

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217759Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 30, 2023
Requesting Office or Division: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number: NDA 217759
Product Name and Strength: Joenja (leniolisib) Tablets, 70 mg
Applicant/Sponsor Name: Pharming Technologies
OSE RCM #: 2022-750-1
DMEPA 1 Safety Evaluator: Lissa C. Owens, PharmD
DMEPA 1 Team Leader: Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on January 6, 2023 and January 27, 2023 for Joenja. Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Joenja (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.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Owens, L. Label and Labeling Review for Joenja (NDA 217759). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 NOV 21. RCM No.: 2022-750.

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/

LISSA C PRINGLE-OWENS
01/30/2023 04:16:14 PM

IDALIA E RYCHLIK
02/01/2023 02:04:23 PM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 217759
Submission Number	001
Submission Date	7/29/2022
Date Consult Received	8/11/2022
Drug Name	Leniolisib film-coated tablets (JOENJA)
Indication	Treatment of activated PI3KÎ´ syndrome (APDS)
Therapeutic Dose	70 mg BID
Clinical Division	DPACC
Protocol Review	Link

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

This review responds to your consult dated 8/11/2022 regarding the sponsor's QT evaluation report. We reviewed the following materials:

- Previous IRT review for IND 124045 dated [04/21/2022](#) in DARRTS;
- Study report for CCDZ173x2101 (NDA 217759, eCTD 0001; [link](#));
- Investigator's brochure (IND (b) (4) / eCTD 0059; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (IND 124045 / eCTD 0070; [link](#)).

1 SUMMARY

Leniolisib (CDZ173, trade name: JOENJA) did not prolong the QTcF interval in this QTc substitution study under ICH E14 Q&A 5.1 – see table below for overall results. The data from the QTc assessment can be used as a substitute for a thorough QTc study.

The clinical study CCDZ173X2101 was a Phase 1, multicenter, randomized, double-blind, placebo-controlled, single and multiple ascending dose study assessing leniolisib PK following single and multiple oral doses of leniolisib and under fed and fasted conditions. This study was conducted in 3 parts: a randomized, double-blind, placebo-controlled, single ascending dose study (Part 1); a randomized, open-label, 2-way crossover, food effect study (Part 2); and a randomized, double-blind, placebo-controlled, multiple ascending dose study (Part 3). The highest dose provided 3-fold high clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that leniolisib is associated with significant QTc prolonging effect (refer to section 4.5).

QT assessment pathway	<input type="checkbox"/> Thorough QT study <input checked="" type="checkbox"/> Substitute for thorough QT study (5.1) <input type="checkbox"/> Alternative QT study when a thorough QT study is not feasible (6.1)				
Clinical QT study findings	<ul style="list-style-type: none"> Clinical exposure (70 mg BID): 3790 ng/mL Co-administration with strong CYP3A4 inhibitor (1.25x) (section 3.1) 400 mg SD (14300 ng/mL) => 3x coverage over high clinical 				
	ECG parameter	Treatment	Concentration	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
	QTc	70 mg BID	3790 ng/mL	0.0	(-1.4 to 1.4)
	QTc	High clinical	4738 ng/mL	-0.1	(-1.6 to 1.4)
QTc	400 mg SD	14300 ng/mL	-1.1	(-4.1 to 1.9)	
In vitro/in vivo findings	An integrated nonclinical risk assessment was not performed				

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to eCTD 0001 ([link](#)). Our suggestions for labeling are shown below. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At drug exposure greater than three times the exposure (C_{\max}) of the maximum approved recommended dose, JOENJA does not cause clinically significant QTc interval prolongation.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Pharming Technologies B.V developed leniolisib (CDZ173), a kinase inhibitor, for the treatment of rare disease activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adults and adolescents aged 12 or older. The recommended therapeutic dose is 70 mg BID with or without food.

IRT has previously reviewed the sponsor's proposed TQT substitution request, which was based on concentration-QTc analysis of the FIH study CCDZ173X2101 (DARRTS [04/21/2022](#)). This study enrolled 188 healthy subjects in 3 parts. Part 1 was a randomized, placebo-controlled, single ascending dose (SAD) study evaluating doses ranging from 10 mg to 400 mg. A total of 108 subjects received the assigned treatments (n=64, leniolisib; n = 44, placebo) under fasting condition. Part 2 was an open label, randomized, two-way cross-over single oral dose study under fed and fasted condition. A total of 12 subjects were randomized 1:1 to receive leniolisib with food and without food. Part 3 was a randomized, double-blind, placebo controlled, multiple ascending dose (MAD) study evaluating 20 mg BID, 40 mg BID, 70 mg BID, and 140 mg BID. A total of 68 subjects were randomized to receive leniolisib (n = 42) or placebo (n = 26). Intensive ECG/PK samplings were performed on day 1 of all parts and day 15 in the MAD part. In all 3 parts, 12-lead ECGs were collected in triplicates. Digital ECGs are not available, but the ECGs were read fully-automatically ([Response to IR – 08/26/2022](#)).

3.1.1 Clinical pharmacology

Leniolisib was 60% metabolized by the liver, with CYP3A4 being the most predominant enzyme involved (95%) in the primary oxidative metabolism of leniolisib with minor contribution from other enzymes (3.5% CYP3A5, 0.7% CYP1A2 and 0.4% CYP2D6). Leniolisib is the major circulating moiety with an effective half-life of approximately 7 hours (accumulation ratio Racc ~1.4 for BID dosing). Tmax is approximately 1 hr under fast condition. High fat meal prolonged the rate of absorption (Tmax ~ 4 hrs) and decreased Cmax on average by 41% but not the extent of absorption (AUC).

No dedicated renal or hepatic impairment studies have been conducted. Based on the label, leniolisib is not recommended in patients with moderate to severe hepatic impairment. The high clinical exposure scenario for leniolisib is when co-administered with strong CYP3A4 inhibitors at steady state; this would result in 1.25-fold increase in Cmax at steady state. See highlights of clinical pharmacology and cardiac safety.

Reviewer's comment: *The study medication in CCDZ173X2101 was formulated as hard gelatin capsules for oral administration. The to-be marketed formulation is film-coated tablet. The two formulations are bioequivalent for Cmax and AUC.*

Table 1: Summary of dose and exposure assessment

		Mean C _{max}
Highest therapeutic or clinical trial dosing regimen	70 mg BID, oral tablets, fasted	3790 ng/mL (C _{max,ss})

Sponsor's High clinical exposure scenario	1.25-fold increase with strong CYP3A4 inhibitor	4738 ng/mL
Highest dose in QT assessment	400 mg SD	14300 ng/mL
C_{max} Ratio	3	

3.1.2 Nonclinical Safety Pharmacology Assessments

Leniolisib did not inhibit the cardiac Nav1.5 and Cav1.2 voltage-gated sodium and calcium channels. In the in vitro IKr assay, leniolisib inhibited the hERG potassium channel expressed in HEK293 cells with an IC₅₀ value of 11.9 μM (5.4 μg/mL). The hERG IC₅₀ is 27-fold higher than the C_{max}, unbound at steady state in humans dosed with 70 mg leniolisib (bid).

Reviewer's comment: *The sponsor assessed the effects of leniolisib in three hERG assays ([1014539](#); [1114548](#); [1170425](#)) with similar findings ([1014539](#): 42.8% at highest concentration of 30 μM with estimated IC₅₀ of 45 μM assuming hill slope of 1; [1114548](#): 17 μM; [1170425](#): 11.9 μM). These findings suggest a possibility of direct interaction of hERG based on the safety margin ~20x (MW: 450.47 g/mol; PB: 94.5%; High clinical C_{max}: 4738 ng/mL or C_{max,free} of 0.6 μM). Sponsor also characterized the effects of leniolisib in an ion channel screen indicating IC₅₀ for Nav1.5 and Cav1.2a > 50 μM – sensitivity of this assay is unclear.*

In the cardiovascular safety pharmacology study in cynomolgus monkeys, leniolisib induced QT prolongation with a mean increase of 32 ms compared to the baseline-adjusted vehicle control following single oral dosing at 150 mg/kg. The leniolisib plasma exposure in male monkeys at 150 mg/kg/day is approximately 6-fold the human steady state exposure at the therapeutic dose. A trend to QTc prolongation was also evident in monkeys treated with doses of 40 mg/kg/day for 39 weeks. At this dose level, the combined-sex plasma exposure (AUC_{0-24h}, unbound) was 2.3-fold the human steady state exposure at the therapeutic dose.

Reviewer's comment: *QTc (individual correction) prolongation (32 msec) was observed following a single 150 mg/kg dose in male monkeys ([1170163](#)). This dose provides a ~6.7x margin over high clinical exposure ([1070281](#): C_{max} for 150 mg/kg: 17900 ng/mL; PB: 90.2% [[1100674](#)]). An increase in QTc was observed in other in vivo QT studies.*

Altogether, the in vitro and in vivo QT findings suggest a possibility of clinical QT prolongation. However, no QTc prolongations were shown at clinically relevant exposure in the clinical data.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for leniolisib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *FDA reviewer could not locate any by-time analysis in sponsor's report. Please see section 4.3 for the detail FDA reviewer's by-time analysis.*

3.2.1.1 Assay Sensitivity

Not applicable.

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).

Reviewer's comment: *Similar to sponsor's analysis, none of the subjects experienced QTcF >500 msec or ΔQTcF >60 msec in any of the dose levels of leniolisib. FDA reviewer could not locate categorical analysis of other intervals in sponsor's report. FDA analysis shows that one subject in below therapeutic group of leniolisib and 4 subjects in therapeutic and above group of leniolisib experienced HR greater than 100 beats/min. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. The results of the sponsor's analysis show an absence of significant QTc prolongation.

Reviewer's comment: *Conclusions from the FDA analysis were consistent with the sponsor's results.*

3.2.4 Safety Analysis

There were no deaths and one SAE (supraventricular tachycardia [SVT] of moderate severity) in this study. The subject who experienced the SAE received 70 mg BID and the SVT was observed on day 3 of the study. A lateral bypass tract identified during electrophysiology study was considered to be the source of the SVT, though contribution from study drug could not be ruled out. See page 114 in [CSR](#) for the narrative.

There were three TEAEs that resulted in study drug discontinuation: SVT SAE, AE (rash, maculo-papular) in 140 mg BID group and AE (microscopic hematuria) in the placebo group.

Reported AEs tended to be of mild severity with 6 subjects reported an AE of moderate severity. There were no reported AEs in the Torsade de Pointes/QT MedDRA SMQ.

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

4 REVIEWERS' ASSESSMENT

FDA's by-time and concentration-QTc analyses excluded part 2 (food effect) while the categorical analysis included all three parts.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

Reviewer's Comment: The Fridericia correction reduced but did not completely remove the slope of the QTc versus RR regression; a significant slope remained ($p < 0.05$), the sponsor used population-derived corrected QTcP as sensitivity analysis. The exponent was estimated at 0.352, i.e., $QTcP = QT/RR^{0.352}$. The results were similar to QTcF.

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs of 148 subjects were submitted. The sponsor is still working on the remaining ECGs from 40 subjects. The ECG intervals of raw observations of replicates were submitted. Overall, ECG acquisition and interpretation for the available ones appear 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. Data from Day 1 and Day 15 were used for the by-time analysis. The statistical reviewer evaluated the $\Delta QTcF$ effect using descriptive statistics.

Treatment arms were pooled into two groups: below therapeutic (10 mg SD, 20 mg SD, 20 mg BID, 40 mg SD, and 40 mg BID) and therapeutic and above (70 mg BID, 80 mg SD, 110 mg SD, 140 mg SD, 140 mg BID, 200 mg SD, 300 mg SD, and 400 mg SD).

4.3.1 QTc

Figure 1 displays the time profile of $\Delta \Delta QTcF$ for different treatment groups. The maximum $\Delta \Delta QTcF$ values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-course (unadjusted CIs).

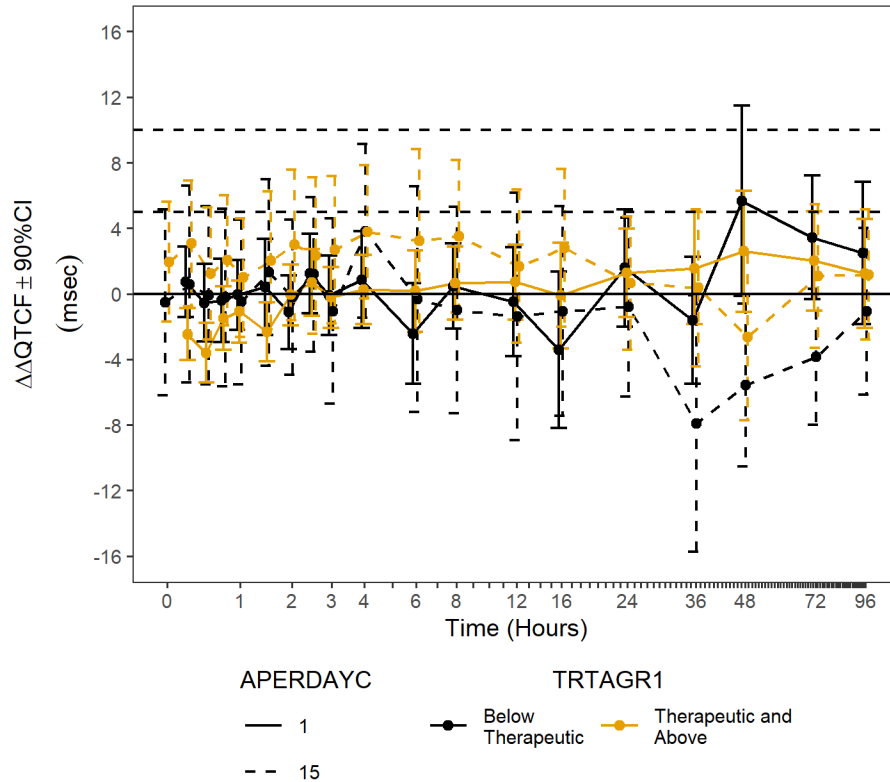


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

TRTAGR1	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Below Therapeutic	1	22 / 44	48.0	5.7	(-0.1 to 11.5)
Therapeutic and Above	1	42 / 44	48.0	2.6	(-1.1 to 6.3)
Below Therapeutic	15	12 / 22	4.0	3.8	(-1.5 to 9.1)
Therapeutic and Above	15	23 / 22	6.0	3.2	(-2.4 to 8.8)

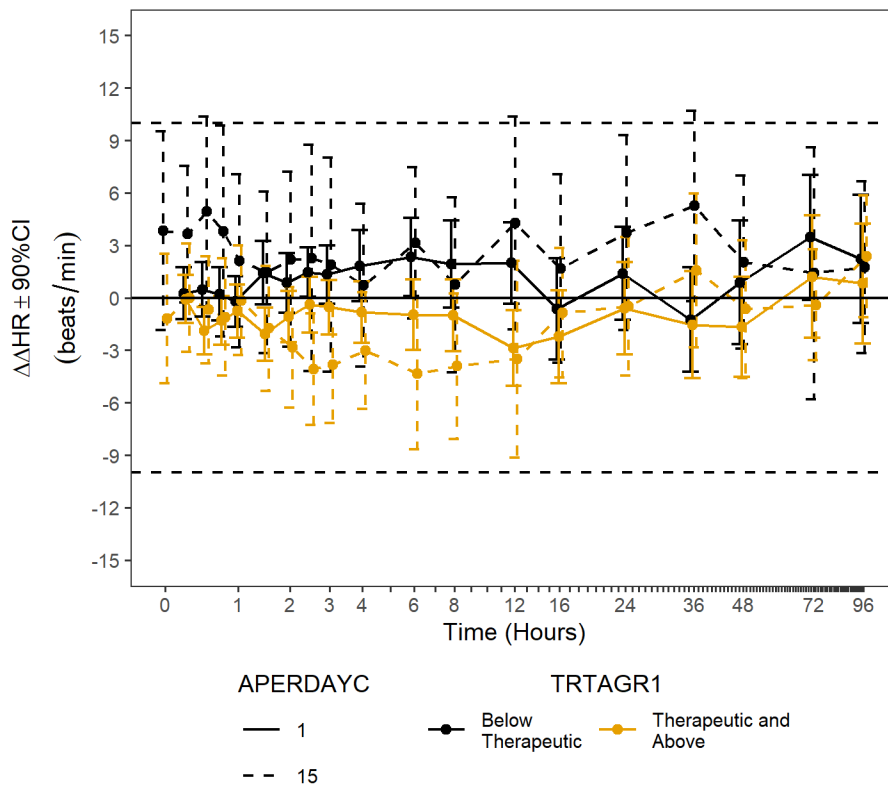
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

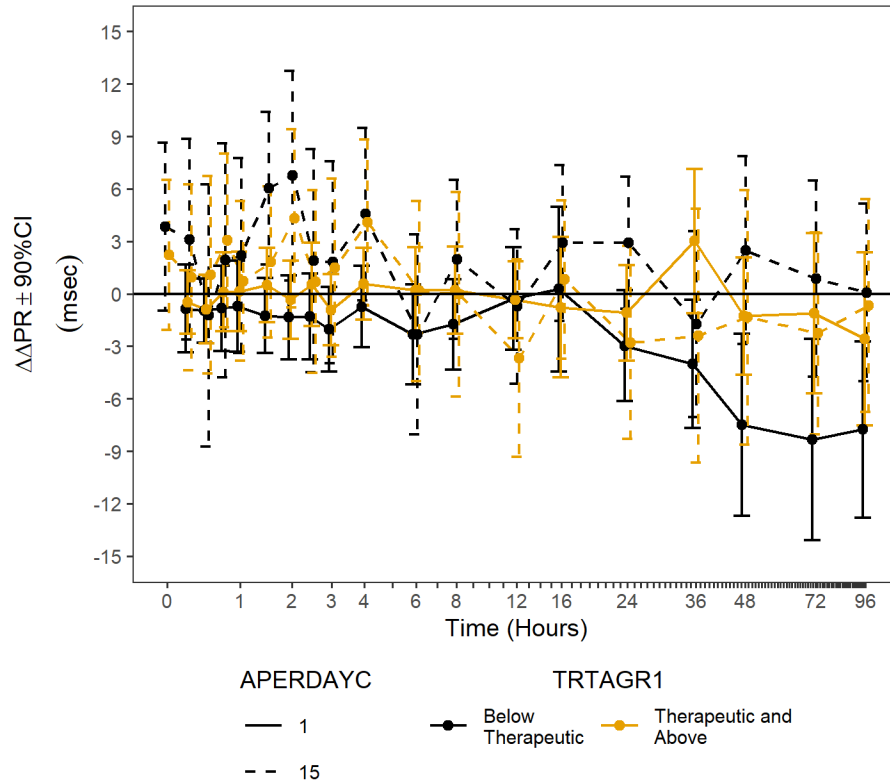
Figure 2: Mean and 90% CI of $\Delta\Delta\text{HR}$ Time-course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for different treatment groups.

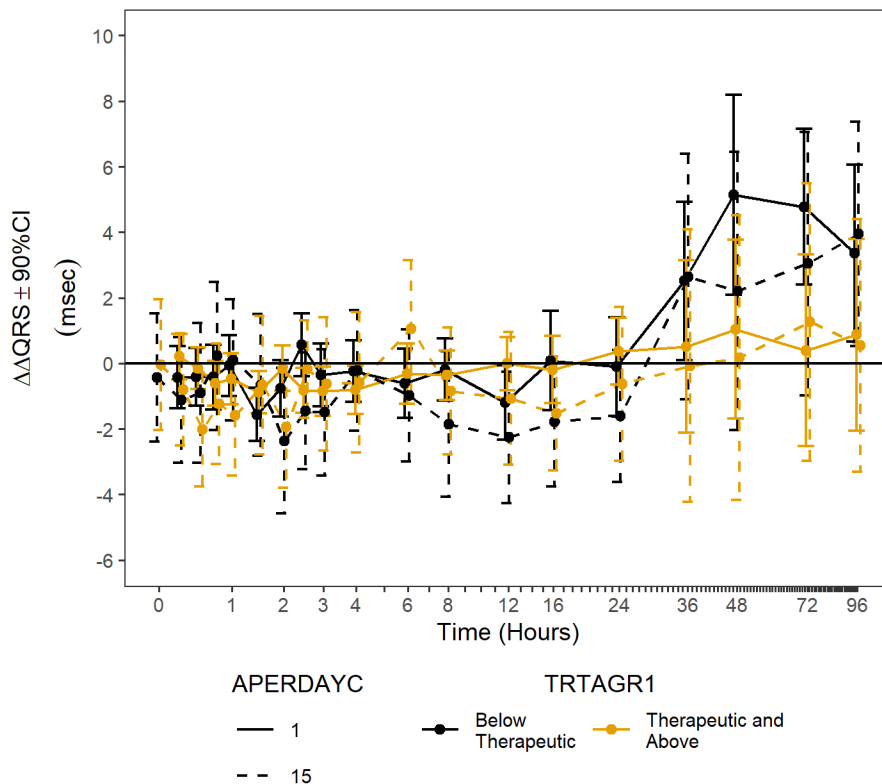
Figure 3: Mean and 90% CI of $\Delta\Delta PR$ Time-course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta QRS$ for different treatment groups.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS 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, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF values >450 msec with or without a change from baseline >60 msec for any of the dose levels of leniolisib.

4.4.2 HR

Table 3 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in below therapeutic group and 4 subjects in therapeutic and above group experienced HR greater than 100 beats/min.

Table 3: Categorical Analysis for HR (maximum)

Treatment Group	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Below Therapeutic	34	936	33 (97.1%)	935 (99.9%)	1 (2.9%)	1 (0.1%)
Therapeutic and Above	72	1941	68 (94.4%)	1937 (99.8%)	4 (5.6%)	4 (0.2%)
Food Effect Study	12	288	12 (100.0%)	288 (100.0%)	0 (0%)	0 (0%)
Placebo	70	1862	68 (97.1%)	1860 (99.9%)	2 (2.9%)	2 (0.1%)

4.4.3 PR

None of the subjects experienced PR >220 msec; with and without 25% increase over baseline for any of the dose levels of leniolisib.

4.4.4 QRS

None of the subjects experienced QRS >120 msec with 25% increase over baseline for any of the dose levels of leniolisib.

4.5 EXPOSURE-RESPONSE ANALYSIS

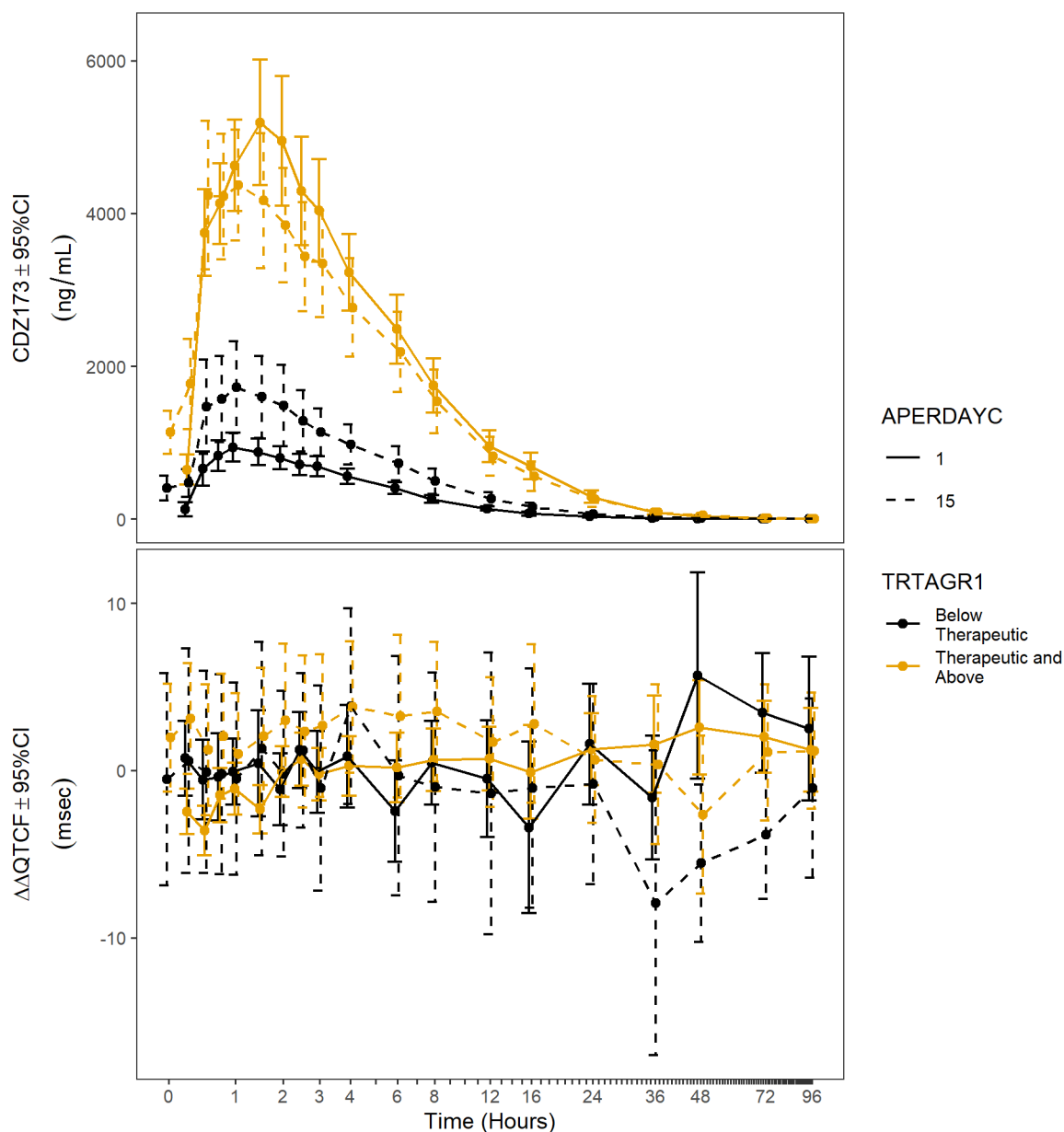
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need 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) absence of delay between plasma concentration and $\Delta\Delta\text{QTcF}$; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, with an absence of significant $\Delta\Delta\text{HR}$ changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta\Delta\text{QTcF}$, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)^{1 2}

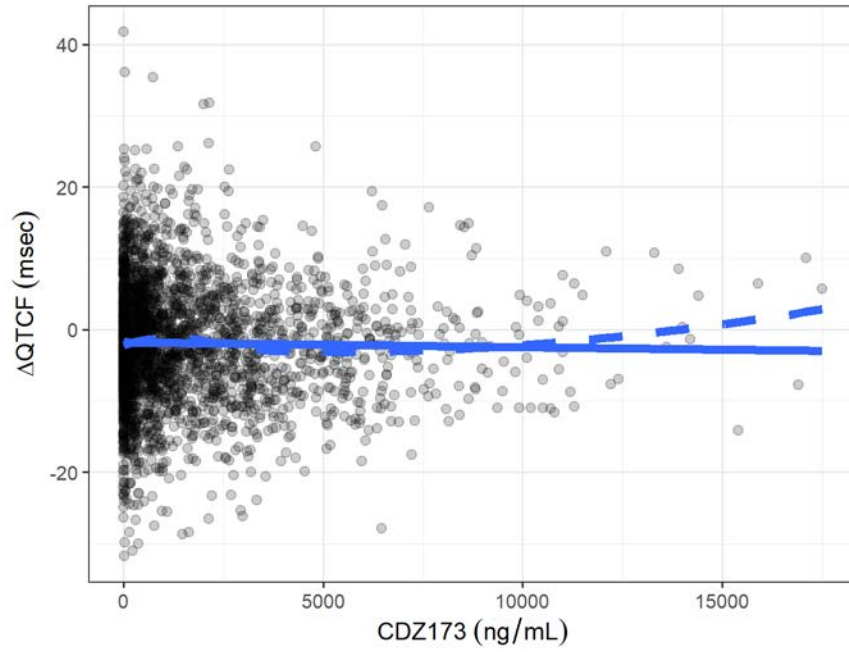


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¹ ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

² SD (Part 1) and BID (Part 3) dosing were pooled into [below therapeutic] and [therapeutic and above], see section 4.3. The “Day 15” data only included BID dosing while “Day 1” data included both SD and BID dosing on day 1. The “Day 1” therapeutic and above group included some higher dose levels than the “Day 15” group, such as 400 mg SD, therefore it had higher exposure than “Day 15”.

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

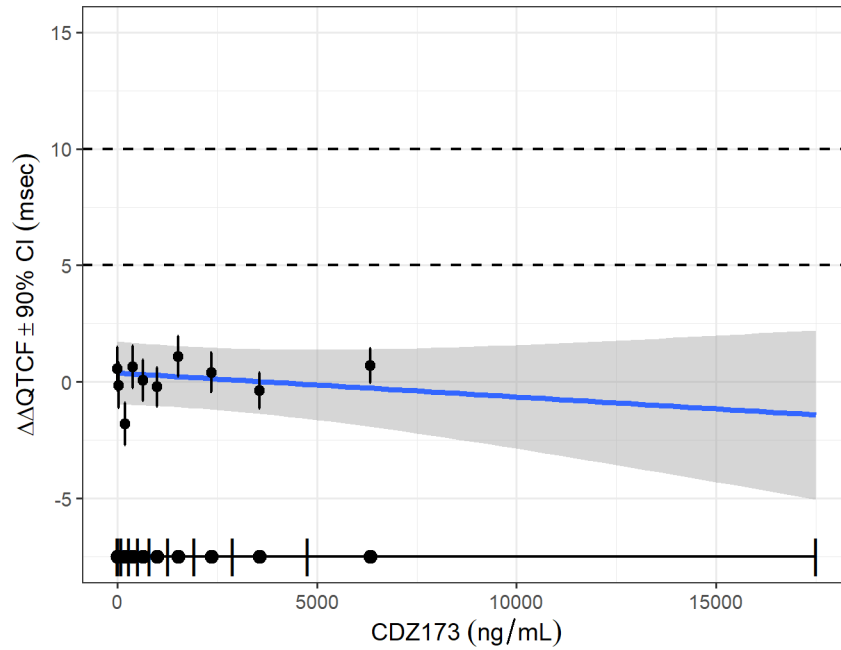


Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	CDZ173 (ng/mL)	$\Delta\Delta$QTcF (msec)	90.0% CI (msec)
70 mg BID	3,790.0	0.0	(-1.4 to 1.4)
High clinical	4,738.0	-0.1	(-1.6 to 1.4)
400 mg SD	14,300.0	-1.1	(-4.1 to 1.9)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

QT assessment plan was reviewed previously (see DARRTS [04/21/2022](#)).

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/s/

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Clinical Inspection Summary

Date	January 11, 2023
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Katherine Clarridge M.D., Clinical Reviewer Stacy Chin, M.D., Clinical Team Leader Elaine Sit, PharmD, Senior Regulatory Project Manager Division of Pulmonary, Allergy, and Critical Care (DPACC)
NDA #	217759
Applicant	Pharming Technologies B.V.
Drug	Joenja (leniolisib phosphate)
NME (Yes/No)	Yes
Proposed Indication(s)	Treatment of activated PI3K delta syndrome (APDS)
Consultation Request Date	August 22, 2022
Summary Goal Date	February 28, 2023
Action Goal Date	March 29, 2023
PDUFA Date	March 29, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Vemulkonda Koneti Rao and Anna Sediva were inspected in support of NDA 217759 covering one clinical study CCDZ173X2201. Despite some minor protocol deviations pertaining to missing high sensitivity C-Reactive Protein (hsCRP) lab results at Dr. Rao's clinical site, the study appears to have been conducted adequately, and the data generated by these clinical investigator (CI) sites appear acceptable in support of this NDA.

II. BACKGROUND

NDA 217759 was submitted in support of the use of Joenja (leniolisib phosphate) for treatment of activated PI3K delta syndrome (APDS), a rare autosomal dominant primary immunodeficiency causing accumulation of transitional B cells and senescent T cells, lymphadenopathy, and recurrent infections. The sponsor submitted a single Phase 3 study to support this NDA. The study consisted of three parts. Part 1 was an open-label, dose-titration study evaluating safety, tolerability for three 4-week treatment periods. Part 2 was the pivotal safety and efficacy, 12-week study. The third part was an open label extension study. Approval will be mainly dependent on the review of Part 2 of the study. The following briefly describes Part 2 of the protocol:

CCDZ173X2201, Part 2 "An open-label, non-randomized, within-patient dose-finding study followed by a randomized, double-blind placebo controlled study with extension to assess the safety and efficacy of CDZ173 in patients with APDS/PASLI (Activated

phosphoinositide 3-kinase delta syndrome/ p110 δ -activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)”

Protocol CCDZ173X2201, Part 2 was a Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of leniolisib for the treatment of APDS in adults and adolescents aged 12 or older. The primary objective was to assess the clinical efficacy (lymphadenopathy and immunophenotype normalization) of leniolisib in patients with Activated Phosphoinositide 3-kinase-Delta Syndrome (APDS)/ p110 δ -activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency (PASLI).

Sites: The study was conducted at 10 sites: 2 in Italy and 1 each in United States, United Kingdom, Czech Republic, Netherlands, Ireland, Belarus, Russia and Germany.

Subjects: Total of 31 subjects were randomized into Part 2 of the study (i.e., 21 subjects received leniolisib and 10 subjects received placebo).

Study initiation and completion dates: December 5, 2017 (first patient, first visit); August 16, 2021 (last patient, last visit)

Database lock date of Part 2 of the study: December 23, 2021

Subjects were randomized 2:1 to receive either 70 mg twice daily leniolisib or matching placebo via oral administration for 12 weeks. The main inclusion criteria were male and female patients 12 to 75 years of age (inclusive), who had a documented APDS/PASLI-associated genetic PI3K delta mutation. Subjects with mutations in either PIK3CD or PIK3R1 could be included. Subjects with nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver) also could be included. Additionally, in Part II, patients were to have at least one measurable nodal lesion on a CT or MRI scan to be included in the study.

Co-Primary Efficacy Endpoints:

- Change from baseline in the log₁₀ transformed sum of product of diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging. Note: Baseline was at Visit Screen (SCR), Days -50 to -2.
- Change from baseline in percentage of naïve B cells out of total B cells. Note: Baseline was assessed at Day -1.

For the assessment of the impact leniolisib on lymphadenopathy, subjects were scanned either by contrast-enhanced MRI of neck, chest, abdomen, and pelvis or contrast-enhanced CT scan of neck, chest, abdomen, and pelvis at the clinical site. The same imaging modality was to be used throughout the study for the same subject to allow consistent comparison of lesions. The clinical site was to transfer the images to [REDACTED]^{(b) (4)} via Trial Tracker, a web-interfaced image data management system within two business days from the date of the subject scan. [REDACTED]^{(b) (4)} was responsible for reviewing the image data by using the Cheson criteria. Dominant lesions were identified at baseline and were then followed for a response. The

response criteria for index lesions were based on the sum of the product of diameters (SPD) for all index lesions. Review of image data was conducted in the (b) (4) core lab by qualified and trained radiologists. Because the MRI/CT images were centrally read at (b) (4), the sponsor sent certified copies of the source records from (b) (4) to the clinical investigator sites and the application for efficacy endpoint data verification.

For the second efficacy endpoint pertaining to changes from baseline in percentage of naïve B cells out of total B cells, immunophenotyping was to be assessed by flow cytometry. Whole blood samples were collected from subjects, stained, lysed/fixed and frozen at a central laboratory. Prior to the clinical inspections, the sponsor contacted the central lab, (b) (4), who then sent certified copies of the flow cytometry results to the clinical sites and to the application for efficacy endpoint data verification.

Rationale for Site Selection

The CIs Drs. Vemulkonda Koneti Rao (Site #1001) and Anna Sediva (Site #3001) were selected for GCP inspections using a risk-based approach that considered numbers of enrolled subjects, treatment effect, and prior inspectional history.

III. RESULTS (by site):

1. Dr. Vemulkonda Koneti Rao

Site #1001

National Institutes of Health Clinical Center

10 Center Drive

Bethesda, Maryland, 20892

PDUFA Inspection Dates: October 3-7, 2022

At this site, 19 subjects were screened and 16 were randomized. All 16 randomized subjects completed Part 2 of the study.

Source documents were reviewed for all 16 randomized subjects. Records reviewed included, but were not limited to, protocol versions, IRB submissions, for FDA 1572s, financial disclosures, eligibility records, informed consent forms, source data evaluation, adverse event reports, laboratory reports, clinical source data, concomitant medications, questionnaires, paper case report forms, investigational product accountability, staff training, and sponsor/monitor correspondence, and co-primary efficacy endpoint source records.

The sponsor submitted certified copies of the source records which included flow cytometry results and a compilation of MRI images in a PowerPoint presentation from (b) (4) to the clinical site for data verification of the co-primary efficacy endpoints. The history and physical assessments and lab results were primarily in the CRIS Electronic Medical Record hospital system. All other source records, including paper case report forms and questionnaires, were paper. The raw values for the co-primary efficacy endpoint data, specifically the lymphadenopathy as measured by the log10 transformed sum of product of

diameters (SPD) in the index lesions and the percentage of naïve B cells out of total B cells at Baseline and Day 85, as documented in the certified source records from centralized imaging and lab centers were compared with the data line listings provided by the sponsor. No discrepancies were noted. There was no evidence of underreporting of adverse events.

For 11 of the 16 randomized subjects, high sensitivity C-Reactive Protein (hsCRP) lab results were missing for Baseline (Day of Randomization) and Visit 101 (Day 1 Dosing Day).

Reviewer's comment: The protocol requires that clinical investigators obtain hsCRP labs at Screening, Baseline, Visit 101 (Day 1), Visit 102 (Day 15), Visit 103 (Day 29), Visit 104 (Day 57), and Visit 105 (Day 85) as one of the biomarkers in addition to LDH to be collected to assess systemic inflammation as a secondary objective. The missing hsCRP values were discussed with the clinical reviewer and team leader and assessed as not clinically significant for their review. This reviewer has read the Clinical Investigator's corrective and preventative action (CAPA) plan to institute a check list to ensure all tests results are completed per protocol, and the CAPA appears appropriate.

2. Dr. Anna Sediva

Site #3001

Motol University Hospital

Department of Immunology

V Uvalu 84

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PDUFA Inspection dates: November 7-8, 2022

At this site, 5 subjects were screened and 3 were randomized. All 3 randomized subjects completed Part 2 of the study.

Source documents were reviewed for all 3 randomized subjects. Records reviewed included, but were not limited to, protocol versions, ethics committee oversight, informed consent, eligibility records, protocol adherence, concomitant medications, adverse events, test article accountability, financial disclosures, and co-primary efficacy endpoint source records.

The sponsor submitted certified copies of the source records which included flow cytometry results and a compilation of MRI images in a PowerPoint presentation from [REDACTED] (b) (4) to the clinical site for data verification of the co-primary efficacy endpoints. All other source records were paper. The raw values for the co-primary efficacy endpoint data, specifically the lymphadenopathy as measured by the log10 transformed sum of product of diameters (SPD) in the index lesions and the percentage of naïve B cells out of total B cells at Baseline and Day 85, as documented in the certified source records from centralized imaging and lab centers were compared with the data line listings provided by the sponsor. No discrepancies were noted. There was no evidence of underreporting of adverse events or of unreported protocol deviations.

{ See appended electronic signature page }

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Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
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OSI/ GCP Program Analysts/
OSI/Database PM/

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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 29, 2022

To: Elaine Sit, Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP
Kyle Snyder, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for JOENJA® (leniolisib) tablets, for oral use

NDA: 217759

Background:

In response to DPACC's consult request dated August 8, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for JOENJA® (leniolisib) tablets, for oral use.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 21, 2022, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on December 22, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	November 21, 2022
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217759
Product Name and Strength:	Joenja (leniolisib) Tablets, 70 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pharming Technologies
FDA Received Date:	July 29, 2022
TTT ID #:	2022-750
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Joenja (leniolisib) Tablets, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Joenja prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

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 CONCLUSION AND RECOMMENDATIONS

The proposed container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Pharming Technologies.

4 RECOMMENDATIONS FOR PHARMING TECHNOLOGIES

Table 2. Identified Issues and Recommendations for Pharming Technologies (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	(b) (4) is present on the container and carton of an oral tablet.	The dosage form is a solid oral tablet (b) (4). In addition, this statement may compete for prominence with more important information on the container label.	Delete the statement: (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Joenja that Pharming Technologies submitted on July 29, 2022.

Table 3. Relevant Product Information for Joenja	
Initial Approval Date	N/A
Active Ingredient	leniolisib
Indication	treatment of activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adults and adolescents aged 12 or older
Route of Administration	oral
Dosage Form	tablet
Strength	70 mg
Dose and Frequency	70 mg orally twice daily approximately 12 hours apart, with or without food
How Supplied	supplied in bottles of 60 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)

APPENDIX F. LABELS AND LABELING

F.1 List 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 Joenja labels and labeling submitted by Pharming Technologies.

- Container label(s) received on July 29, 2022
- Carton labeling received on July 29, 2022
- Prescribing Information (Image not shown) received on July 29, 2022, available from <\\CDSESUB1\EVSPROD\nda217759\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf>

F.2 Label and Labeling Images

Container label(s)



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

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Clinical Analyst's Consult Review Memorandum

Submission: NDA 217759
Sponsor: Pharming Technologies B.V.
Product: Leniolisib
Requested by: Elaine Sit, Office of Immunology and Inflammation (OII)/Division of Pulmonology, Allergy, and Critical Care (DPACC)
Consulting reviewer: Hadi Bagheri, OSM/DIRM
Through: Shane Masters, OSM/DIRM
Deputy Director: Alex Hofling, OSM/DIRM
Date: 10/14/2022

Consulting Division's Question's to DIRM:

This is a new NME NDA for leniolisib to treat rare disease, activated phosphoinositide 3-kinase delta (PI3K δ) syndrome (APDS) in adults and adolescents aged 12 years or older.

The Applicant is evaluating leniolisib for the treatment of APDS/PASLI, a very rare, combined immunodeficiency that causes accumulation of transitional B cells and senescent T cells and presents with lymphadenopathy and recurrent infections. The Sponsor has chosen a radiographical co-primary endpoint of change from baseline in the log₁₀ transformed sum of product of diameters (SPD) of the index lymph nodes selected as per the Cheson methodology from MRI/CT imaging. Given our lack of experience with radiographic endpoints, DPACC requests assistance from DIRM on the following:

- 1) Has the Sponsor selected an accepted method for measuring differences in lymph node size over time?
- 2) Based on review of the provided imaging charter, did the Sponsor use appropriate processes for image acquisition and analysis?
- 3) Is the Cheson methodology an accepted methodology for selecting index lesions (lymph nodes)?

Summary of Response:

Q1: Has the Sponsor selected an accepted method for measuring differences in lymph node size over time?

The proposed method for measuring differences in lymph node size over time was developed and published by a 1999 International Working Group to assess response in non-Hodgkin's

lymphoma (Cheson et al. 1999). Examining the change in the sum of the product of the diameters for assessing response in patients with lymphoma is a common practice.

As discussed previously by DPACC, it is unclear how strongly lymph node size correlates with clinical status in APDS. Imaging endpoints should typically be sufficiently validated with clinical data, particularly before use as a primary endpoint. Additionally, if lymph node size is a reasonable surrogate for clinical status, approaches that focus on change in short axis diameter or other measurements may be as good or better than the Applicant's proposed method.

Regarding choice of imaging modality, while CT usually has better spatial resolution and therefore the potential for better accuracy of size measurements, both CT and MRI are capable of providing sufficient anatomic detail for lymph node diameter measurements.

We defer to Statistics on the suitability of \log_{10} transformed data for the primary analysis. However, consider also examining non-transformed results at both the patient level and the lesion level to ease interpretation of the magnitude of the differences and to look for heterogeneity of response among lesions. We recommend caution if the volume (as opposed to the diameter) measurements provided by the Applicant as secondary and exploratory endpoints are used for decision making. This is because the protocol allowed relatively thick slices, which can introduce significant error in the measured volume.

Q2: Based on review of the provided imaging charter, did the Sponsor use appropriate processes for image acquisition and analysis?

The plans for image acquisition and interpretation in Study 2201 part 2 are generally reasonable. However, ideally imaging primary endpoint data would be shown to be reproducible, for example through assessment of intra-reader variability, or for multiple readers, inter-reader variability. Assessment of intra-reader variability is not found in the imaging charter for this single reader study, and the apparent lack is a weakness. Another potential advantage to multiple readers is improved accuracy of measurements, and a multi-reader approach may have been preferable.

Because of the use of imaging data for a co-primary endpoint, you could consider an OSI consult to discuss inspection of the imaging contract research organization.

We note that at least 3 patients appeared to have deviated from the protocol by having different imaging modalities (i.e., CT versus MRI) at baseline and week 12. While we do not expect this to have a major impact, because use of different modalities could contribute to an apparent change in size and because of the relatively large fraction of the study population affected, we recommend that a sensitivity analysis be performed excluding these patients.

Q3: Is the Cheson methodology an accepted methodology for selecting index lesions (lymph nodes)?

The method for selection of index lesions used by the Applicant incorporates the criteria described in the Cheson citation along with additional criteria emphasizing ease of measurement and representativeness of the overall disease status. We believe the method is reasonable. As with most methods that involve measuring index lesions rather than all lesions, there will be subjectivity in lesion selection. In this study, blinding of the reader to whether patients received placebo or leniolisib should be sufficient to prevent biased lesion selection.

Additional comment:

The guidance document "Clinical Trial Imaging Endpoint Process Standards" (<https://www.fda.gov/media/81172/download>) contains additional information on considerations for use of imaging endpoints in clinical trials.

Background and Rationale:

Leniolisib is a selective phosphoinositide 3 kinase delta (PI3K δ) inhibitor that is being developed for treatment of activated PI3K δ syndrome (APDS), a rare combined immunodeficiency disorder. This disorder results in dysregulated production of B-cells and T-cells, with preferential accumulation of non-functional or poorly functional immature B-cells and senescent T-cells. Resulting clinical features include recurrent sinopulmonary infections, susceptibility to herpesvirus infections, lymphadenopathy, splenomegaly, hepatomegaly, enteropathy, autoimmunity, and lymphoid malignancies.

The primary source of evidence for effectiveness of leniolisib in patients with APDS provided by the Applicant is Study 2201 part 2. This was a double-blinded, placebo-controlled study of 70 mg leniolisib twice daily for 12 weeks. A total of 31 adult and pediatric patients were enrolled, 10 in the placebo arm and 21 in the leniolisib arm. The primary endpoints were 1) change from baseline in log₁₀ transformed sum of the product of diameters (SPD) of up to 14 index lesions and 2) change from baseline in % of naïve B-cells relative to total B-cells. Secondary and exploratory imaging related endpoints included:

- Change in volume of index and non-index lesions
- Change in volume and bidimensional size of the spleen
- Change in volume and bidimensional size of the liver

Protocol defined imaging included MRI or CT of the neck, chest, abdomen, and pelvis, which was obtained at baseline and 12 weeks (or earlier if the study drug was prematurely discontinued). Pre- and post-contrast imaging was performed for MRI. The MRI protocol was based on routine site practice, but the reference protocol included axial T2FS, axial T1, and axial T1FS of the neck, coronal T2 of the abdomen, and axial T2FS and axial T1FS of the chest, abdomen, and pelvis. Postcontrast imaging included axial T1FS of the neck, chest, abdomen, and pelvis. CT was done with intravenous and oral contrast. Slice thickness of ≤ 5 mm was

recommended for both modalities. The same modality was to be used at each time point. MRI scanners were qualified using a uniformity and linearity phantom. No CT qualification is found in the Image Review Charter or Patient Scanning Guide.

Images were sent to a central CRO for evaluation. It is not clear from the Image Review Charter whether a technologist or other image analyst was responsible for initial identification and markup of lesions. In any case, a single radiologist was responsible for approving all imaging results. This reader was blinded to treatment, but not timepoint. Images were read sequentially in time order, and prior images and reads were available for comparison. Results of prior reads were not to be changed without approval of a CRO technical expert and any modifications were documented.

After lesions or organs were outlined, automated tools extracted the diameter and volume measurements. Up to 14 index lesions (6 lymph nodes, 4 liver or spleen, and 4 other extranodal) were selected based on size, ease of accurate measurement, and ability to represent overall nodal disease burden. To be considered measurable, lesions were required to measure at least twice the slice thickness and be at least 1.5 cm long axis (for nodes) or be at least 1 cm in both long and short axis (for non-nodal lesions). Index lesions were to be from multiple body regions if possible and were to include mediastinal and retroperitoneal lesions if present. On follow up scans, lesions that disappeared were recorded as 0 cm and lesions that were less than 5 mm as 5 mm.

Dr. Cheson has been involved in multiple sets of lymphoma response criteria. The criteria referenced by the Applicant are from the 1999 International Working Group (Cheson et al. 1999). Lesion selection is a relatively minor component of this reference, as most response categories required assessment of all lesions. However, for partial response, index lesions were defined as:

≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

These rules have been incorporated into the index lesion selection method used for Study 2201.

Reference:

Cheson, BD, SJ Horning, B Coiffier, MA Shipp, RI Fisher, JM Connors, TA Lister, J Vose, A Grillo-Lopez, A Hagenbeek, F Cabanillas, D Klippensten, W Hiddemann, R Castellino, NL Harris, JO Armitage, W Carter, R Hoppe, and GP Canellos, 1999, Report of an international workshop to standardize response criteria for non-Hodgkin's Lymphomas. NCI Sponsored International Working Group, J Clin Oncol, 17(4):1244.

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