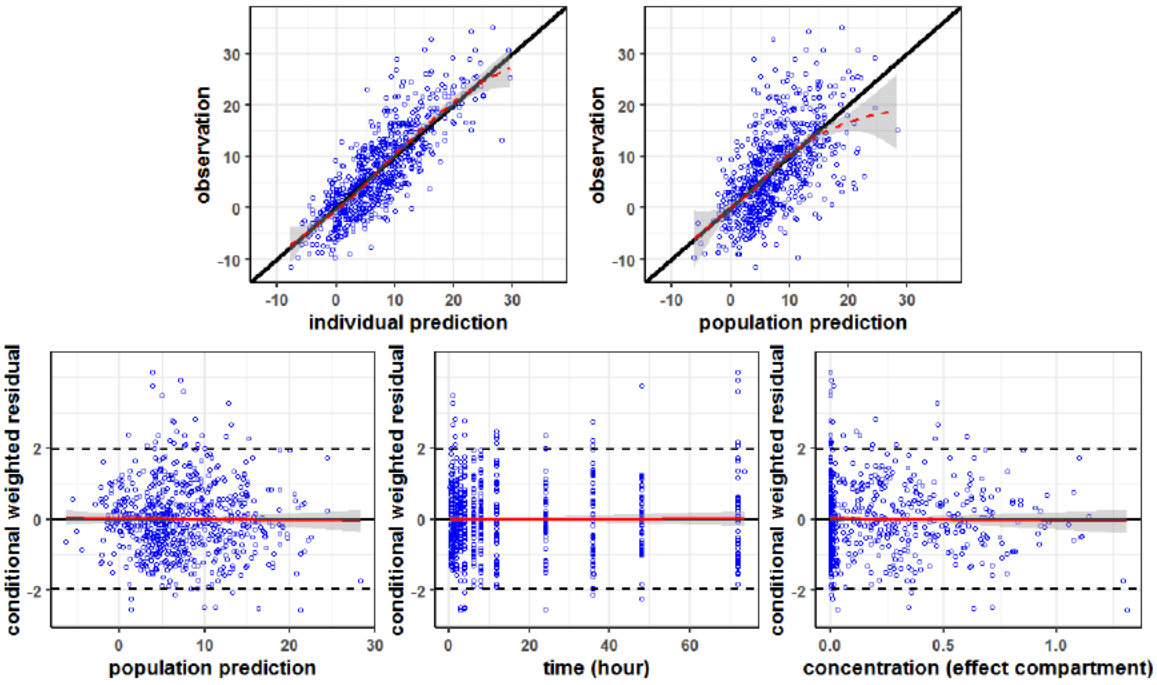
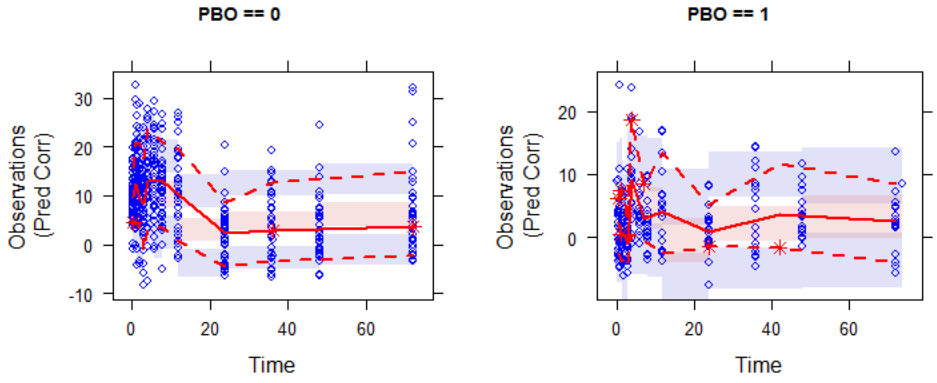


Figure 15: Prediction corrected Visual Predictive Check for HR. PBO==1: placebo treatment; PBO==0: drug treatment.



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Signing on behalf of Mike as he is on leave

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 02, 2020

To: Maureen DeMar, BSN, RN, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRAND NAME (trilaciclib) for injection, for intravenous use (trilaciclib)

NDA: 214200

In response to DNH's consult request dated July 22, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for trilaciclib.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Maureen DeMar) on November 16, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 28, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 13, 2020
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 214200
Product Name, Dosage Form, and Strength:	trilaciclib* for injection 300 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	G1 Therapeutics
FDA Received Date:	June 15, 2020 and September 25, 2020
OSE RCM #:	2020-1259
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

*The proprietary name for this application has not yet been determined; therefore, the product will be referred to by the nonproprietary name, trilaciclib, throughout this review.

1. REASON FOR REVIEW

G1 Therapeutics submitted NDA 214200 trilaciclib for injection on June 15, 2020. Trilaciclib is proposed for [redacted] (b) (4) of chemotherapy-induced myelosuppression in adult patients [redacted] (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for small cell lung cancer. We evaluated the proposed container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for trilaciclib to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, container label, and carton labeling identified areas that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for G1 Therapeutics in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. General Comments
   1. We note some whole numbers are expressed with trailing zeros (e.g., 3.0). We recommend removing all trailing zeros (e.g., 3) to avoid a ten-fold misinterpretation.[a]
   2. We recommend replacing the error-prone abbreviation "IV" wherever it appears with the intended meaning "intravenous" to prevent confusion or misinterpretation.[b]

B. Highlights of Prescribing Information
   1. Dosage and Administration
      a. We recommend revising the recommended dosage statement to improve clarity and to align with the recommended dosage statement in Section 2.1. Revise to read, "The recommended dose of BRAND NAME is 240 mg/m^2 as a 30-minute intravenous infusion (b) (4) 4 hours prior to chemotherapy on each day chemotherapy is administered".
      b. We recommend adding a second bullet point that reads "See Full Prescribing Information for instructions on preparation and administration (2.3)."

   2. Dosage Forms and Strengths
      a. We recommend revising the dosage form and strength statement to read "For injection: 300 mg of trilaciclib as a lyophilized cake in a single-dose vial".

C. Dosage and Administration [2]
   1. Recommended Dosage [2.1]
      a. To improve clarity of the information presented, we recommend revising the dosage information. For example, revise as follows:

The recommended dose of BRAND NAME is 240 mg/m^2 administered as a 30-minute intravenous ~~(IV)~~ infusion (b) (4) 4 hours prior to chemotherapy on each day chemotherapy is administered.

(b) (4)

[redacted]

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf
[b] https://www.ismp.org/tools/errorproneabbreviations.pdf

2. Dose Modification [2.2]
    a. We recommend replacing "0.9% normal saline" and "5% dextrose" with the appropriate terminology. Revise to "0.9% Sodium Chloride Injection, USP" and "5% Dextrose Injection, USP" wherever they appear.
    b. We recommend removing the information about (b) (4) from Table 1 as this information is described in the administration section of Section 2.3.

3. Preparation and Administration [2.3]
    a. To improve clarity of the information presented, we recommend revising the instructions for reconstitution and dilution. For example, revise as follows:

(b) (4)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution of BRAND NAME:

- Calculate the BRAND NAME dose based on the patient's BSA, the total volume of reconstituted BRAND NAME solution required, and the number of BRAND NAME vials needed.
- Reconstitute each 300 mg vial (b) (4) with 19.5 mL of 0.9% Sodium Chloride Injection, ~~United States Pharmacopeia (~~USP~~)~~ or 5% Dextrose Injection, USP to obtain a concentration of 15 mg/mL of trilaciclib ~~.~~ (b) (4)
- Swirl the vial gently until the sterile lyophilized cake is completely dissolved. *Do not shake.* (b) (4)
- Inspect the reconstituted solution for discoloration and particulate matter. Reconstituted BRAND NAME solution ~~is~~ should be a clear, yellow solution. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates.
- If needed, the unused reconstituted solution in the vial can be stored at 20°C to 25°C (68°F to 77°F) (b) (4) for up to 4 hours prior to transfer to the infusion bag. Do not refrigerate or freeze.
- Discard any unused portion after use.

Dilution of Reconstituted BRAND NAME Solution

- Withdraw the required volume from the vial(s) of reconstituted BRAND NAME solution and dilute (b) (4) into an intravenous ~~IV~~ infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. (b) (4) The final concentration of the diluted BRAND NAME solution should be (b) (4) between 0.5 mg/mL and (b) (4) 3.~~0~~ mg/mL.
- Mix diluted solution by gentle inversion. *Do not shake.*
- The diluted BRAND NAME solution for infusion is a clear, yellow solution.
- If not used immediately, store the diluted BRAND NAME solution in the ~~IV~~ infusion bag as specified in Table 2. Discard if storage time exceeds these limits. Do not refrigerate or freeze.

Table 2: Diluted BRAND NAME Solution Storage Conditions (b) (4) (b) (4)

~~IV~~ Infusion Bag Material	Diluent	Diluted BRAND NAME Storage Duration[a]
Polyvinyl chloride (PVC), Ethylene vinyl acetate (EVA), Polyolefin (PO), or Polyolefin/polyamid (PO/PA)	5% Dextrose for Injection, USP	Up to 12 hours at 20°C to 25°C (68°F to 77°F)
PVC, EVA, or PO	0.9% Sodium Chloride Injection, USP (b) (4)	Up to 8 hours at 20°C to 25°C (68°F to 77°F)
PO/PA	0.9% Sodium Chloride Injection, USP (b) (4)	Up to 4 hours at 20°C to 25°C (68°F to 77°F)

[a] To ensure product stability, do not exceed specified storage durations.

Administration

- Administer diluted BRAND NAME solution as a 30-minute ~~IV~~intravenous infusion (b) (4) (b) (4) 4 hours prior to chemotherapy. (b) (4)
- Diluted BRAND NAME solution must be administered with an infusion set, including an in-line filter (0.2 or 0.22 micron). Compatible in-line filters include polyethylene sulfone, polyvinylidene fluoride, and cellulose acetate.
- Do not administer diluted BRAND NAME solution with a polytetrafluorethylene (PTFE) in-line filter. PTFE in-line filters are not compatible with diluted BRAND NAME solution.
- Do not co-administer other drugs through the same infusion line.
- Do not co-administer other drugs through a central access device unless the device supports co-administration of incompatible drugs.
- Upon completion of infusion of diluted BRAND NAME solution, the infusion line/cannula must be flushed with at least 20 mL sterile 5% Ddextrose Injection, USP or 0.9% Ssodium Cehloride Injection, USP (b) (4)

4. How Supplied/Storage and Handling [16]
   a. We recommend revising the how supplied statements to read "BRAND NAME (trilaciclib) for injection is a yellow lyophilized cake supplied in a single-dose vial. Each carton (NDC 73462-101-01) contains one 300 mg single-dose vial.

4.2 RECOMMENDATIONS FOR G1 THERAPEUTICS

A. General Comments for All Labels and Labeling

1. The "O" in the proprietary name is presented as (b) (4) that may decrease the readability of the name. Misinterpretation of the letters within the name may contribute to product selection medication errors. We request that you revise the presentation of the proprietary name so that the letters are legible and not open to potential misinterpretation.

2. As currently presented the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name considering all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

3. We recommend unbolding the "Rx Only" statement so that it does not compete in prominence with other critical information on the principal display panel (PDP).

4. To ensure consistency with the Prescribing Information, we recommend revising the prescribing information statements on the vial and the carton to read "Recommended Dosage: see prescribing information".

B. Container Label

1. We recommend revising "(b) (4)" to read "For Intravenous Infusion After Reconstitution and Dilution" as space will allow to ensure this information is not overlooked.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for trilaciclib received on June 15, 2020 from G1 Therapeutics

Table 2. Relevant Product Information for trilaciclib	
Initial Approval Date	N/A
Active Ingredient	trilaciclib
Indication	(b) (4) chemotherapy-induced myelosuppression in adult patients (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for small cell lung cancer
Route of Administration	intravenous infusion
Dosage Form	for injection (lyophilized powder)
Strength	300 mg/vial
Dose and Frequency	240 mg/m^2 as a 30-minute intravenous infusion no more than 4 hours prior to chemotherapy on each day chemotherapy is administered
Preparation	Reconstitution: Add 19.5 mL of 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP into each 300 mg vial being reconstituted. Swirl the vial gently until the sterile lyophilized cake is completely dissolved. The final reconstituted concentration in each vial is 15 mg/mL. Dilution: Withdraw the required volume from the vial(s) of reconstituted BRAND NAME solution and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted BRAND NAME solution should be no less than 0.5 mg/mL and no more than 3 mg/mL.
How Supplied	300 mg of trilaciclib as a sterile, preservative-free, yellow, lyophilized cake in a single-dose vial for reconstitution and further dilution
Storage	Store vials at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. After reconstitution and dilution, the solution may be stored at room temperature for up to 4, 8, or 12 hours depending the diluent used and the infusion bag material.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,[c] along with post-market medication error data, we reviewed the following labels and labeling submitted by G1 Therapeutics:

- Container Label received on June 15 and September 25, 2020
- Carton Labeling received on June 15 and September 25, 2020
- Prescribing Information (no image shown) received on June 15, 2020
  \\cdsesub1\evsprod\nda214200\0002\m1\us\m1-14-1-3-draft-pi.docx

G.2 Labels and Labeling

Container Label

(b) (4)

[redacted]

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.
[d] Park, L. Correspondence: Proprietary Name Denied. 2020 SEP 11. Available at:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805951b3&_afrRedirect=572129448744462

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Division of Nonmalignant Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	[redacted] (b) (4) (trilaciclib) for injection, for intravenous use
Applicant	G1 Therapeutics, Inc.
Application/Supplement Number	NDA 214200
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	[redacted] (b) (4) is a kinase inhibitor indicated [redacted] (b) (4) chemotherapy-induced myelosuppression in adult patients [redacted] (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for small cell lung cancer.
Date FDA Received Application	6/15/2020
Review Classification (Priority/Standard)	Priority
Action Goal Date	02/15/2021
Review Date	10/08/2020
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: The Applicant has submitted an application for trilaciclib, an NME, for the proposed indication "[redacted] (b) (4) chemotherapy-induced myelosuppression in adult patients [redacted] (b) (4) a platinum/etoposide-containing regimen or topotecan-containing regimen for small cell lung cancer".

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

Reviewer Comments: I have reviewed the draft labeling and edited it to be consistent with regulations, guidances, and current labeling practices. This review is conducted prior to the first multidisciplinary labeling meeting. Further edits may be suggested by the review team during labeling meetings.

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions.

24 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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CLINICAL INSPECTION SUMMARY

Date	September 15, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew Dmytrijuk, M.D., Medical Officer Kathy Robie Suh, M.D., Ph.D., Team Leader Ann Farrell, M.D., Division Director Charlene Wheeler, Regulatory Project Manager Division of Nonmalignant Hematology (DNH)
NDA	214200
Applicant	G1 Therapeutics, Inc.
Drug	(b) (4)™ (trilaciclib)
NME	Yes
Division Classification	Cell cycle inhibitor
Proposed Indication	(b) (4) chemotherapy-induced myelosuppression in adult patients with small cell lung cancer
Consultation Request Date	July 28, 2020 (Priority Review)
Summary Goal Date	November 15, 2020
Action Goal Date	November 15, 2020
PDUFA Date	June 15, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators (Davey Daniel, M.D., and David Spigel, M.D.) were inspected in support of NDA 214200.

A remote record review was conducted for one clinical investigator (Jerome Goldschmidt, M.D.) due to the COVID-19 pandemic travel restriction.

Study data derived from the above investigators' clinical sites, based on the results of the inspections and remote investigation, are considered reliable for Study G1T28-05. Data are acceptable in support of this application and consistent with Good Clinical Practice.

II. BACKGROUND

Trilaciclib is a cell-cycle inhibitor that transiently maintains immune cells and haemopoietic stem and progenitor cells in G1 arrest. By protecting the immune cells and bone marrow from chemotherapy-induced damage, trilaciclib, a cyclin-dependent kinase (CDK) 4 and 6 transient inhibitor, has the potential to minimize myelotoxicity.

Three Phase 1b/2A studies and one Phase 2 randomized placebo-controlled study (Study G1T28-05) were submitted to the Agency in support of trilaciclib for (b) (4) of chemotherapy-induced myelosuppression.

Study G1T28-05, in part, will form the basis for the regulatory decision-making process for this application.

Study G1T28-05

Study G1T28-05 was a Phase 2, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of trilaciclib or placebo in patients being treated with etoposide, carboplatin, and atezolizumab for newly diagnosed extensive-stage SCLC. Patients were randomly assigned in a 1:1 fashion to trilaciclib 240 mg/m2 or placebo administered intravenously once daily on Days 1 to 3, with therapy for up to four 21-day cycles (Induction). Randomization was stratified by Eastern Cooperative Oncology Group performance status (fully active or ambulatory and able to carry out work of a light or sedentary nature versus ambulatory and capable of all self-care but unable to carry out any work activities) and presence of brain metastases. The primary study objective was to evaluate the potential of trilaciclib compared with placebo to reduce chemotherapy-induced myelosuppression in patients with small cell lung cancer.

The primary efficacy endpoint was the duration of severe neutropenia in treatment Cycle #1 and the occurrence of severe neutropenia.

Study G1T28-05 was conducted at 56 study centers in the U.S., Spain, France, Bulgaria, Estonia, Latvia, Ukraine and Georgia. The first patient was enrolled on June 29, 2017 and the last patient observed for the clinical study report was on June 28, 2019. A total of 107 subjects were enrolled.

Rationale for Site Selection

DNH requested inspection of three domestic clinical study sites with high patient enrollment. The sites also had significant pertinent results, with a potential impact to the application decision-making.

III. RESULTS (by site)

1. **Davey B. Daniel, M.D./ Site 1221**
   605 Glenwood Dr, Ste 200Chattanooga, TN 37404

   Inspection dates: August 24 to 27, 2020

Five screened study subjects enrolled in the study. No subjects completed the study, all were discontinued. Four study subjects discontinued due to disease progression and one patient discontinued due to an adverse event.

(b) (4) served as the governing board during the study's initiation. (b) (4) .

Source documents were reviewed for study eligibility, review/approval, monitoring, test article accountability, concomitant medication, and adverse event/serious adverse event reporting; radiology documents such as imaging. Records review of the five screened and enrolled study participants indicated that the eligibility criteria for enrollment were met. There were no limitations during conduct of the clinical investigation.

Source records utilized a combination of paper and electronic records. Paper source records included original informed consent forms, lab requisitions, subject completed questionnaires, and ECG printouts. Study visits notes, laboratory reports, and all other research chart information were included in the site's electronic medical record system ((b) (4)).

The study was managed by (b) (4), a site management organization. Physicians at Tennessee Oncology (formally Chattanooga Oncology) contract with (b) (4) to provide research staff and review potential studies. The relationship between Tennessee (TN) Oncology and (b) (4) began approximately 15 years ago.

The primary efficacy data endpoint was verifiable at the study site for investigator-assessed treatment response. There was no under-reporting of adverse events. At the end of the inspection, one discrepancy found in the investigational (IP log) was discussed and corrected during the inspection.

2. Jerome Goldschmidt, M.D./ Site 1215
Oncology and Hematology Associates of Southwest Virginia, Inc.
2600 Research Center Drive, Suite A
Blacksburg, VA 24060

Remote Site Investigation dates: August 17 to 21, 2020

A remote record review was conducted due to the COVID-19 pandemic travel restriction. During the investigation, video conferencing via WebEx, document sharing via an online platform (box.com), and read-only access to the online electronic medical records were utilized to exchange information.

A total of eight participants were screened. Seven study patients were enrolled and completed the study.

Source documents were reviewed for study eligibility, informed consent, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. Records review of the eight screened subjects indicated that the eligibility criteria for enrollment were met. The Institutional Review Board (IRB) was administered by (b) (4) .

Source documents were verified against the case report forms and sponsor data line listings. There were no limitations during conduct of the clinical site inspection.

The principal efficacy raw data endpoint was verifiable. There was no under-reporting of adverse events.

3. David Spigel, M.D./Site 1030
Tennessee Oncology PLLC
250 25th Ave. N., Suite 100
Nashville, TN 37203

Inspection dates: August 17 to 25, 2020

A total of seven subjects consented for the study, and five study subjects were enrolled. Four study patients completed the study. A single study subject continues on active treatment.

Source documents were reviewed for study eligibility, informed consent and delegation of authority. Records review of the screened study patients indicated that the eligibility criteria for enrollment were met.

(b) (4) was the initial approving body for the G1 Therapeutics study. (b) (4) .

Electronic records, created, captured, and maintained with several electronic record systems were verified for this study. Monitoring and safety event reporting was conducted by (b) (4) Continuous monitoring of the site during the study was found to be adequate. Investigational agent accountability records for drug vials were reviewed and verified. Labeling information was verified as consistent with those labels documented in the subject CRFs.

Source documents were verified against the case report forms and sponsor data line listings. The onsite audit also reviewed the following and found to be adequate: protocol deviations, primary efficacy endpoints and serious adverse events.

There were no limitations during conduct of the clinical site inspection. At the end of the inspection, undocumented minor protocol deviations for the collection of pre-infusion and

post-infusion vital signs and verification/traceability of laboratory collection procedures were discussed.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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MIN LU
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KASSA AYALEW
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