CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208712Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	October 13, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	208712
Product Name and Strength:	Vonjo (pacritinib) capsules, 100 mg
Applicant/Sponsor Name:	CTI Biopharma
OSE RCM #:	2016-113-1
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 22, 2021 for Vonjo. We reviewed the revised container label and carton labeling for Vonjo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Rezvani, N. Label and Labeling Review for Vonjo (208712). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 10. RCM No.: 2016-113.

Reference ID: 4871681

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 22, 2021

Container labels

Carton labeling

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HINA S MEHTA
10/13/2021 02:39:31 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-208712
Submission Number	013 (New NDA)
Submission Date	3/30/2021
Date Consult Received	4/9/2021
Drug Name	Pacritinib
Indication	Treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
Therapeutic dose	200 mg twice daily
Clinical Division	DNH

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 4/9/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-078406 dated 09/28/2010 in DARRTS (link);
- Previous IRT review for IND-078406 dated 01/19/2011 in DARRTS (link);
- Previous IRT review for IND-078406 dated 09/29/2014 in DARRTS (link);
- Sponsor's clinical study protocol # PAC107 (SN0002; link);
- Sponsor's statistical analysis plan # PAC107 (SN0002; link);
- Sponsor's QT assessment report # PAC107 (SN0002; link);
- Sponsor's clinical study report # PAC107 (SN0002; link);
- Sponsor's clinical study protocol # PAC203 (SN0012; link);
- Sponsor's clinical study protocol # PAC203 (SN0012; link);
- Investigator's brochure V13.0 under IND-078406 (SN0638; link);
- Sponsor's proposed product label (SN0012; link); and
- Highlights of clinical pharmacology and cardiac safety (Appendix; SN0013; link).

1 SUMMARY

The risk of QT prolongation associated with oral administration of pacritinib is not adequately characterized in the thorough QT study (Study # PAC107). This was a phase-I, randomized, double-blinded (partially), placebo- and positive-controlled, (3-period) crossover study. The study evaluated QT effects of pacritinib using a 400 mg single dose. The peak concentration (Cmax: ~3774 ng/mL) observed with the studied dose is not expected to cover the therapeutic exposures (Cmax: ~9400 ng/mL; POP-PK) associated with the proposed dose at the steady state (i.e., 200 mg twice daily).

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Since the TQT study cannot be used for QT assessment, we evaluated the QTc effects in Study #PAC203 which was performed in patients with primary or secondary myelofibrosis. In this study, 12-lead ECGs, collected in triplicate, were performed for all patients, at 1 hour pre-dose and 4 hours post-dose on Day 1 of Week 1 and the end of Weeks 4, 12, and 24. In 54 subjects receiving 200 mg pacritinib BID, the largest mean increase in QTc was 11 (90% CI: 5.3 – 16.7) msec. The increase in QTc was not dose or concentration dependent (Figure 10). Two patients (3.7%) had post-baseline QTcF > 60 msec above baseline. None of the patients had QTcF > 500 msec. One subject had a grade 3 syncope event with prolonged QTcF (QTcF 491 msec, versus 423 to 435 msec at Screening; range of 418 to 436 msec prior to event).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

1. In study PERSIST-2 which included safety ECGs, subjects on both pacritinib arms had slightly higher proportions of subjects with QTc increases than the BAT arm. The worst QTc interval was >500 msec in 3/210 (1.4%) pacritinib QD + BID pooled arms, and 1/98 (1.0%) BAT subjects. Worst QTc was >60 msec above baseline in 4/210 (1.9%) pacritinib QD + BID pooled arms and 1/98 (1.0%) BAT subjects. TEAEs of QTc prolongation were reported for 8/210 (3.8%) in the pacritinib QD + BID pooled arms and 2/98 (2.0%) subjects in the BAT arm.
2. Given the mechanism to inhibit hERG and the increase in QTc in Study PAC203 at the therapeutic dose, we recommend that the label includes Warnings and Precautions for QTc prolongation:
    - The percent of patients who had an absolute QTc value of greater than 500 msec during treatment in the safety database.
    - The percent of patients in which their QTc interval increased from baseline of 60 msec or higher in the safety database.
    - The steps to be taken to prevent or mitigate the risk of QTc interval prolongation or clinically relevant adverse reactions associated with QTc interval prolongation (e.g., assess QTc interval and electrolytes, correct serum electrolyte abnormalities, avoid concomitant use of drugs to prolong QTc interval).
    - The potential effect of drug interactions (such as cytochrome P4503A inhibitors) on the ability of pacritinib to prolong the QTc interval.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The sponsor only included QT labeling in Section 12.2 Pharmacodynamics. Below are proposed edits to the label submitted to SN0012 (link). Our changes are highlighted

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(*addition*, ~~*deletion*~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

In a 24-week study of 54 patients with MF treated with VONJO 200 mg twice daily, the maximum mean (90% confidence interval) change in QTcF from baseline was (b) (4) *11 (90% CI: 5 – 17) msec.* (b) (4)

(b) (4)

we recommend that QTc effects observed in patients taking 200 mg BID from Study PAC203 are only described.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

CTI BioPharma Corp. is developing pacritinib for the treatment of patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (adult population). Pacritinib (Vonjo®, (b) (4) SB1518, citrate salt; MW: 472.59 as a free base) is a kinase inhibitor with activity against Janus Associated Kinase 2, interleukin-1 receptor-associated kinase 1, colony-stimulating factor 1 receptor, and Fms-like receptor tyrosine kinase 3.

The product is formulated as immediate-release capsule formulation containing 100 mg pacritinib (as free base) for oral administration. The maximum proposed therapeutic dose for the present indication is 200 mg twice daily (for patients with a baseline platelet count of less than 50×10^9/L). The peak concentrations of ~9400 ng/mL (Tmax: 2 to 8 h; half-life: ~35 h) are expected at steady-state with the proposed therapeutic dose in MF patients (POP-PK Predicted). Considerable accumulation is expected at steady-state with the proposed maximum therapeutic dose (Cmax Racc: ~2.64; POP-PK). The maximum studied dose is 600 mg once daily (Cmax: ~9225 ng/mL; Study # SB1518-2007-001).

The studies indicate that pacritinib is extensively metabolized (mainly by CYP3A4) forming several metabolites (M1, M2, M3, M5, M6, M7, M8, M9, M12, M13, M14, M14a, M15 etc). M1 (~9.6% of parent; Tmax: 2 to 6 h; half-life: ~16.5 h) and M2 (~10.5% of parent; Tmax: 2 to 24 h; half-life: ~16 h) were considered as major metabolites. Concomitant administration of pacritinib with a strong inhibitor of CYP3A4 is expected to result in increased exposures of pacritinib (Cmax: ~1.3-fold & AUC: ~1.8-fold; Study # PAC104). No dose adjustment is proposed by the sponsor for concomitant administration of pacritinib with inhibitors of CYP3A4. The human mass balance study indicates that

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~85.5 (as TR) of the drug is excreted in feces, and 3.22% (as TR) in urine (Study # PAC102). Pacritinib peak plasma concentration and total plasma exposure were slightly higher (Cmax: ~1.32-fold) for subjects with renal impairment compared to healthy subjects (Study # PAC105). There was no significant increase in pacritinib exposure (Cmax: ~47% decrease) in subjects with hepatic impairment compared to healthy subjects (Study # PAC103). No dose adjustment is proposed by the sponsor for administration of pacritinib in subjects with hepatic impairment or renal impairment.

Previously, the IRT reviewed the sponsor's thorough QT study protocol (Study # PAC107). This was a phase-I, randomized, double-blinded (partially), placebo- and positive-controlled, (3-period) crossover study evaluating the effect of pacritinib on the QT/QTc interval in healthy subjects (n=42/44). Subjects were planned to receive 3 treatments (400 mg pacritinib, placebo, and 400 mg moxifloxacin, open label) in a crossover design. Refer to previous IRT reviews for IND-078406 dated 09/28/2010 (link), 01/19/2011 (link), and 09/29/2014 (link) in DARRTS. The sponsor proposed 400 mg once daily dosing claiming that there is no considerable accumulation with multiple dosing. Previous review described the requirement of exposure coverage for all relevant intrinsic and extrinsic factors with the final proposed doses (Dt: 09/29/2014). The peak concentration (Cmax: ~3774 ng/mL) observed with the studied dose (i.e., 400 mg single dose) is not expected to cover the therapeutic exposures (Cmax: ~9400 ng/mL; POP-PK) associated with the maximum proposed dose at the steady state. Considering that the risk of QT prolongation of pacritinib is not adequately characterized in the thorough QT study and administration of pacritinib is associated with cardiac events, we evaluated ECG data from Study # PAC203 (Section 4.6).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety. The expected peak concentrations of ~9400 ng/mL (Free: ~239 nM; PPB: ~98.8%) at steady-state with twice daily dosing of 200 mg offers ~8-fold margin (hERG IC50 ~1.84 μM). The hERG data for metabolites are not included in the submission.

In-vitro hERG binding: Binding of pacritinib to binding of pacritinib to hERG in human recombinant HEK-293 cells in a radioligand assay indicated that pacritinib inhibited hERG function in vitro with an IC50 of 3.51 μM However, given the high plasma protein binding observed for pacritinib in humans (98.8%), the steady-state plasma concentrations of free pacritinib achieved at the top clinical dose (200 mg BID) are estimated to be ~254 nM which would be more than 10-fold lower than the concentration expected to exert a significant effect on the hERG channel.

A functional in-vitro electrophysiology voltage clamp assay was conducted to characterize the effects of pacritinib on 13 major ion channels that influence ventricular action potential duration and regulate heart rate. The study results demonstrated that pacritinib only inhibited hERG channel (IC50 1.84 μM) at clinically relevant concentrations. Given the high plasma protein binding observed for pacritinib in humans (98.8%), the mean peak plasma concentration of free pacritinib achieved at steady state at the top clinical dose level in the PAC203/326 trial (200 mg BID) is estimated to be approximately 254 nM. This concentration corresponds to an approximate around 7.3-fold safety margin for inhibitory effects on the hERG channel.

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Cardiovascular effects in conscious dogs:

GLP-compliant safety pharmacology study was conducted to evaluate cardiovascular systems of conscious Beagle dogs after a single oral dose with 30 mg/kg pacritinib free base. there were no treatment-related effects with respect to ECG parameters, heart rate, blood pressure, respiratory rate, body temperature or serum chemistry parameters. Also, cardiovascular effects were assessed in a 39 week repeat dose toxicity study in which dogs were treated with pacritinib at doses up to 10 mg/kg (pacritinib free base), bid for 39 weeks. it was concluded that pacritinib showed no effect on any qualitative and quantitative ECG parameters during repeat administration in a 39 week repeat dose toxicity study in the dog and therefore, a cardiac safety concern cannot be deduced from this study.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

By-time is the primary analysis for this review. Pacritinib excluded the 10 msec threshold at the 400 mg dose level for ΔΔQTcF. Sponsor also presented by-time analysis for other intervals.

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that assay sensitivity was established by the moxifloxacin arm.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (>100 beats/min), 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.*

3.2.3 Exposure-Response Analysis

In addition to primary by-time analysis, the sponsor performed PK/PD analysis to explore the relationship between plasma concentration of pacritinib (and its M1 metabolite) and ΔΔQTcF (placebo corrected, change from baseline in QTcF) using a linear mixed-effects approach. The sponsor's analysis did not indicate a significant positive relation between plasma concentration of pacritinib and QT interval with slope of -1.21×10^{-3} msec per ng/mL (90% CI: -1.79 to -0.64; intercept of 0.46 msec). The model predicted ΔΔQTcF (upper confidence interval) values of -4.12 (-2.05) msec at the mean peak concentrations for the studied dose (400 mg single dose; geomean Cmax ~3780 ng/mL). The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the studied dose.

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Reviewer's comment: *The peak concentration observed with the studied dose is not expected to cover the therapeutic exposures associated with the maximum proposed dose at the steady state. Thus, the study is not adequate for characterization of QT prolongation risk of pacritinib. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

In this 3-period crossover study, a total of 41 of 42 subjects received a single dose of each study medication. There were no deaths, SAEs, or AEs of special interest reported during the study. No subjects discontinued treatment due to an AE.

Overall, 18 subjects experienced a TEAE after receiving pacritinib, while TEAEs were reported in 9 subjects each for placebo and moxifloxacin treatments. The most commonly reported TEAEs following pacritinib administration were classified as GI disorders; specifically, diarrhea (29.3%) and nausea (12.2%) were the most frequently reported AEs. Most TEAEs in this study resolved without concomitant therapy. The majority of AEs were Grade 1 and related to the GI system. There were no trends or clinically significant findings observed in clinical laboratory tests, vital signs, physical examinations, or ECG assessments during the study.

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

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e., |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

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 used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and a compound symmetry covariance matrix to explain the associated between repeated measures within period.

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4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 1.

Figure 1: Mean and 90% CI of ΔQTcF Timecourse (unadjusted CIs).

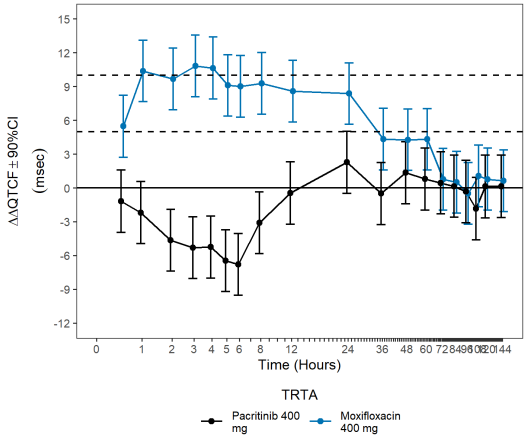

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Treatment	N_{act} / N_{pbo}	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Pacritinib 400 mg	40 / 42	24.0	2.3	(-0.5, 5.0)

4.3.1.1 Assay sensitivity

Assay sensitivity was assessed using by-time analysis. The statistical reviewer used the same linear mixed model as treatment arms to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF, ΔHR etc.) independently. The time-course of changes in ΔΔQTcF 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 2).

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔQTcF

Treatment	N_{act}/N_{pbo}	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	40 / 42	3.0	10.8	(8.1 to 13.6)	(7.1 to 14.6)

4.3.2 HR

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

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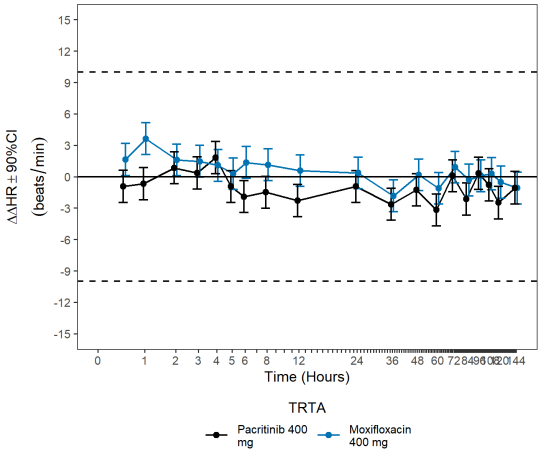
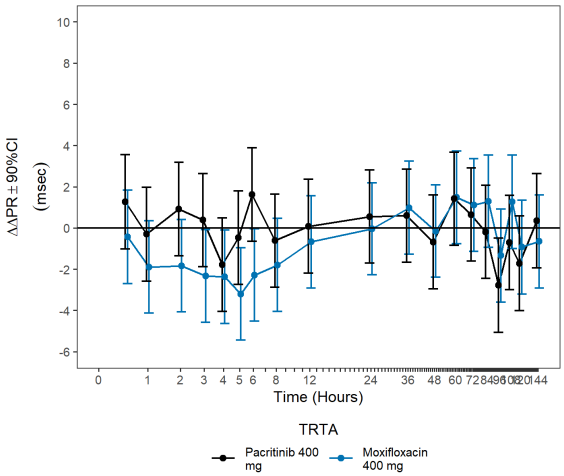
Figure 2: Mean and 90% CI of ΔHR Timecourse



4.3.3 PR

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

Figure 3: Mean and 90% CI of ΔPR Timecourse



4.3.4 QRS

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

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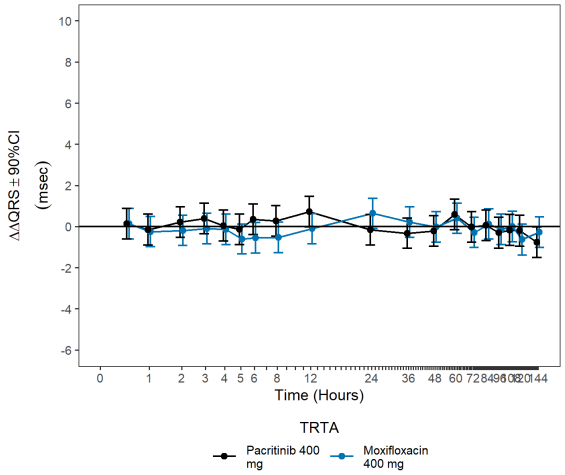
Figure 4: Mean and 90% CI of ΔQRS Timecourse



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 QTcF greater than 480 msec or ΔQTcF greater than 30 msec in pacritinib 400 mg treatment group.

4.4.2 HR

None of the subjects experienced HR greater than100 beats/min in pacritinib 400 mg treatment group.

4.4.3 PR

None of the subjects experienced PR above 220 msec with and without 25% increase over baseline in pacritinib 400 mg treatment group.

4.4.4 QRS

None of the subjects experienced QRS above 120 msec with 25% increase over baseline in pacritinib 400 mg treatment group.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of pacritinib (and its M1 metabolite) and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between pacritinib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease

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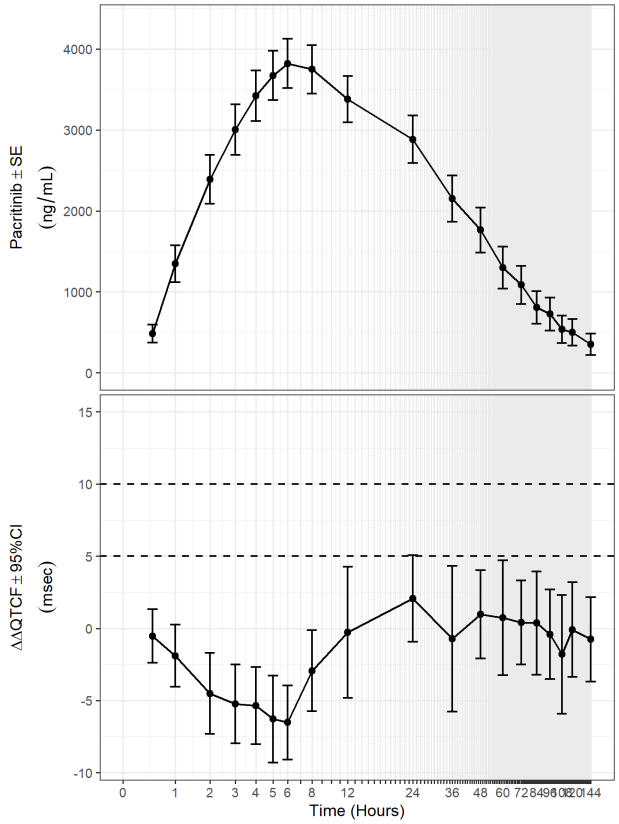
in mean HR); 2) delay between pacritinib concentration and ΔQTc and 3) a non-linear relationship.

An evaluation of the time-course of pacritinib concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of pacritinib (or its M1 metabolite, *data not shown*) indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of pacritinib concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between pacritinib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between pacritinib concentration and ΔQTcF and supports the use of a linear model.

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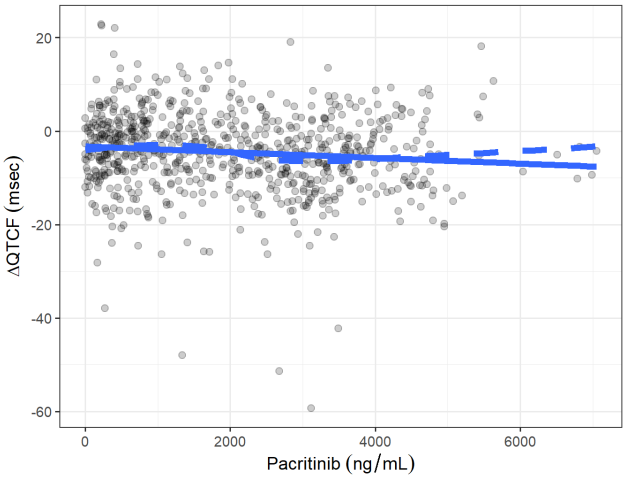
Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. The study indicated a concentration dependent QT shortening with numerical reduction in QT interval at sub-therapeutic levels (~4.5 msec at ~3774 ng/mL). Predictions from the concentration-QTc model are provide in Table 3.

Figure 7: Goodness-of-fit plot for QTc

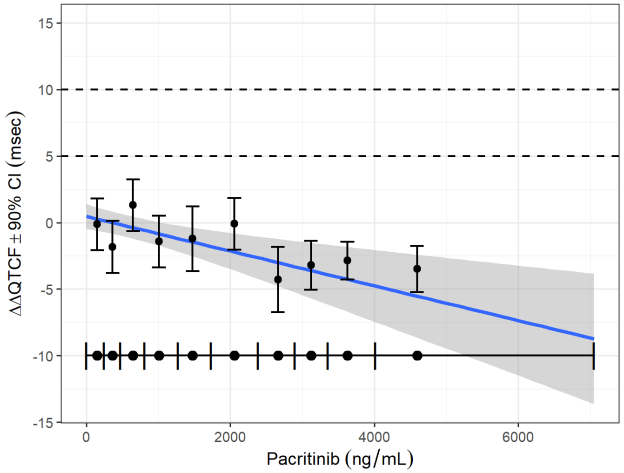


Table 3: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	Pacritinib (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Pacritinib 400 mg	1	3774.3	-4.5	(-7.0 to -1.9)

4.5.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control detecting small increases from baseline for QTcF in this study. The PK profile in the moxifloxacin group is generally consistent with the ascending, peak, and

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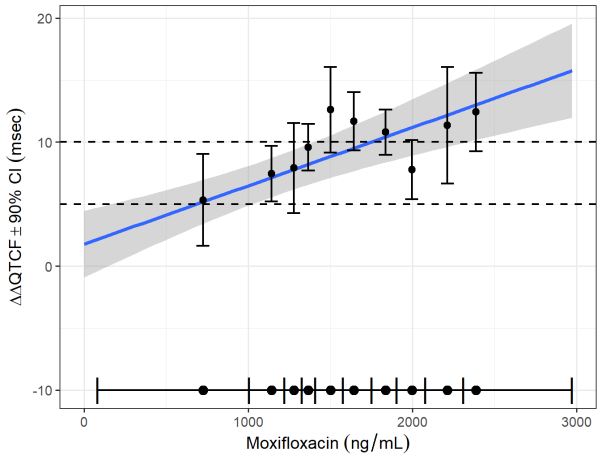
descending phases of historical data (*data not shown*). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔΔQTcF and the plasma concentration of moxifloxacin. The lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations of moxifloxacin is above 5 ms. Therefore, assay sensitivity is established.

Figure 8: Goodness-of-fit plot for ΔQTc for moxifloxacin



The goodness-of-fit plot for moxifloxacin is shown in Figure 8 and the predicted QTc at the geometric mean Cmax is listed in Table 4Table 5. Assay sensitivity was also established using by time analysis. Please see Section 3.2.1.1 for additional details.

Table 4: Predictions from concentration-QTc model for moxifloxacin

Actual Treatment	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400mg	1956.9	11.0	(8.8 to 13.2)

Reviewer's comments: *The peak concentration (Cmax: ~3774 ng/mL) observed with the studied dose (i.e., 400 mg single dose) is not expected to cover the therapeutic exposures (Cmax: ~9400 ng/mL; POP-PK) associated with the maximum proposed dose at the steady state. Thus, the present study (Study # PAC107) is not adequate for characterization of QT prolongation risk of pacritinib. Since the risk of QT prolongation of pacritinib is not adequately characterized in the thorough QT study, we evaluated ECG data from Study # PAC203 (see below).*

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4.6 STUDY # PAC203

This was an open-label, randomized, parallel-group, dose-finding study evaluating safety, pharmacokinetics, and pharmacodynamics of pacritinib (100 mg q.d., 100 mg b.i.d., and 200 mg b.i.d.). The study was performed in patients with primary or secondary MF (n=150; 50/dose group) who were previously treated with ruxolitinib. In this study, 161 subjects received any dose of study drug: 52 in the 100 mg pacritinib QD group, 55 in the 100 mg pacritinib BID group, and 54 in the 200 mg pacritinib BID group.

A 12-lead ECG (collected in triplicate) were planned for all subjects, including QTc calculation corrected by the Fridericia formula (QTcF), at 1 hour pre-dose and 4 hours post-dose on Day 1 of Week 1 and the End of Weeks 4, 12, and 24. All ECGs were centrally read by a blinded independent cardiologist. The study also included sparse PK collection in all patients (at pre-dose, 4 and 8 h post-dose at end of Week 12 and end of Week 24). Rich PK samples (at 2, 4, 6, 8, 24 h on Day 1 Week 1; and also, at pre-dose, 2, 4, 6, 8 h on End of Week 12 and Week 24) were also planned in a sub-set of population (6 to 8 subjects / dose group). The peak concentrations of ~5438 ng/mL, ~6204 ng/mL and ~9301 ng/mL are predicted at steady state with 100 mg q.d., 100 mg b.i.d., and 200 mg b.i.d. dosing regiments, respectively (POP-PK Report; link). The steady-state concentrations are expected to reach on Day 8.

The maximum change in QTcF from baseline across the treatment groups was 11 ms (Figure 9 and **Error! Reference source not found.**). Upper bound of 90% CI was below 20 ms. There were no apparent dose-response relationships. No subjects had QTcF > 500 ms at any timepoint. Two subjects (3.7%) in the 200 mg pacritinib BID group had worst post-baseline QTcF > 60 ms above baseline.

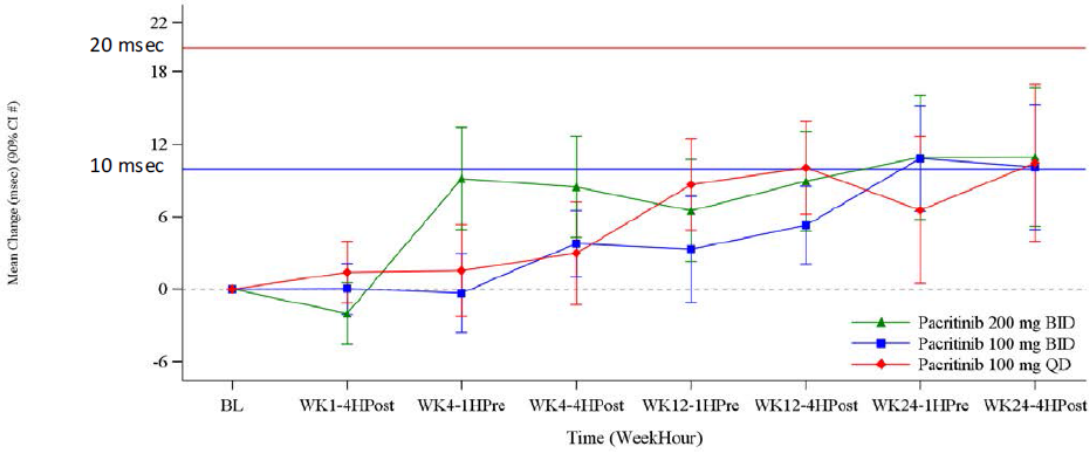
Nine subjects (5.6%) had non-serious AEs of Electrocardiogram QT prolonged (PT, MedDRA v16.0) with toxicity grade < 3. Eleven subjects (6.8%) had cardiac arrythmias-related AEs (MedDRA HLGT “cardiac arrhythmias”). AEs that occurred in more than one subject were atrial fibrillation (5 subjects) and supraventricular extrasystoles (2 subjects). No ventricular tachycardia, ventricular fibrillation, or cardiac death were reported.

One SAE of grade 3 syncope (QTcF 491 ms, versus 423 to 435 ms at Screening; range of 418 to 436 ms prior to event) was reported in Subject (b) (6) from the pacritinib 100mg QD group. The investigator assessed syncope as possibly related to study drug as it was thought that the syncope may have been due to an arrhythmia. Subsequent QTcs after the event, both from W24 and 30-day-post EOT, were normal (~440) and the subject had no further syncopal events. The subject had syncopal episodes prior to enrolling in PAC203.

In conclusion, the mean change QTcF from baseline across the treatment groups was 11 msec. The number of QTcF outliers was low. No ventricular tachycardia/fibrillation were reported.

Reference ID: 4862350

Figure 9: QTcF Mean change from Baseline Over Study Time by Treatment Group (Sponsor's Analysis)



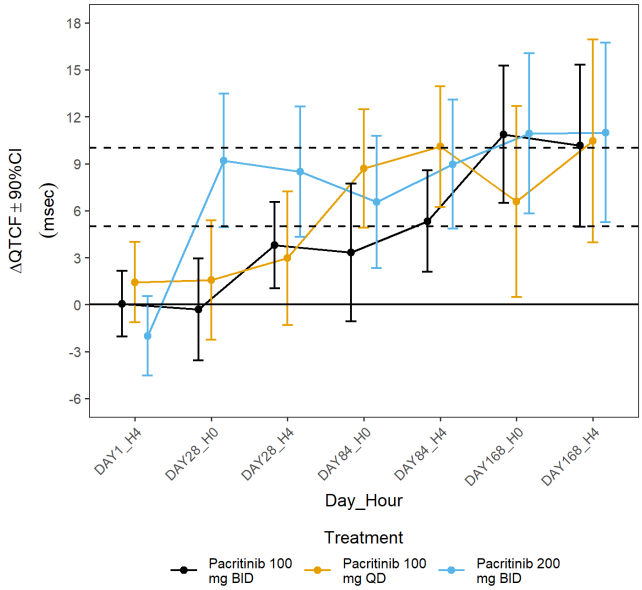
Number of Subjects								
Pacritinib 200 mg BID	54	52	40	45	34	34	25	23
Pacritinib 100 mg BID	55	52	44	45	38	39	23	20
Pacritinib 100 mg QD	52	50	43	41	38	33	22	23

Abbreviations: BID = twice per day; BL = Baseline; H = hour; QD = once daily; WK = Week.
Source: Figure 8.1.1

4.6.1 By-time Analysis results

Figure 10 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 5.

Figure 10: Mean and 90% CI of ΔQTcF Timecourse (unadjusted CIs).



Reference ID: 4862350

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

Actual Treatment	N	Day_Hour	ΔQTCF (msec)	90.0% CI (msec)
Pacritinib 100 mg BID	20	Day168_H4	10.2	(5.0 to 15.3)
Pacritin b 100 mg QD	23	Day168_H4	10.5	(4.0 to 16.9)
Pacritinib 200 mg BID	23	Day168_H4	11.0	(5.3 to 16.7)

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CHRISTINE E GARNETT
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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:	09/10/2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 208712
Product Name, Dosage Form, and Strength:	Vonjo (pacritinib) capsules, 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CTI Biopharma Corp.
FDA Received Date:	March 30, 2021
OSE RCM #:	2016-113
DMEPA Safety Evaluator:	Niloofar Rezvani, Pharm D
DMEPA Team Leader:	Hina Mehta, PharmD

Reference ID: 4854972

1 REASON FOR REVIEW

CTI Biopharm Corp. submitted NDA 208712 Vonjo (pacritinib) capsules on March 30, 2021. Vonjo is proposed for the treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. We evaluated the proposed Vonjo prescribing information (PI), container label, carton labeling, and patient information sheet for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

NDA 208712 pacritinib was originally submitted on December 30, 2015. The application was withdrawn by the applicant on February 10, 2016.

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 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 postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

CTI Biopharma Corp. submitted a 505(b)(1) application to obtain marketing approval of Vonjo capsules. We performed a risk assessment of the proposed prescribing information (PI), container label, carton labeling, and patient information sheet for Vonjo to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, container label, carton labeling and patient information sheet for Vonjo identified areas of vulnerability that may lead to medication errors. For the Division, we recommend clarifying the patient administration requirements and the storage information for Vonjo. For the Applicant, we recommend revising the format of the expiration date presented on the container label and carton labeling, decrease prominence of the net

Reference ID: 4854972

quantity statement, and inclusion of the linear barcode. We provide our recommendations below for the Division in Section 4.1 and for CTI Biopharma Corp. in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Vonjo Prescribing Information (PI), container label, carton labeling, and patient information sheet identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations for the Division of Non-Malignant Hematology in Section 4.1 and for CTI Biopharm Corp in Section 4.2. We ask that the Division convey Section 4.2 in its entirety to CTI Biopharma Corp. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlights of Full Prescribing Information
   1. Dosage and Administration
      a. We recommend revising the first bullet to include the dosage as the first part of the statement. Revise to "Recommended dosage is 200 mg orally twice daily (b) (4) . (2.1)".

B. Full Prescribing Information
   1. Section 2: Dosage and Administration
      a. We recommend revising the first sentence to include the dosage as the first part of the statement. Revise to "Recommended dosage is 200 mg orally twice daily (b) (4) .".
      b. We note Section 2.1 states Vonjo can be taken with or without food. Additionally, we note Vonjo capsules should be swallowed whole. We recommend including the statement "Swallow capsules whole. Do not open, break, or chew capsules.".
      c. We recommend placing the dosage reductions described in Section 2.5 in a table format as shown below:

Dosage	Reduction level
200 mg twice daily	Starting dosage
100 mg twice daily	1
100 mg once daily	2
Discontinue	3

   2. Section 3: Dosage Forms and Strengths
      a. As currently presented, the dosage form is not presented at the beginning of the section. We recommend displaying the dosage form as

the first word of the section. Revise Section 3 to read "Capsule: 100 mg, oblong, size 0 hard gelatin capsule…".

b. We note in the description that C78837 is presented with quotations at the start, but the ending quotations are lacking. We recommend including both the beginning and ending quotations around the printed text.

3. Section 16: How Supplied/Storage and Handling

a. As currently presented, the storage temperature requirements for Vonjo are presented in terms of Celsius without the Fahrenheit equivalent value presented in parenthesis. We recommend providing the Fahrenheit equivalent value in parenthesis after all Celsius temperature values. Revise the storage temperature requirements to read "Store below 30°C (86°F)".

b. We note the proposed container label and carton labeling contain the statement "Store and dispense in original package. Keep the bottle tightly closed (b) (4) protect from light". We recommend including these statements in Section 16.2 after the storage temperature requirements.

C. Patient Information Sheet

1. We note under How Should I store Vonjo the storage temperature requirements are provided. Additionally, we note from the proposed container label and carton labeling that Vonjo is to be stored in original package and kept tightly closed (b) (4) to protect from light. We recommend the statements "Keep Vonjo in its original package. Keep the bottle tightly closed (b) (4) to protect from light" next to the storage temperature requirements.
2. We note under How Should I Take Vonjo that information regarding swallowing Vonjo capsules whole is not provided. We recommend including the statement "Swallow capsules whole. Do not open, break, or chew capsules."

4.2 RECOMMENDATIONS FOR CTI BIOPHARMA CORP.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, we note the proposed container label and carton labeling state (b) (4) on the principal display panel. We recommend removing the statement as it is not needed on the principal display panel (b) (4) .
2. We note the net quantity is prominently displayed on the principal display panel of the proposed container label and carton labeling. We recommend decreasing the prominence of the net quantity statement as currently presented it is more prominent than the strength statement.
3. We note the proposed container label and carton labeling contain a placeholder for the expiration date with the proposed format of "MM/YYYY". We

recommend revising the format for the expiration date to "YYYY-MM" if only numerical characters are used or "YYYY-MMM" if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4. As currently presented, the inclusion and location of a linear barcode is not indicated. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label. Add the product's linear barcode to the proposed Vonjo container label and carton labeling in accordance with 21 CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in a vertical position on the container label to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature of the bottle.
5. We recommend revising the "Recommended dose" statement to "Recommended dosage" for consistency in language with the prescribing information. Revise to "Recommended dosage: See prescribing information".
6. We recommend removing [redacted] (b) (4) from the labeling at this information is not necessary.
7. We recommend removing the [redacted] (b) (4) statement as this is duplicative. [redacted] (b) (4) .
8. We recommend adding the statement "Swallow capsules whole. Do not open, break, or chew capsules" on the principal display panel to ensure this important information is not missed.
9. As the product needs to be stored in the original container we recommend adding a statement stating this to ensure this important information is not missed. We recommend adding "Attention: Dispense and store Vonjo in original package.".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vonjo received on March 30, 2021 from CTI Biopharma Corp..

Table 2. Relevant Product Information for Vonjo	
Initial Approval Date	N/A
Active Ingredient	Pacritinib
Indication	For the treatment of adult patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).
Route of Administration	Oral
Dosage Form	Capsule
Strength	100 mg
Dose and Frequency	The recommended dose of VONJO for patients with platelet counts of less than 50×10^9/L is 200 mg orally twice daily. VONJO may be taken with or without food.
How Supplied	Bottle of 120 capsules
Storage	Store below 30°C (86°F)

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Vonjo labels and labeling submitted by CTI Biopharma Corp.

- Container label received on March 30, 2021
- Carton labeling received on March 30, 2021
- Prescribing Information (Image not shown) received on March 30, 2021, available from \\CDSESUB1\evsprod\nda208712\0012\m1\us\1-14-1-3-draft-labeling-text-docx.docx
- Patient Information Sheet received on March 30, 2021, available from \\CDSESUB1\evsprod\nda208712\0012\m1\us\1-14-1-3-draft-labeling-text-docx.docx

G.2Label and Labeling Images

- Proposed container label

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Proposed carton labeling

(b) (4)

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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: September 3, 2021

To: Caden Brennen, MS, 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 VONJO (pacritinib), for oral use

NDA: 208712

In response to DNH's consult request dated April 1, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for VONJO.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Carleveva Thompson) on August 25, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on September 2, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 30, 2021, 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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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 2, 2021
To:	Caden Brennen, MS Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VONJO (pacritinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 208712
Applicant:	CTI BioPharma Corp

1 INTRODUCTION

On March 30, 2021, CTI BioPharma Corp. submitted for the Agency's review an original New Drug Application (NDA) 208712 for [SB1518] VONJO (pacritinib) capsules proposed for the following indication: for the treatment of adult patients with intermediate and high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF) who have severe thrombocytopenia) baseline platelet counts of less than 50 X 10^9/L. We note that the Applicant's proposed tradename VONJO was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis on June 11, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on April 12, 2021 and April 1, 2021, for DMPP and OPDP, respectively, to review the Applicant's proposed Patient Package Insert (PPI) for VONJO (pacritinib) capsules.

2 MATERIAL REVIEWED

- Draft VONJO (pacritinib) capsules PPI received on March 30, 2021, and received by DMPP on August 25, 2021.
- Draft VONJO (pacritinib) capsules Prescribing Information (PI) received on March 30, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on August 25, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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CLINICAL INSPECTION SUMMARY

Date	August 11, 2021
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 (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Andrew Dmytrijuk, M.D., Medical Officer Albert Deisseroth, M.D., Ph.D., Deputy Division Director Charlene Wheeler, Chief Project Manager Brittany Gar-Colon, Regulatory Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
NDA	NDA 208712
Applicant	CTI Biopharma Corp.
Drug	Pacritinib
NME	Yes
Division Classification	Tyrosine kinase inhibitor
Proposed Indication	Treatment of adult patients with intermediate or high-risk (b) (4) primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF).
Review Type	Priority
Consultation Request Date	April 22, 2021
Summary Goal Date	August 9, 2021 [Extension Date: August 30, 2021]
Action Goal Date	October 29, 2021
PDUFA Date	December 30, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies (PAC325 [PERSIST-1] and PAC326 [PERSIST-2]) were submitted to the Agency in support of a New Drug Application (NDA 208712) for pacritinib for treatment of patients with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. Two clinical investigators (John Mascarenhas, M.D. and Huong Nguyen, M.D. [currently Moshe Talpaz, M.D.]) and the sponsor (CTI Biopharma Corp.) were inspected in NDA 208712 Study PAC326 [PERSIST-2].

Albeit regulatory deficiencies were observed at two investigator sites in Study PAC326 (PERSIST-2], the deficiencies appear unlikely to have significant impact on the efficacy and safety results. CTI Biopharma Corp.'s oversight of Studies PAC325 and PAC326 appears to be adequate. Based on these inspections, the data from the two studies submitted to the Agency appear acceptable in support of this NDA for the proposed indication.

II. BACKGROUND

Autologous stem cell transplant is the only means of altering the natural history of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). Stem cell transplant could reverse the fibrosis in bone marrow and restore normal hematopoiesis. However, such treatment is only available to young patients with few to non-existent co-morbidities.

Pacritinib (SB1518) is an inhibitor of cytoplasmic tyrosine kinases JAK2 and FLT3 kinase activities and JAK2V617F mutant kinase activity, involved in signaling pathways of hormones, growth factors, and cytokines. Pacritinib is also a potent inhibitor of cellular proliferation in human leukemia and lymphoma cell lines selected for their dependence on the target kinases.

Two randomized clinical trials (Studies PAC325 [PERSIST-1] and PAC326 [PERSIST-2]) were submitted in support of the applicant's NDA. For this NME NDA under the PDUFA program review with priority therapy designation, CDER Division of Nonmalignant Hematology (DNH) requested inspections at two clinical investigator sites in PERSIST-2. The sites enrolled large numbers of patients and showed good response to treatment. DNH also requested sponsor inspection for Study PERSIST-1 and Study PERSIST-2.

Study PAC325

Study PAC325 (PERSIST-1) was a Phase 3 world-wide multicenter, randomized controlled clinical trial. The primary objective of Study PAC325 was to compare the efficacy and safety of pacritinib with that of best available therapy (BAT) in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. Spleen magnetic resonance imaging or computed tomography scan without contrast were to be obtained at screening and every 12 weeks thereafter and if spleen size increase was suspected by other assessments (such as physical examination).

The primary efficacy measure for the analysis was the proportion of subjects achieving a 35% or greater reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging or computed tomography scan.

Subjects were to be followed for survival and transformation to acute myeloid leukemia for three years after Week 24 or termination of study treatment, whichever occurred first. Subjects on BAT were allowed to cross over to pacritinib at the time of splenic volume progression, any time after splenic volume progression, or after completing 24 weeks of treatment with or without splenic volume progression. Crossover was not to be allowed if transformation to AML, splenectomy, or splenic irradiation had occurred.

There were 253 subjects analyzed for the primary efficacy analysis. There were 326 study patients analyzed for safety. The first study subject enrolled on January 8, 2013. The last subject termination visit was April 22, 2016.

Study PAC326

Study PAC326 (PERSIST-2) was a Phase 3, randomized, controlled study to evaluate the safety and efficacy of two-dose schedules of oral pacritinib in pooled and individual arm analyses compared to BAT in subjects with thrombocytopenia and primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. Subjects were to be randomized in a 1:1:1 allocation to either pacritinib 400 mg oral, QD; pacritinib 200 mg oral, BID; or investigator-determined BAT. Subjects were stratified by geographic region (US, Canada, Europe, and the rest of the world), risk category (intermediate-1, intermediate-2, and high-risk), and by rebound platelet count (less than or equal to 100,000 per microliter, and greater than 100,000 per microliter).

The primary objective of this study was to compare the efficacy of pacritinib pooled once-daily and twice-daily dosing arms with that of BAT in subjects with thrombocytopenia and PMF, PPV-MF, or PET-MF.

The efficacy co-primary endpoints for this analysis were the proportion of subjects achieving a 35% or greater spleen volume reduction (SVR) from baseline to Week 24 as measured by magnetic resonance imaging or computed tomography scan, and the proportion of subjects achieving a fifty percent or greater reduction in total symptom score (TSS) from baseline to Week 24 on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0).

There were 311 subjects randomized (104 [33.4%] to pacritinib 400 mg QD, 107 [34.4%] to pacritinib 200 mg BID, and 100 [32.1%] to BAT; 2 subjects randomized to pacritinib BID and one subject randomized to BAT did not receive any dose of study treatment.

Study PAC326 was a multicenter study. The first subject enrolled on July 2, 2014. The last subject had termination visit April 26, 2016.

On February 8, 2016, IND 078406 (including PERSIST-1 and PERSIST-2) was put on full clinical hold due to increased mortality noted in the pacritinib arm compared to best available therapy (BAT) in Study PAC325 (PERSIST-1) and in the interim results of Study PAC326 (PERSIST-2). The sponsor later submitted the updated results of PERSIST-2 and agreed to conduct a dose-finding study. The full clinical hold was removed on January 3, 2017.

III. RESULTS (by site)

1. John Mascarenhas, M.D. / Site #10014 (PAC326 [PERSIST-2])
Mount Sinai School of Medicine (Hess Building)
1470 Madison Ave
New York, NY 10029

Mailing address:
One Gustave L. Levy Place, Box 1079
New York, NY 10029

Inspection dates: June 14 to July 1, 2021

A total of 20 study subjects were screened and 18 study subjects were enrolled and received study treatment. Sixteen patients completed the study with two patients died.

Records reviewed included but were not limited to the following: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and informed consent documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, electronic case report forms (eCRFs), subject source records, test article control records, adverse event/serious adverse event documentation.

Source records for six enrolled study patients at the site were reviewed and compared with the submitted data listings for the site. Source document consisted of paper forms, print-out of electronic medical records, electrocardiogram printouts, paper copies of laboratory reports, questionnaire and subject responses, and progress report notes.

The primary efficacy endpoint data in the source records were verified against the data in patient line listings. No discrepancies were noted.

At the end of the inspection, a Form 483, inspectional observations, were issued related to inadequate or inaccurate study record maintenance:

(1) Three subjects' adverse events were under-reporting, and four subjects' concomitant (non-study) medications were not accurately recorded in the eCRF.

For example,
Subject (b) (6) reported an upper respiratory episode, nausea and spleen-related discomfort, diarrhea and flatulence.

Subject (b) (6) reported three early satiety, a mechanical fall episode, and worsening fatigue.

Subject (b) (6) had lateral abdominal pain that subsided after three hours without intervention.

Subject (b) (6) received loperamide, but not recorded in the safety database.

Subject (b) (6) received triamcinolone, and prophylactic cefuroxime treatment by an physician outside of the study trial.

Subject (b) (6) received metformin 1000 mg, rather than the incorrectly reported 500 mg daily dose.

Subject (b) (6) was administered nitrofurantoin for urinary tract infection at an incorrect 100 mg dose, instead of a 200 mg total daily dose.

(2) Investigational records (i.e., the study eCRFs) were not maintained at the clinical study site for two years following approval of a drug's marketing application. The eCRF was not found at this clinical trial study site.

Reviewer's comments:
Dr. Mascarenhas responded to the Form FDA 483 adequately on July 21, 2021. Site #10014 instituted preventive and corrective actions related to inaccurate or under-reported adverse events and concomitant medications. There was no evidence of significant pacritinib drug to drug interactions with unrecorded/missed non-study drug medications, that had an impact on patient clinical outcomes.

The occurrences of these adverse events that were under-reported appeared sporadic. Furthermore, physical signs or symptoms such as spleen-related discomfort, early satiety, fatigue and nausea could be part also of the myelofibrosis-disease clinical feature, disease severity or mechanical-complication related effects on the GI tract. Dr. Mascarenhas clarified that the abdominal discomfort, flatulence and diarrhea report was from a single event.

While the eCRF was not located at the study site, records were for the most part verifiable. There was no evidence that the source study records at Dr. Mascarenhas' site were compromised. In his response, sponsor was able to confirm with Dr. Mascarenhas that a federal express tracking of the mailed eCRF digital optic compact disc (CD) was mailed to his site. Currently, Site #10014 received a copy of the eCRF CD and corresponding audit trail records.

Despite these regulatory deficiencies related to lack of comprehensive data recording and inaccuracies, these appear unlikely to have significant impact on the efficacy and safety results.

2. Huong Nguyen, M.D. (currently Moshe Talpaz)/ Site #10048 (PAC326 [PERSIST-2])
NCRC Bldg. 300 Main 2800 Plymouth Rd., SPC Rm. 325
Ann Arbor, MI 48109

Inspection dates: May 25 to June 17, 2021

Huong Nguyen, M.D. was the original principal investigator of study site for PAC326 (PERSIST 2). FDA placed all study sites initially under clinical hold (See above reasons for the entire new drug application). for Study PAC326 on February 8, 2016. On February 9 and 10, 2016, the study site (10048) became aware of this full clinical hold for the entire Study PAC326. Dr. Nguyen left the study site to join the pharmaceutical industry on May 19, 2016. Moshe Talpaz, M.D., previously a co-investigator, took over site responsibility as the principal investigator of the study site 10048 on June 7, 2016, when the agreement was signed by Dr. Talpaz. For the 14 study subjects re-consented, informed consent changes were not submitted to the sponsor until September 17, 2016.

A total of 19 study subjects were screened and consented. Fourteen study subjects were randomized, and 11 patients completed the study. Three subjects did not complete the study (two deaths and one withdrawn).

Records reviewed involved the following items: IRB approvals and informed consent documentation, screening and enrollment log, monitoring reports, electronic case report forms (eCRFs), subject source records, test article control records, adverse event reporting.

The primary efficacy data in the source records were verified against the data in the patient line listings. No discrepancies were noted. No under-reporting of serious adverse events or data discrepancies were observed.

At the end of the inspection, Dr. Talpaz, the continuing site principal investigator received a Form FDA 483. Specifically, the site participants did not receive updated informed consent and re-consent based on the following regulatory violations: (1) latest clinical investigator information overseeing the study, (2) latest telephone contact information of the new clinical investigator, (3) details regarding study termination and new findings, and (4) revised “new” significant updated drug serious adverse events (including fever, anemia, swelling of the limbs, life threatening cardiac events, serious bleeding [such as bleeding in the throat, intracranial hemorrhage, subdural hemorrhage, cerebral hemorrhage, nosebleeds], stroke, skin cancer), reproductive disorders, and kidney and bladder disorders.

Despite the regulatory violation related to provide the re-consented of clinical study site participants with “new” [emerging] safety update information, there was no evidence of study harms. Dr. Talpaz’s took over as investigator for Site 10048 after FDA placed sponsor’s application (including Study PAC326) on clinical hold. The departure of Dr. Houng Nguyen, with Dr. Moshe Talpaz, as the lead site investigator replacement, had no bearing to CITI Biopharma Corp.’s clinical hold status FDA placed on the entire application.

Dr. Talpaz provided an adequate response to the Form FDA 483 on July 8, 2021.

3. **CTI Biopharma Corp.**
   3101 Western Avenue, Suite 800
   Seattle, WA 98121

   Inspection dates: May 17 to 25, 2021

   An inspection assessed CTI Biopharma Corp's responsibilities for oversight of Study PAC325 [PERSIST-1] and Study PAC326 [PERSIST-2]. The inspection included an evaluation and document review of the following and found to be adequate: (a) signed investigator and sub-investigator agreements and financial disclosures with the sponsor, (b) organizational charts, training records, monitoring records, reports and correspondence, (c) ethics review committee and institutional review board committee documents and correspondence, (d) selection of clinical investigators and training of in-house monitors, (e) electronic records and signatures (f) data collection, handling and management systems, (g) protocol deviation and serious adverse event reports, (h) noncompliance reports at the study sites and (i) independent data monitoring committee documents.

   In Study PAC325, study site records for Sites 36002 and 36003, and in Study PAC326 study site records for Sites 10011 and 10014 were assessed. No discrepancies were noted including serious adverse event reporting.

   An FDA Form 483, Inspectional Observations, was not issued at the close of the sponsor inspection. The procedures needed to address the registration of clinical trials and appropriate storage of electronic media were discussed at the end of inspection. The Sponsor appears to have maintained adequate study oversight of the clinical trial study sites for the two studies.

{See appended electronic signature page}
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/s/

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

Product Title	VONJO® (pacritinib) capsules, for oral use
Applicant	CTI Biopharma Corp
Application/Supplement Number	NDA 208712
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
Approved Indication(s)	n/a; NME
Date FDA Received Application	03/30/2021
Review Classification (Priority/Standard)	Standard
Action Goal Date	11/30/2021
Review Date	07/01/2021
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format 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: CTI Biopharma Corp has submitted this new NDA after previously withdrawing it.

Reviewer Comments: This review was conducted prior to all labeling meetings. Comments are in place from the RPM.

Regulatory Recommendation: This NDA is recommended for approval upon completion of labeling negotiations.

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

19 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[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.

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/s/

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