CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210868Orig1s000

OTHER REVIEW(S)

Summary Consultative Review

NDA (Serial Number)	**210868**
Sponsor:	**Pfizer**
Drug:	**Lorlatinib**
Proposed Indication:	**Non-Small Cell Lung Cancer**
Material Submitted:	**Consultation Request**
Date Consult Requested:	**5/22/18**
Date Received By Reviewer:	**6/8/18**
Date Review Completed	**10/31/18**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This summary consultative review responds to a request from the Division of Oncology Products-2 (DOP2) of the Office of Oncology and Hematology Products.

This consultation request is in regard to an initial New Drug Application (NDA), #210868, for lorlatinib.

Lorlatinib is an inhibitor of anaplastic lymphoma kinase and c-ros oncogene 1 (ROS1) receptor tyrosine kinases.

Under NDA 210868, which was submitted and received by the Agency on December 5, 2017, the sponsor (applicant) has sought the approval of lorlatinib (PF-06463922) for the treatment of patients with anaplastic lymphoma kinase-positive non-small cell lung cancer who were previously treated with one or more anaplastic lymphoma kinase tyrosine kinase inhibitors

In this consultation request, DOP2 has asked this Division several questions about cognitive outcome measures used in a clinical trial (B7461001) of lorlatinib whose report has been submitted as part of NDA 210868. This consultation request was issued on May 22, 2018, and was received by this reviewer on June 8, 2018. Preliminary comments responding to this consultation request were conveyed by this reviewer to DOP-2 on June 14, 2018

Please note that this NDA was granted priority review status by the Agency (in a letter dated February 3, 2018) with a user fee goal date of August 5, 2018. However, after the receipt of a major amendment to this application on July 3, 2018, the user fee goal date for this application was extended to November 5, 2018.

2. Text Of Consultation Request

The text below has been extracted verbatim from, and explains the basis for, this consultation request.

COMMENTS / SPECIAL INSTRUCTIONS: As part of the dose expansion portion of Study B7461001, an ongoing dose escalation/dose expansion study of lorlatinib, an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) in patients with treatment-naïve or previously treated ALK-positive non-small cell lung cancer (NSCLC), patients were administered assessments of cognitive function (5-part battery test consisting of verbal learning, psychomotor function, attention, working memory, and delayed recall) that were analyzed by a central vendor, (b) (4) In the submission for NDA 210868 for lorlatinib, the statistical analysis report from (b) (4) is provided (page 4686 of the Interim Clinical Study Report) for a total of 213 patients enrolled in the dose expansion phase of Study B7461001.

Please comment on whether these assessment tools are validated to assess changes in cognitive function and whether the reported findings are clinically meaningful as they relate to changes in patients receiving lorlatinib.

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3. Outline Of Design Of Study B7461001

Study B7461001 is designated as a Phase "1/2" study, with an initial Phase 1 segment, followed by a later Phase 2 segment. The cognitive test battery to which this consultation applies was used during the second (Phase 2; dose expansion) segment of this study. However, the summary below is that for both phases of this study.

(The summary below is based on the report of Study B7461001 included in the original submission of NDA 210868. Study B7461001 was ongoing at that time and the data included in that report had a cut-off date of March 15, 2017).

The design of Study B7461001 was very complex and only the elements of that design that may be most pertinent to this consultation are summarized below.

This was an open-label, uncontrolled, multiple-center, multiple-dose, dose-escalation exploratory study in patients with metastatic non-small cell lung cancer.

The primary objective of the initial (Phase 1) segment of Study B7461001 was to evaluate the safety and tolerability of lorlatinib as a single agent at increasing dose levels in patients with advanced anaplastic lymphoma kinase-positive or advanced ROS1-positive non-small cell lung cancer so as to estimate the maximum tolerated dose and select the recommended dose for Phase 2. The starting dose of lorlatinib in this study was to be 10 mg once daily administered in 21-day cycles. Subsequently, escalating lorlatinib doses of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, and 400 mg, each administered once daily in 21-day cycles. Subsequently, lorlatinib doses of 25 mg BID, 35 mg BID, 50 mg BID and 75 mg BID were to be administered in 21-day cycles. Each dose cohort was to have a minimum of 3 patients.

The primary objective of the second (Phase 2) segment of Study B7461001 was to evaluate overall (intracranial and extracranial) and intracranial anti-tumor activity of lorlatinib at the recommended dose for this segment of the study, as derived from the results of the first segment. The dose of lorlatinib administered

in this segment was designated as 100 mg QD but could range from 25 mg QD to 100 mg QD administered in 21-day cycles, according to the study protocol. The population enrolled in Phase 2 was to consist of 6 different subpopulations.

The second phase of Study B7461001 is also referred to as the dose expansion segment of that study.

Approximately 260 patients were evaluated in Phase 2 of this study, with patient numbers in the individual subpopulations ranging from 24 to 50.

The (b) (4) components used in Phase 2 of Study B7461001 were as follows: Detection Test; Identification Test; One Back Test; International Shopping List Test; and International Shopping List Test-Delayed Recall. These were performed on Day 1 of each of 24 consecutive dosing cycles and at the end of treatment. A statistical analysis report of the data for those tests has been provided by (b) (4) and is included in the interim report of Study B7461001 contained in the original submission of this NDA.

4. Summary Comments

(The summary comments below are similar to those conveyed to the DOP-2) on June 14, 2018. They are based on the interim report of that study which was part of the original submission of this NDA on December 5, 2017).

The dose expansion phase of Study B74610001 was open-label and uncontrolled.

The cognitive tests used in this phase of Study B7461001 were the following items from the (b) (4) of tests: Detection Test; Identification Test; One Back Test; International Shopping List Test; and International Shopping List Test-Delayed Recall.

The above tests are intended to evaluate the following interrelated cognitive domains: psychomotor speed, attention, working memory, episodic memory, and verbal learning. The same tests can be considered to have been validated in that they are widely-used and appear to measure what they are intended to measure. Our Division is familiar with those tests.

In the second phase of Study B7461001, group mean performance on the Identification Test is reported to have declined from baseline over the course of the study. Group mean scores on the other 4 cognitive tests evaluated are reported to have remained relatively stable over the course of the study. However, in the absence of a placebo or other control arm, there is no means of determining if these or any other changes in cognitive test scores, or the lack of such changes, in that study had any relationship to the administration of lorlatinib (PF-06463922).

We do not generally consider it feasible to determine if the effect of an intervention on a cognitive outcome is by itself clinically meaningful. Our determination of whether any numerical change on a cognitive measure is clinically meaningful is usually made by determining if that change is accompanied by a change on a functional outcome (i.e., a measure of activities of daily living) or on a more global assessment. (We have not used patient-rated outcomes for that purpose). Thus, we are not able to determine whether any changes in cognitive test scores that may have occurred during the dose expansion phase of Study B7471001 were clinically meaningful.

Ranjit B. Mani, M.D.
Medical Reviewer
Division of Neurology Products

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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/

RANJIT B MANI
10/31/2018

NICHOLAS A KOZAUER
10/31/2018

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

NDA	210868
Brand Name	LORBRENA
Generic Name	Lorlatinib
Sponsor	Pfizer Global Research and Development
Indication	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs)
Dosage Form	Film-coated tablets
Drug Class	Inhibitor of ALK and ROS1 tyrosine kinases
Therapeutic Dosing Regimen	100 mg QD administered orally
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD not reached formally, but DLTs observed above 100 mg QD
Submission Number and Date	SDN# 001, 12/05/2017
Review Division	DOP2

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Study B7461001 supports the conclusion that no large mean increases in the ΔQTc interval (i.e., >20 ms) are anticipated with the proposed therapeutic dosing regimen of lorlatinib (100 mg QD), based on central tendency analysis (largest 90% CI upper bound was 12.1 ms with a mean of 10.1 ms). There was no placebo or positive control in the study. The QTc effects did not have any direct relationship with lorlatinib exposures. However, a PR interval prolongation was seen, based on central tendency analysis (largest 90% CI upper bound was 16.1 ms with a mean of 14.2 ms) and atrioventricular (AV) block events have been reported in patients receiving lorlatinib. There was a statistically significant relationship with lorlatinib concentration-dependent increase in PR prolongation and this concentration-dependent relationship was also supported by preclinical findings.

In this open-label, multicenter, single-arm, Phase 2 study (Phase 2 part of a Phase 1/2 Study B7461001), 275 patients received lorlatinib 100 mg QD dosing. Overall summary of findings are presented in Table 1 and Table 2.

Table 1: The Point Estimates and the 90% CIs of ΔQTcF Corresponding to the Largest Upper Bounds for 100 mg QD lorlatinib treatment in Phase 2 part of Study B7461001 (FDA Analysis)

Treatment	Time	N	Mean (ms)	90% CI (ms)
100 mg QD lorlatinib	Cycle 5 Day 1, 2 h post-dose	201	10.1	[8.0, 12.1]

Table 2: The Point Estimates and the 90% CIs of ΔPR Corresponding to the Largest Upper Bounds for 100 mg QD lorlatinib treatment in Phase 2 part of Study B7461001 (FDA Analysis)

Treatment	Time (hour)	N	Mean (ms)	90% CI (ms)
100 mg QD lorlatinib	Cycle 5 Day 1, 1 h post-dose	210	14.2	[12.4, 16.1]

The dose used in this study (100 mg QD) is the proposed therapeutic dose for the oncology indication. There is no accumulation of C_{max} for the drug with multiple dosing. Population PK analyses indicated lack of clinically significant effect of mild/moderate renal impairment and mild hepatic impairment on lorlatinib exposures. Formal hepatic and renal impairment studies are pending, and thus the information about the impact of severe hepatic or renal impairment is unknown. Based on the available data at the current time, the worst-case scenario would be drug interaction with strong CYP3A inhibitor (itraconazole), which results in 24% increase in C_{max}.

2 PROPOSED LABEL

The following is the sponsor's updated proposed labeling language for section 12.2 after the initial labeling edits by the Division with assistance from QT-IRT. Overall, the updated language is acceptable to the QT-IRT and we have only minor suggested edits as shown in red font below.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In 295 patients who received LORBRENA at the recommended dose of 100 mg once daily and had a ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper CI 19.4 ms) (b) (4) (b) (4) Among the 284 patients with baseline PR interval <200 ms, 14% had PR interval prolongation ≥200 ms after starting LORBRENA. The prolongation

of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1% of patients.

In 275 patients who received LORBRENA at the recommended dose in the activity-estimating portion of Study B7461001, no large mean increases from baseline in the QTcF interval (i.e., >20 ms) were detected.

***Reviewer's comments**: The values provided by the sponsor for the PR prolongation in the above proposal differ slightly from the reviewers' results (analysis differences explained below). The reviewers have confirmed the values quoted in the sponsor's analysis/proposal. These are more conservative (higher PR effect) than the reviewers' analysis and QT-IRT does not have any issues with labeling with these values.*

The differences between the reviewers' and sponsor's analyses are as follows:

i) Reviewer's analysis used data from subjects treated with 100 mg QD dose in Phase 2 part of Study B7461001 (n=275). Sponsor's analysis used all the subjects treated with 100 mg QD dose in Study B7461001 (n=295; 275 subjects from Phase 2, 17 from Phase 1, 3 from Japan LIC).

ii) Reviewer's central tendency results are based on by-time analysis. The sponsor used following methodology: "The absolute change from baseline was derived from the on treatment change from baseline. The largest absolute change was chosen per subject. If the increase and the decrease share the same maximum absolute change value, the increase from baseline was kept for further analysis. The summary statistics were calculated based on the on treatment change from baseline for records selected as the maximum absolute change from baseline."

3 BACKGROUND

3.1 PRODUCT INFORMATION

Lorlatinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). The proposed therapeutic dose is 100 mg QD administered orally.

3.2 MARKET APPROVAL STATUS

Lorlatinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The sponsor conducted 4 non-clinical *in vitro* electrophysiology studies to understand the safety and electrophysiology effects of lorlatinib (PF-0463922) and its major metabolite (PF-06895751). These studies assessed lorlatinib effects on the hERG potassium channel current (1702.07.QHJ and 170313.QHJ), L-type Ca^{2+} current (17GR038), and peak and late Na^{+} currents (17GR038 and 13GR078).

In vitro electrophysiology studies showed that lorlatinib does not affect peak Na^{+} current at 100 µM. It suppressed hERG current with an IC_{50} of 203.1 µM, L-type Ca^{2+} current (at 0 mV) with an IC_{50} of 44.0 µM, and increased a standing current at -40 mV (100 µM,

310.5 ± 130.4% increase) that could reflect either late Na^+ current or L-type Ca^{2+} current. Lorlatinib's major metabolite, PF-06895751-02, marginally affected hERG current (300 µM, 11.8% suppression). Whether PF-06895751-02 affects other cardiac ion channels of concern for proarrhythmia propensity was not addressed.

The sponsor also conducted an *ex vivo* study to explore the effect of lorlatinib in cardiac function in the guinea pig isolated heart (16LJ106). Concentration dependent and significant PR prolongation was observed at 1, 3 and 10 µM in this *ex vivo* study. In addition, PR prolongation was also observed in a non-clinical study that assessed lorlatinib's effects in the ECG in dogs (12LJ083).

Reviewer's comments: *Considering that lorlatinib's unbound human clinical exposure level at 100 mg QD is ~0.58 µM (C_{max} = 695 ng/mL or 1.7 µM), effects of lorlatinib on cardiac Ca^{2+}, Na^+, and hERG channels is not anticipated to translate to effects on QT_C (either shortening or prolongation). While the electrophysiology experiments suggested lorlatinib has low potential to block L-type Ca^{2+} current at clinical concentrations (IC_{50} of 44.0 µM vs. 1.7 µM total plasma C_{max}), PR prolongation was observed at concentrations close to clinical exposure in the ex vivo study (PR prolongation started at 1 µM). Thus, the PR prolongation observed in lorlatinib's clinical studies could be attributable to L-type Ca^{2+} channel block.*

For a complete assessment of the preclinical in vitro electrophysiology data, please see the consult review from Division of Applied Regulatory Science (DARS) by Dr. Tracey Lee in DARRTS.

3.4 Previous Clinical Experience

Refer to clinical cardiac safety section in Appendix 6.1.

3.5 Clinical Pharmacology

Appendix 6.1 summarizes the key features of lorlatinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 Overview

The sponsor submitted the following items for our review:

- Study report for a Phase 1/2 Study B7461001 in patient population (multiple dosing)
- Study report for a DDI Study B7461012 in healthy volunteers (single dose study)
- A population PK/PD report for analysis on pooled data from 8 different studies for evaluation of effect of drug concentration on QTc and PR intervals.
- Electronic datasets for the above reports
- Waveforms for Study B7461012 to the ECG warehouse.

Our review is primarily focused on data from Phase 2 part of Study B7461001, where 275 patients were dosed with the therapeutic dose of 100 mg QD. Also, our review evaluated data from a DDI Study B7461012 where 12 healthy subjects were dosed with 100 mg single dose (with and without concomitant administration of itraconazole) as a supportive

assessment, where ECGs were assessed using continuous holter monitoring for characterization of ECG intervals.

4.2 QT STUDIES

4.2.1 Design

The following table includes the details of the design of the two clinical studies evaluated in this submission.

Table 3: Details of study designs

Protocol number	Study B7461001	Study B7461012
Title	Phase 1/2 Study of PF-06463922 in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations	Phase 1, Open-Label, Fixed Sequence, 2-Period Study to Investigate the Effect of Multiple Doses of Itraconazole on the Pharmacokinetics of Single Dose PF-06463922 in the Fasted Condition
Population	Cancer patients	HV
Study Dates (Start – End)	8 January 2014 – TBD (15 March 2017 as data cutoff date)	16 August 2016 - 31 March 2017
QT Objective	To characterize the effect of multiple doses of lorlatinib on ECG parameters	To assess the Concentration-QTc and Concentration-PR relationship using holter monitor data in this dedicated QT study
Design, blinding and controls	Open label, multicenter, multiple dose, dose escalation; no placebo, no moxifloxacin	Non-randomized, open-label, 2 treatment, 2 period study to assess the effect of a strong CYP3A4/5 inhibitor (itraconazole) on the PK; no placebo, no moxifloxacin
Sample size and dosing regimen	<u>Phase 1 (Dose escalation)</u> 54 patients enrolled Doses from 10 to 200 mg QD <u>Phase 2</u> 276 patients enrolled 100 mg QD dosing	12 healthy subjects for 100 mg dose cohort. Lorlatinib 50 (n=2), 75 (n=2) or 100 mg (n=12) alone in Period 1 and then 50, 75, or 100 mg in combination with multiple dose itraconazole in Period 2 after a washout period of at least 10 days Only subjects receiving a 100 mg lorlatinib dose underwent 24-hour continuous Holter monitoring on two of the study days in each period as shown below. • Period 1, Day -1: Baseline • Period 1, Day 1: 100 mg lorlatinib

		• Period 2, Day 4: 200 mg QD itraconazole • Period 2, Day 5: 200 mg QD itraconazole + 100 mg lorlatinib
Dosing in fasted/fed state	With or without food (outpatient)	Fasted
ECG and PK assessments	Triplicate ECGs in the 7 day lead-in cohort at pre-dose, 1 and 4 h post-dose. In both Phase 1 and Phase 2, triplicate ECGs were on Cycle 1, Days 1, 8, and 15 at pre-dose and 1 h post-dose and on Cycles 2-5, Day 1 at pre-dose and 1 h post-dose. Time matched PK samples for above ECGs.	PK samples were collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, and 120 h post-dose. In addition to the Holter monitoring, triplicate ECGs were collected at pre-dose, 1, 2, 4, 12, and 24 h post-dose of each period and were paired with a PK collection.
Core Lab for ECG measurement?	No	Yes

4.2.1.1 Sponsor's Justification for Doses

Not applicable.

Reviewer's Comment: *While the MTD was not formally reached, lorlatinib was considered tolerable at the 100 mg QD in the dose escalation part, and it was declared the recommended Phase 2 dose, in patients with ALK-positive or ROS1-positive NSCLC. Phase 2 of Study B7461001 used this 100 mg QD dosing in patients and it is the proposed therapeutic dose. There is no accumulation of C_{max} for the drug with multiple dosing. Population PK analyses indicated lack of clinically significant effect of mild/moderate renal impairment and mild hepatic impairment on lorlatinib exposures. Formal hepatic and renal impairment studies are pending, and thus the information about the impact of severe hepatic or renal impairment is unknown. Based on the available data at the current time, the worst-case scenario would be DDI with strong CYP3A inhibitor (itraconazole), which results in 24% increase in C_{max}.*

4.2.1.2 Instructions with Regard to Meals

See Table 3.

Reviewer's Comment: *Dosing irrespective of food is acceptable as the food effect study with administration in fed state (high-calorie, high-fat meal) yielded 9% lower C_{max} and 5% higher AUC_{inf} relative to dosing in the fasted state, suggesting no significant food effect.*

4.2.1.3 ECG and PK Assessments

See Table 3.

Reviewer's Comment: *The ECG/PK sampling is appropriate to capture effects near T_{max} for the drug (~ 1-2 h) in both the studies. Further, the sampling also captures effects near T_{max} for most abundant metabolite, PF-06895751 (~24 h) and any delayed effects due to*

drug up to at least 24 h in the single dose study. While there is no accumulation for the drug (lorlatinib) with multiple dosing, the metabolite (PF-06895751) can accumulate and as per the sponsor the steady state for the metabolite is reached by day 15 with multiple dosing. The plasma concentration of this metabolite was measured only at a single visit of Cycle 1 Day 15 and the measurements were done in only a few subjects (n=10) in the Study B7461001. Thus, the metabolite PK was not adequate to analyze E-R relationship for QTc effects corresponding to metabolite concentrations.

4.2.2 Baseline

B7461001 Phase 2

Pre-dose baseline was used in this study.

B7461012

Time-matched baseline was used in this study.

4.2.3 ECG Collection

B7461001 Phase 2

Triplicate 12-lead ECGs were recorded at specified time points.

B7461012

12-lead ECGs (holter) were recorded after the subject had rested quietly for at least 10 minutes in a supine position. Triplicate 12-lead ECGs were obtained at different time points.

4.2.4 Sponsor's Results

4.2.4.1 Statistical Analyses

B7461001 Phase 2

The proportion of patients with absolute ECG results that met the criteria for categorical summarization is provided in Table 4.

Table 4: Categorical Summary of Post-Baseline Maximum ECG Data, All Cycles (Phase 2) - Safety Population

Parameter	Criteria	N	Total n (%)
Absolute values (msec), n (%)			
Maximum PR interval (msec)	<160	274	94 (34.3)
	160-<180	274	77 (28.1)
	180-<200	274	56 (20.4)
	200-<220	274	28 (10.2)
	220-<240	274	8 (2.9)
	240-<260	274	5 (1.8)
	≥260	274	6 (2.2)
Maximum QTcB (msec)	450-<480	275	101 (36.7)
	480-<500	275	30 (10.9)
	≥500	275	10 (3.6)
Maximum QTcF (msec)	450-<480	275	52 (18.9)
	480-<500	275	7 (2.5)
	≥500	275	2 (0.7)

Source: Table 14.3.4.3.3.1.2
Abbreviations: ECG=electrocardiogram; N=number of patients evaluated, n=number of patients meeting specified criterion.

Table 5: Shift Summary of Maximum Absolute PR Results (Phase 2) – Safety Analysis set

	Maximum Absolute PR Results (msec) n (%)							
Baseline (N=272)	**<160**	**160-<180**	**180-<200**	**200-<220**	**220-<240**	**240-<260**	**≥260**	**Total n (%)**
<160	94 (34.6)	71 (26.1)	17 (6.3)	4 (1.5)	1 (0.4)	2 (0.7)	0	189 (69.5)
160-<180	0	6 (2.2)	34 (12.5)	13 (4.8)	1 (0.4)	0	0	54 (19.9)
180-<200	0	0	4 (1.5)	11 (4.0)	3 (1.1)	2 (0.7)	1 (0.4)	21 (7.7)
200-<220	0	0	0	0	3 (1.1)	1 (0.4)	3 (1.1)	7 (2.6)
220-<240	0	0	0	0	0	0	1 (0.4)	1 (0.4)
240-<260	0	0	0	0	0	0	0	0
≥260	0	0	0	0	0	0	0	0
Total	94 (34.6)	77 (28.3)	55 (20.2)	28 (10.3)	8 (2.9)	5 (1.8)	5 (1.8)	272 (100)

Source: Table 14.3.4.4.2
Abbreviations: n=number of patients meeting specified criterion; N=number of patients evaluated.

Table 6: Categorization of ECG Maximum increase from Baseline (Phase 2)- Safety Analysis Set

Parameter	Criteria	N	Total n (%)
Maximum PR INTERVAL increase from baseline (msec)	>25%	272	40 (14.7)
	40-<60	272	19 (7.0)
	60-<80	272	9 (3.3)
	>=80	272	5 (1.8)
Maximum QTC INTERVAL increase from baseline (msec)	30<=Change<60	275	81 (29.5)
	Change>=60	275	17 (6.2)
Maximum QTCB INTERVAL (BAZETT'S CORRECTION) increase from baseline (msec)	30<=Change<60	275	87 (31.6)
	Change>=60	275	16 (5.8)
Maximum QTCF INTERVAL (FRIDERICIA'S CORRECTION) increase from baseline (msec)	30<=Change<60	275	71 (25.8)
	Change>=60	275	5 (1.8)

Baseline is defined as the average of the triplicate measurements prior to the first dose of study drug.
N = number of subjects with both baseline and post-baseline ECG measurements; n = number of subjects meeting criteria.
PFIZER CONFIDENTIAL Source Data: Table 16.2.8.3.4.2 Date of Reporting Dataset Creation: 25MAY2017 Date of Table Generation: 28MAY2017 (22:14)

B7461012

Table 7: QTcF outliers per absolute category and per change-from-baseline category (ECG Population)*

	Category	PF-06463922 100 mg	PF-06463922 100 mg + itraconazole 200 mg
Subject	Total	12	12
	QTcF >450 and ≤480 msec	0 (0%)	0 (0%)
	QTcF >480 and ≤500 msec	0 (0%)	0 (0%)
	QTcF > 500 msec	0 (0%)	0 (0%)
	ΔQTcF >30 and ≤60 msec	0 (0%)	0 (0%)
	ΔQTcF >60 msec	0 (0%)	0 (0%)
Timepoint	Total	120	120
	QTcF >450 and ≤480 msec	0 (0%)	0 (0%)
	QTcF >480 and ≤500 msec	0 (0%)	0 (0%)
	QTcF > 500 msec	0 (0%)	0 (0%)
	ΔQTcF >30 and ≤60 msec	0 (0%)	0 (0%)
	ΔQTcF >60 msec	0 (0%)	0 (0%)

**Baseline for the PF-06463922 100 mg group was Day -1 in Period 1, while baseline for the PF-06463922 100 mg+itraconazole 200 mg group was Day 4 in Period 2.*

Table 8: Categorical analyses for HR, PR, and QRS (ECG Population) *

	Category	PF-06463922 100 mg	PF-06463922 100 mg + itraconazole 200 mg
Subject	Total	12	12
	HR > 100 (bpm) with an increase in ΔHR > 25%	0 (0%)	0 (0%)
	HR < 50 (bpm) with a decrease in ΔHR > 25%	0 (0%)	0 (0%)
	PR > 220 (msec) with an increase in ΔPR > 25%	0 (0%)	0 (0%)
	Absolute PR ≥200 and <220 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥220 and <240 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥240 and <260 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥260 (msec)	0 (0%)	0 (0%)
	Absolute ΔPR ≥40 and <60 (msec)	0 (0%)	1 (8.3%)
	Absolute ΔPR ≥60 and <80 (msec)	1 (8.3%)	1 (8.3%)
	Absolute ΔPR ≥80 (msec)	0 (0%)	0 (0%)
	Relative ΔPR > 25%	2 (16.7%)	2 (16.7%)
	QRS > 120 (msec) with an increase in ΔQRS > 25%	0 (0%)	0 (0%)
Timepoint	Total	120	120
	HR > 100 (bpm) with an increase in ΔHR > 25%	0 (0%)	0 (0%)
	HR < 50 (bpm) with a decrease in ΔHR > 25%	0 (0%)	0 (0%)
	PR > 220 (msec) with an increase in ΔPR > 25%	0 (0%)	0 (0%)
	Absolute PR ≥200 and <220 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥220 and <240 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥240 and <260 (msec)	0 (0%)	0 (0%)
	Absolute PR ≥260 (msec)	0 (0%)	0 (0%)
	Absolute ΔPR ≥40 and <60 (msec)	0 (0%)	1 (0.8%)
	Absolute ΔPR ≥60 and <80 (msec)	1 (0.8%)	1 (0.8%)
	Absolute ΔPR ≥80 (msec)	0 (0%)	0 (0%)

	Category	PF-06463922 100 mg	PF-06463922 100 mg + itraconazole 200 mg
	Relative ΔPR > 25%	2 (1.7%)	7 (5.8%)
	QRS > 120 (msec) with an increase in ΔQRS > 25%	0 (0%)	0 (0%)

**Baseline for the PF-06463922 100 mg group was Day -1 in Period 1, while baseline for the PF-06463922 100 mg+itraconazole 200 mg group was Day 4 in Period 2.*

4.2.4.2 Safety Analysis

B7461001 Phase 2

In Phase 2, a total of 2 (0.7%) patients experienced AV block first degree (both Grade 1), and 1 (0.4%) patient experienced AV block complete (Grade 3, non-treatment-related). The events of AV block first degree reported for Patients (b) (6) were both treatment-related. The Grade 3 AV block complete for Patient (b) (6) was an SAE and resulted in temporary discontinuation of lorlatinib. No other patients had permanent discontinuations of lorlatinib due to AV block AEs. No patients in Phase 2 required dose reductions due to AV block AEs. No permanent discontinuations associated with AV block were reported.

Treatment-related QT interval prolongation events were reported for 16 (5.8%) patients. There were no SAEs of ECG QT prolonged. One (1) patient (b) (6) had a Grade 3 AE of ECG QT prolonged which required a temporary discontinuation. No other dose reductions or temporary discontinuations associated with QT interval prolonged.

Subject (b) (6) (83 year old woman) had a pre-existing history of prolonged QTc interval. On (b) (6) (Cycle 1 Day 1), the prolonged QTc interval (QTcF>500 ms) was reported as Grade 3 adverse event. On (b) (6) (Cycle 1 Day 7) a decision was made to permanently discontinue the patient from further treatment due to a protocol violation, specifically that the patient had machine read ECG of >500 msec at Screening, which is exclusionary per the protocol. The study drug was permanently discontinued from (b) (6) (Cycle 1 Day 8). The subject refused further follow-up and was withdrawn from the study on (b) (6). The AE of prolonged QTc interval was still present at the time of last report. No clinical signs or symptoms of torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia were reported. The investigator assessed the causality of the event as unrelated to the study drug, but related to high QTc interval at baseline.

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There were no deaths or SAEs reported in the study.
One (1) subject (b) (6) in Cohort 4 had increases in PR interval following dosing with both PF-06463922 100 mg and itraconazole 200 mg multiple dose; at 1 hour postdose, the increase in PR interval was 65 msec and at 2 hours postdose, the increase in PR interval was 54 msec. Both represented a percent increase from baseline of ≥25%. No other subject in Cohorts 3 and 4 had ECG parameter values that met predefined criteria. Also, no subject had PR interval ≥200 msec at any time during the study.

4.2.4.3 Clinical Pharmacology

B7461001 Phase 2

No exposure-response analysis was presented by the sponsor for this study alone.

B7461012

A linear mixed effects model was used for holter monitor data from Study B7461012 to assess the relationship between QTc and plasma concentrations. The model showed a significant association between increasing lorlatinib concentrations and a shortening of the QTc interval. At the average steady state observed maximum plasma concentration (C_{max}) from lorlatinib 100 mg QD dosing, the estimated decrease in the length of the QTcF interval was -22.11 msec (95% CI: (-25.96, -18.64)). The analysis with the pooled dataset from 8 studies including Study B7461001 and B7461012 showed that at the steady state lorlatinib C_{max} from 100 mg QD dosing, the estimated decrease in the length of the QTcF interval was -7.03 msec (95% CI: (-8.09, -5.88)).

Similarly, a linear mixed effects model for PR change from baseline was developed using the holter monitor data from Study B7461012 that included three parameters: an intercept, a baseline PR interval effect, and a slope for concentration. The model showed a significant association between increasing lorlatinib concentrations and a prolonging of the PR interval. Simulations of the PR interval change from baseline using three potential baseline PR interval lengths (138.8 msec, 150 msec, and 170 msec) and the average single dose and steady-state C_{max} concentration observed in the phase 2 portion of B7461001 for lorlatinib 100 mg dosing, showed a prolonging of the length of the PR interval with increasing concentrations of lorlatinib.

Reviewer's comments: Reviewer's analysis is presented in Section 5.3. Time profiles for multiple dosing suggested that QTc effects did not have a direct relationship with lorlatinib exposures. So, further exposure-response relationship is not presented for QTc effects. PR prolongation effects had a statistically significant positive relationship with lorlatinib exposures, which is in line with the sponsor's findings.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate (>10 bpm) were observed (Section 5.2.3). The reviewer's analysis was also carried out using QTcF.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

B7461001 Phase 2

Table 9 presents the descriptive statistics (mean and 90% CI) for ΔQTcF ordered by cycle, cycle day and time points and graphically presented in Figure 1 (only timepoints where sample size is at least 70% of total population is used for this representation).

Table 9: Descriptive Statistics for ΔQTcF

Analysis Variable : ΔQTCF							
CYCLE	CYCDAY	TIME	#Obs	# Subj	Mean	Lower 90% CL	Upper 90% CL
1	1	1	267	267	-9.04	-10.22	-7.87
1	1	2	234	234	-5.54	-6.79	-4.28
1	8	0	191	191	2.04	0.55	3.52
1	8	1	192	192	-2.17	-3.91	-0.43

Analysis Variable : ΔQTCF							
CYCLE	CYCDAY	TIME	#Obs	# Subj	Mean	Lower 90% CL	Upper 90% CL
1	8	2	169	169	1.44	-0.33	3.21
1	15	0	198	198	6.01	4.15	7.88
1	15	1	197	197	1.84	0.07	3.61
1	15	2	184	184	4.98	2.95	7.01
2	1	0	237	237	8.09	6.34	9.83
2	1	1	251	250	4.42	2.76	6.07
2	1	2	229	229	7.83	6.14	9.52
3	1	0	223	223	8.30	6.37	10.24
3	1	1	233	233	4.65	2.79	6.52
3	1	2	220	220	7.32	5.34	9.31
4	1	0	220	220	8.89	7.03	10.75
4	1	1	227	227	4.84	2.97	6.70
4	1	2	214	214	9.06	7.15	10.97
5	1	0	207	207	8.51	6.63	10.39
5	1	1	212	212	6.09	4.17	8.01
5	1	2	201	201	**10.07**	**8.00**	**12.13**

Figure 1: Mean and 90% CI ΔQTcF (Study B7461001 Phase 2)

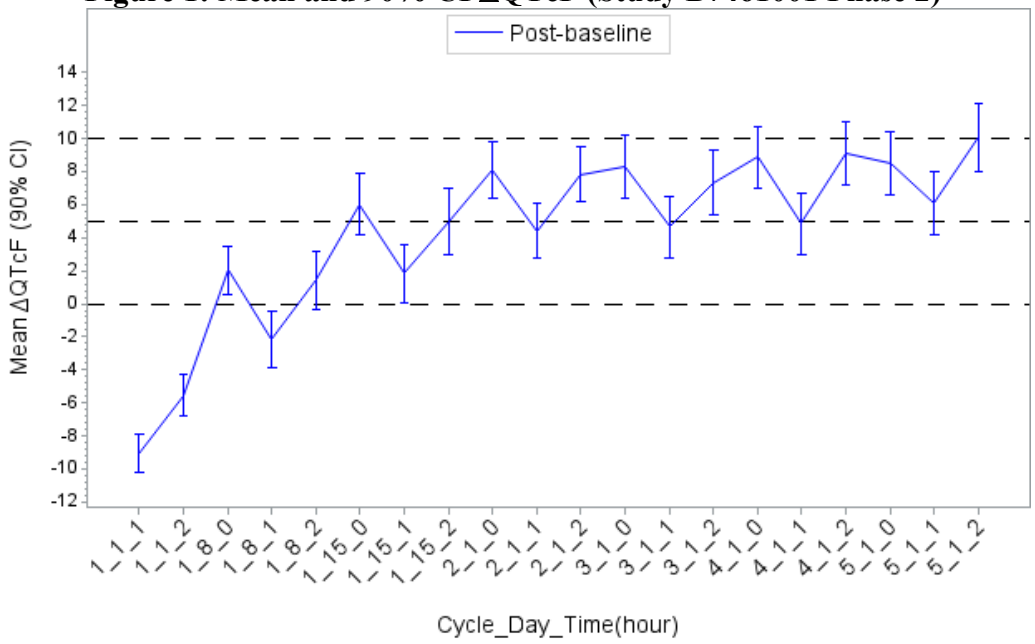

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are < 350 ms, between 350 ms and 450 ms, between 450 ms and 480 ms., between 480 ms and 500 ms and >= 500 ms. There were two subjects whose QTcF were above 500 ms in post-baseline group, which matched with the sponsor's analysis.

Table 10: Categorical Analysis for QTcF

	Total N		300 ms<=Value<350 ms		350 ms<=Value<450 ms		450 ms<=Value<480 ms		480 ms<=Value<500 ms		Value>=500 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	275	275	1 (0.4%)	1 (0.4%)	261 (94.9%)	261 (94.9%)	12 (4.4%)	12 (4.4%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)
Post-baseline	275	5019	6 (2.2%)	8 (0.2%)	273 (99.3%)	4738 (94.4%)	61 (22.2%)	250 (5.0%)	8 (2.9%)	19 (0.4%)	2 (0.7%)	4 (0.1%)

Note: Number of subjects in each category are not mutually exclusive.

Table 11 lists the categorical analysis results for ΔQTcF. Five subjects had QTcF value greater than 60 ms compared to baseline value, which matched with the sponsor's analysis.

Table 11: Categorical Analysis of ΔQTcF

	Total N		Value<-40 ms		-40 ms<= Value< -20 ms		-20 ms<= Value<0 ms		0 ms<= Value<30 ms		30 ms<= Value<60 ms		Value>=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Post-baseline	275	5014	12 (4.4%)	26 (0.5%)	96 (34.9%)	266 (5.3%)	263 (95.6%)	1725 (34.4%)	260 (94.5%)	2724 (54.3%)	76 (27.6%)	253 (5.0%)	5 (1.8%)	20 (0.4%)

Note: Number of subjects in each category are not mutually exclusive.

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Table 12 presents the descriptive statistics (mean and 90% CI) for ΔQTcF ordered by period, period day and time points.

Table 12: Descriptive Statistics for ΔQTcF

PERIOD	DAY	TIME	N	Mean	Lower 90% CL	Upper 90% CL
1	1	0	12	-0.51	-2.22	1.21
		0.5	12	-7.61	-13.01	-2.21
		1	12	-14.88	-18.80	-10.95
		1.5	12	-15.91	-18.21	-13.60
		2	12	-12.25	-14.99	-9.50
		4	12	-13.19	-15.54	-10.84
		6	12	-12.14	-15.01	-9.27
		8	12	-11.33	-13.85	-8.81
		12	12	-1.74	-4.63	1.14
		24	12	-0.05	-2.50	2.40
2	4	0	12	4.29	1.49	7.09
		0.5	12	1.49	-3.00	5.97
		1	12	-0.24	-3.46	2.97
		1.5	12	0.83	-2.02	3.68
		2	12	3.77	0.92	6.63
		4	12	3.25	0.33	6.16
		6	12	2.94	0.78	5.09
		8	12	7.56	4.45	10.67
		12	12	8.93	4.95	12.91
	5	0	12	-0.46	-3.37	2.45
		0.5	12	-8.02	-13.20	-2.83
		1	12	-12.45	-15.23	-9.67
		1.5	12	-11.92	-14.20	-9.63
		2	12	-8.23	-11.21	-5.25
		4	12	-7.37	-10.17	-4.57
		6	12	-6.28	-9.47	-3.08
		8	12	-4.13	-7.73	-0.54
		12	12	4.27	0.01	8.53
		24	12	4.06	1.30	6.82

Table 13 lists the categorical analysis results for QTcF. No subject's value was greater than 450 ms.

Table 13: Categorical Analysis for QTcF

	Total N		350 ms<=Value<450 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	12	108	12 (100%)	108 (100%)
Post-baseline	12	348	12 (100%)	348 (100%)

Table 14 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 30 ms.

Table 14: Categorical Analysis of ΔQTcF

	Total (N)		-40 ms<= Value< -20 ms		-20 ms<= Value<0 ms		0 ms<= Value<30 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Post-baseline	12	348	6 (50.0%)	15 (4.3%)	12 (100.0%)	200 (57.5%)	12 (100.0%)	133 (38.2%)

Note: Number of subjects in each category are not mutually exclusive.

Reviewer's comments: In the central tendency analysis, there seem to be some negative values for ΔQTcF at the first dose in Study B7461001 Phase 2 and at the single dose in Study B7461012. In the absence of a placebo control in these studies, it is not clear whether this is a real effect or just an artifact. The observations for data from previous TQT studies suggest that the placebo arm itself could show a change from baseline in QTcF of approximately -5 ms at a mean level, which might partially explain these observations.

5.2.2 PR Analysis

B7461001 Phase 2

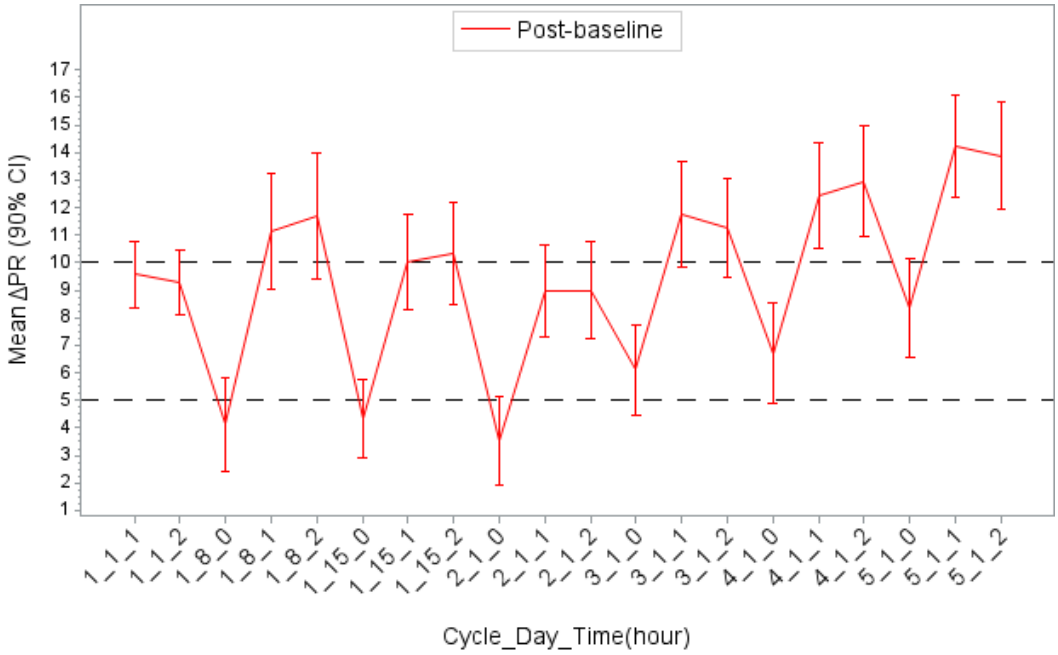
Table 15 presents the descriptive statistics (mean and 90% CI) for ΔPR ordered by cycle, cycle day and time points and graphically presented in Figure 2.

Table 15: Descriptive Statistics for ΔPR

Analysis Variable : ΔPR							
CYCLE	CYCDAY	TIME	#Obs	#Subj	Mean	Lower 90% CL for Mean	Upper 90% CL for Mean
1	1	1	267	264	9.57	8.38	10.76
1	1	2	234	231	9.30	8.13	10.47
1	8	0	191	189	4.12	2.39	5.85
1	8	1	192	190	11.14	9.02	13.25
1	8	2	169	167	11.70	9.39	14.01
1	15	0	198	196	4.35	2.94	5.76
1	15	1	197	194	10.01	8.29	11.73
1	15	2	184	182	10.34	8.48	12.19
2	1	0	237	234	3.53	1.89	5.16
2	1	1	251	247	8.99	7.31	10.66
2	1	2	229	224	9.00	7.21	10.79
3	1	0	223	219	6.11	4.47	7.74
3	1	1	233	231	11.76	9.83	13.69
3	1	2	220	217	11.26	9.46	13.05
4	1	0	220	218	6.70	4.86	8.53
4	1	1	227	225	12.45	10.53	14.38
4	1	2	214	212	12.96	10.96	14.97

Analysis Variable : ΔPR							
CYCLE	CYCDAY	TIME	#Obs	#Subj	Mean	Lower 90% CL for Mean	Upper 90% CL for Mean
5	1	0	207	205	8.34	6.57	10.12
5	1	1	212	**210**	**14.24**	**12.37**	**16.11**
5	1	2	201	199	13.89	11.94	15.84

Figure 2: Mean and 90% CI ΔPR (Study B7461001 Phase 2)



The outlier analysis results for PR are presented in Table 16. There were 45 subjects who had experienced PR interval greater than 200 ms and 19 subjects who had experienced PR interval greater than 220 ms in post-baseline data set. There were 265 patients who had a baseline PR interval less than 200 ms, and out of these 38 (14%) patients had PR interval prolongation greater than 200 ms after starting lorlatinib.

Table 16: Categorical Analysis for PR

	Total (N)		Value<=200 ms		Value>200 ms		Value>220 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	272	272	265 (97.4%)	265 (97.4%)	7 (2.2%)	7 (2.2%)	1 (0.4%)	1 (0.4%)
Post-baseline	272	4973	268 (98.5%)	4625 (93.0%)	45 (16.5%)	348 (7.0%)	19 (7.0%)	152 (3.1%)

Note: Number of subjects in each category are not mutually exclusive.

Table 17 lists the categorical analysis results for ΔPR. Thirty-one subjects had ΔPR value greater than 40 ms.

Table 17: Categorical Analysis for ΔPR

	Total N		Value<=20 ms		Value>20 ms		Value> 40 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Post-baseline	272	4954	269 (98.9%)	4134 (83.4%)	139 (51.1%)	820 (16.6%)	31 (11.4%)	179 (3.6%)

Note: Number of subjects in each category are not mutually exclusive.

There were a total of 12 subjects, who experienced PR greater than 220 ms and ΔPR greater than 40 ms.

B7461012

Table 18 presents the descriptive statistics (mean and 90% CI) for ΔPR ordered by cycle, cycle day and time points.

Table 18: Descriptive Statistics for ΔPR

PERIOD	DAY	TIME	# Subj.	Mean	Lower 90% CL	Upper 90% CL
1	1	0	12	3.05	-0.90	6.99
		0.5	12	3.12	-0.64	6.87
		1	12	15.05	4.70	25.39
		1.5	12	13.31	7.04	19.58
		2	12	9.08	3.33	14.84
		4	12	4.78	0.30	9.26
		6	12	-2.24	-6.77	2.30
		8	12	4.39	1.50	7.28
		12	12	1.75	-0.46	3.96
		24	12	6.17	2.33	10.01
2	4	0	12	0.87	-6.30	8.04
		0.5	12	-0.94	-8.58	6.71
		1	12	9.65	4.36	14.95
		1.5	12	2.75	-1.69	7.19
		2	12	-1.35	-7.55	4.86
		4	12	0.15	-4.15	4.45
		6	12	0.49	-2.22	3.20
		8	12	-2.12	-5.64	1.39
		12	12	2.05	-1.24	5.34
	5	0	12	5.36	-1.15	11.87
		0.5	12	3.32	-3.41	10.06
		1	12	20.34	10.87	29.81
		1.5	12	18.44	11.36	25.51
		2	12	13.88	7.96	19.80
		4	12	7.07	2.27	11.88
		6	12	3.86	0.99	6.73
		8	12	3.69	1.40	5.98
		12	12	6.64	3.51	9.76
		24	12	8.56	1.59	15.52

There are no subjects who experienced post-baseline PR interval greater than 200 ms.

Table 19 lists the categorical analysis results for ΔPR. Two subjects had ΔPR greater than 40 ms.

Table 19: Categorical Analysis for ΔPR

	Total N		Value<=20 ms		Value>20 ms		Value>40 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Post-baseline	12	348	12 (100.0%)	326 (93.7%)	6 (50.0%)	22 (6.3%)	2 (16.7%)	5 (1.4%)

Note: Number of subjects in each category are not mutually exclusive.

5.2.3 HR Analysis

B7461001 Phase 2

Descriptive statistics for HR are presented in Table 20.

Table 20: Descriptive Statistics for ΔHR

Analysis Variable : ΔHR							
CYCLE	DAY	TIME	#Obs	#Subj	ΔHR_Mean	Lower 90% CL	Upper 90% CL
1	1	1	267	267	-8.10	-8.81	-7.39
1	1	2	234	234	-7.92	-8.70	-7.14
1	8	0	191	191	2.65	1.29	4.02
1	8	1	192	192	-4.14	-5.44	-2.83
1	8	2	169	169	-3.85	-5.29	-2.41
1	15	0	198	198	3.47	2.10	4.83
1	15	1	197	197	-3.18	-4.55	-1.81
1	15	2	184	184	-2.50	-3.94	-1.06
2	1	0	237	237	4.32	3.07	5.57
2	1	1	251	250	-3.04	-4.28	-1.80
2	1	2	229	229	-1.43	-2.81	-0.05
3	1	0	223	223	4.04	2.71	5.37
3	1	1	233	233	-2.50	-3.86	-1.14
3	1	2	220	220	-1.60	-3.04	-0.17
4	1	0	220	220	3.92	2.57	5.27
4	1	1	227	227	-2.83	-4.29	-1.38
4	1	2	214	214	-2.18	-3.65	-0.71
5	1	0	207	207	3.54	2.06	5.01
5	1	1	212	212	-2.92	-4.36	-1.48
5	1	2	201	201	-2.31	-3.81	-0.81

Table 21 lists the number of subjects as well as the number of observations whose HR values are greater than 100 bpm. There were 63 subjects who experienced HR above 100 bpm.

Table 21: Categorical Analysis for HR

	Total (N)		Value>100 bpm	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	275	275	14 (5.1%)	14 (5.1%)
Post-baseline	275	5019	63 (22.9%)	246 (4.9%)

Note: Number of subjects in each category are not mutually exclusive.

The sponsor did not provide any data on HR measurements for protocol B7461012. HR was calculated using average RR for FDA data set. Descriptive statistics for HR are presented in Table 22.

Table 22: Descriptive Statistics for HR

PERIOD	DAY	TIME	#Subj	Mean	Lower 90% CL	Upper 90% CL
1	1	0	12	64.22	56.60	71.84
		0.5	12	60.23	54.18	66.29
		1	12	59.43	53.91	64.94
		1.5	12	57.95	52.43	63.47
		2	12	58.57	53.22	63.91
		4	12	60.59	54.56	66.63
		6	12	66.60	60.87	72.32
		8	12	62.12	56.19	68.05
		12	12	68.93	62.05	75.82
		24	12	59.11	53.21	65.01
2	4	0	12	59.35	53.90	64.80
		0.5	12	58.00	53.12	62.87
		1	12	60.29	55.53	65.05
		1.5	12	60.41	55.72	65.11
		2	12	60.43	55.00	65.86
		4	12	61.73	56.80	66.65
		6	12	63.92	58.19	69.66
		8	12	61.43	55.99	66.87
		12	12	64.77	58.80	70.74
	5	0	12	63.67	58.10	69.23
		0.5	12	59.85	54.75	64.96
		1	12	60.77	56.04	65.50
		1.5	12	59.10	54.08	64.11
		2	12	60.27	55.60	64.94
		4	12	59.63	54.62	64.64
		6	12	67.22	61.75	72.69
		8	12	61.91	56.74	67.09
		12	12	66.24	60.21	72.27
		24	12	59.78	55.48	64.08

5.2.4 QRS Analysis

B7461001 Phase 2

The outlier analysis results for QRS are presented in Table 23. There were 30 subjects who experienced post-baseline QRS interval greater than 110 ms.

Table 23: Categorical Analysis for QRS

	Total (N)		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.

	Total (N)		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	275	275	28 (10.2%)	28 (10.2%)	11 (4.0%)	11 (4.0%)
Post-baseline	275	5021	58 (21.1%)	425 (8.5%)	30 (10.9%)	137 (2.7%)

Note: Number of subjects in each category are not mutually exclusive.

B7461012

The sponsor did not provide any data on QRS measurements.

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Study B7461012 studied a single dose of 100 mg lorlatinib with and without itraconazole and itraconazole increased the exposure by just 24%. Furthermore, this study did not have any placebo or positive control and the QTc signal with the single dose in this study was not in line with the overall QTc signal with multiple dosing seen for the therapeutic dose of 100 mg QD in Study B7461001 Phase 2 (refer to Table 12, Table 9 and Figure 1). Thus, the reviewer's assessments for exposure-response relationship focused on data from Study B7461001 Phase 2.

Figure 3 shows the comparison of drug concentration (lorlatinib), ΔPR and ΔQTcF across different cycles for the therapeutic dose of 100 mg QD of lorlatinib in Study B7461001 Phase 2. As there is no accumulation of lorlatinib with multiple dosing, the concentration-time profile across all cycles looked similar.

The comparison of time profiles for lorlatinib concentration and ΔQTcF showed that QTc effects did not have any direct relationship with lorlatinib exposures (Figure 3). Thus, an exposure-response relationship is not presented in this review (an exploratory E-R analysis with lorlatinib concentration showed a large positive intercept and a negative slope; data not shown). While there is no accumulation for the drug (lorlatinib) with multiple dosing, the metabolite (PF-06895751) can accumulate and as per the sponsor the steady state for the metabolite is reached by day 15 with multiple dosing. The plasma concentration of this metabolite was measured only at a single visit of Cycle 1 Day 15 and the measurement was done in only a few subjects (n=10) (Figure 4). Thus, the metabolite sampling was not adequate to analyze E-R relationship for QTc effects corresponding to metabolite concentrations.

The comparison of time profiles for lorlatinib concentration and ΔPR showed that PR effects may have a direct relationship with lorlatinib exposures (Figure 3). There was a statistically significant positive relationship for lorlatinib concentration-ΔPR assessments (Figure 5). The mean slope for lorlatinib concentration-ΔPR relationship was 8 ms per µg/mL (p-value= 0.04). The first decile bin (corresponding to low exposures) for observed ΔPR seems to show high ΔPR value and this discrepancy is largely contributed by measurements in later cycles (e.g., Cycles 4-5) where the ΔPR values at C_{trough} are higher despite similar C_{trough} values as the earlier cycles/visits. Excluding the data from

cycles 4 and 5 leads to a larger mean estimate of slope (11 ms per µg/mL; p-value= 0.003) for lorlatinib concentration-ΔPR relationship. The concentration-dependent relationship for PR prolongation was also supported by preclinical findings.

Figure 3: Time-profile of lorlatinib concentration, ΔPR, and ΔQTcF (Study B7461001 Phase 2)

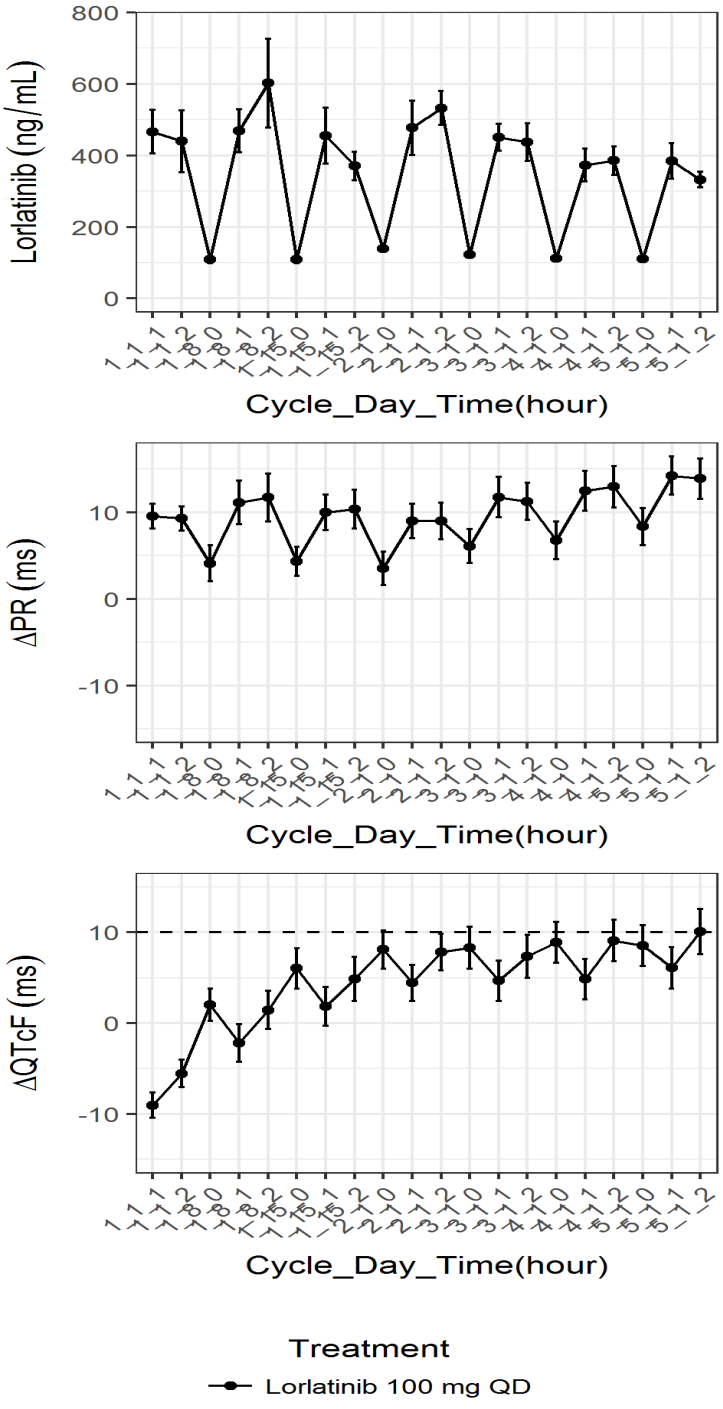


Figure 4: Time-profile of metabolite (PF-06895751) concentration (Study B7461001 Phase 2)

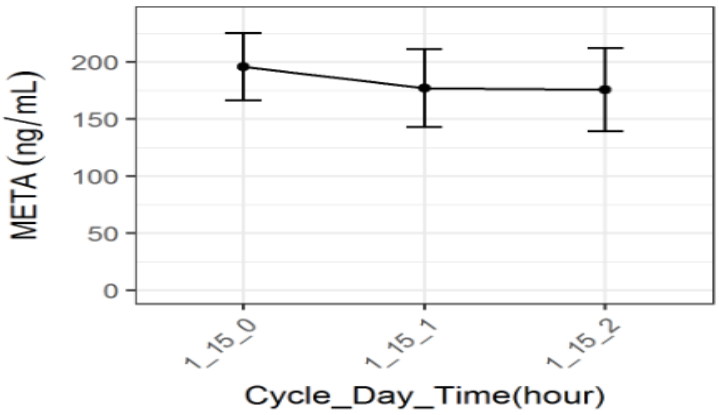
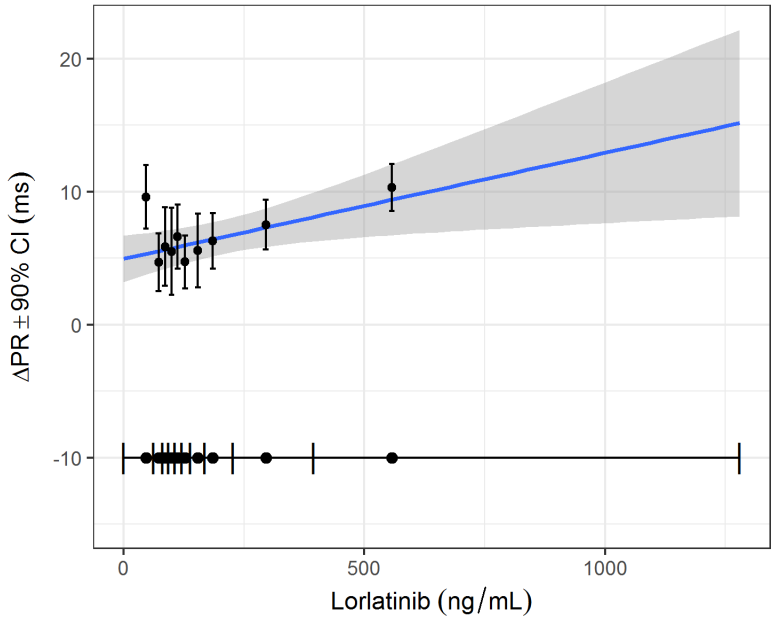


Figure 5: Exposure-response relationship for PR prolongation with lorlatinib concentrations (Study B7461001 Phase 2)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

In Phase 2 of study B7461001, there were 4/276 (1.5%) subjects who reported AEs within the MedDRA SMQ of Torsade de pointes/QTc prolongation. The AEs were cardiac arrest, syncope and loss of consciousness. There was 1 subject who experienced a seizure. There were no reports of torsade de pointes.

MedDRA Preferred Terms	*Events*	*Number of subjects*	*Proportion of 276 (%)*	*Proportion C.I. (lower bound) (%)*	*Proportion C.I. (upper bound) (%)*
Cardiac arrest	1	1	0.36	0.06	2.02
Loss of consciousness	1	1	0.36	0.06	2.02
Syncope	2	2	0.72	0.2	2.6
Seizure	1	1	0.36	0.06	2.02

Source: Reviewer's MAED analysis using dataset advers.xpt

Two subjects had QTcF values above 500 ms in post-baseline group.

- Subject (b) (6) had a baseline QTcF of 509 ms and had three post-treatment QTcF values >500 ms.
- Subject (b) (6) had a baseline QTcF of 417 ms and had a single QTcF value of 508 ms (91 m increase from baselines) on Cycle 1 Day 15 at 2 hours. All other QTcF values were <460 ms. ECG comments state that the subject had ST & T wave abnormalities on all the ECGs. All ECGs were listed as abnormal and not clinically significant.

Five subjects had ΔQTcF value greater than 60 ms.

- Subject (b) (6) is described above.
- Subject had ΔQTcF >60 ms at 15 time points even though none of the QTcF values were >430 ms. This is most likely due to an inaccurate baseline measurement. A single baseline QTcF value of 333 ms was used, although the subject had a normal screening value of 411 ms. If an average of baseline and screening values were used (372 ms), the largest increase from baseline would be <60 ms.
- Subject (b) (6) had a baseline QTcF of 409 ms. At an unscheduled visit on (b) (6) (study day 50), the QTcF was 485 ms (76 ms increase from baseline). At all other visits, the QTcF values were <453 ms. On study day 50, the subject experienced an SAE of pericardial effusion and tachycardia.
- Subject (b) (6) had a baseline QTcF of 390 ms. At the predose time point on Days 12 and 15, the QTcF values were 454 ms and 462 ms, respectively. Following dosing, the QTcF values decreased to 387 ms and 398 ms at T_{max}.
- Subject (b) (6) had baseline QTcF of 418 ms. On Day 1 of Cycle 2, the predose QTcF was 479 ms (61 ms increase from baseline). The QTcF was 475 ms (57 ms increase from baseline) and 469 ms (51 ms increase from baseline) at 1 and 2 hours post-dosing. At all other times, the increase from baseline was <20 ms.

5.4.2 ECG assessments

Triplicate ECG waveforms from study B7461012 in the ECG warehouse were reviewed. According to ECG warehouse statistics based on automated algorithm, 0.14% of ECGs were reported to have significant QT bias. Additional comprehensive assessment of QT bias showed no significant QT or QTcF bias (Table 24 and Table 25). Overall ECG acquisition and interpretation in this study appears acceptable.

Table 24: QT bias assessment for B7461012

Treatment	# of ECGs	Mean (sd)	Slope [95% CI]
ALL	4326	-4.32 (4.73) ms	1.04 [0.55 to 1.53] ms per 100 ms
Active	3295	-4.3 (4.49) ms	1.55 [1 to 2.09] ms per 100 ms
Itraconazole	1031	-4.41 (5.43) ms	0.02 [-1.09 to 1.12] ms per 100 ms

Table 25: QTcF bias assessment for B7461012

Treatment	# of ECGs	Mean (sd)	Slope [95% CI]
ALL	4326	-4.43 (4.75) ms	-5.02 [-5.89 to -4.15] ms per 100 ms
Active	3295	-4.41 (4.51) ms	-4.9 [-5.9 to -3.91] ms per 100 ms
Itraconazole	1031	-4.47 (5.44) ms	-5.94 [-8.01 to -3.88] ms per 100 ms

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen:100 mg QD Single Dose PK at the maximum proposed clinical dosing regimen (100 mg QD) Geometric Mean C_{max} (%CV): 695 (40) ng/mL Geometric Mean AUC_{inf} (%CV): 9088 (35) ng·h/mL Steady-State PK at the maximum proposed clinical dosing regimen (100 mg QD) Geometric Mean C_{max} (%CV): 577 (42) ng/mL Geometric Mean AUC_{tau} (%CV): 5650 (39) ng·h/mL
Maximum tolerated dose	The MTD was not reached in the Phase 1 portion of First In Patient Phase 1 Study B7461001 as only 1 patient met the criteria of a DLT. The patient was treated with lorlatinib at 200 mg QD and did not receive 16 of the planned 21 doses of lorlatinib during Cycle 1 due to toxicities attributed to study drug, which met the protocol definition of a DLT. This patient experienced Grade 1 and Grade 2 CNS effects during Cycle 1, including Grade 2 aphasia and cognitive disorder, and Grade 1 visual impairment and abnormal dreams and lorlatinib was temporarily discontinued for the remainder of the cycle. Additionally, in the 150 and 200 mg QD cohorts, the majority of patients experienced AEs resulting in a temporary discontinuation and/or dose reduction. As a result, it was agreed upon by the Sponsor and the Phase 1 Investigators to evaluate doses lower than 200 mg QD and consider an alternative dosing regimen. BID dosing was subsequently evaluated to assess whether reducing the C_{max} would lessen the CNS effects. Patients did not tolerate the 75 mg or 100 mg BID dosing. Thus, while the MTD was not formally reached, lorlatinib was considered tolerable at the **100 mg QD, which was declared the recommended Phase 2 dose**, in patients with ALK positive or ROS1-positive NSCLC.
Principal adverse events	Study B7461001 is an ongoing Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, PD and antitumor efficacy exploration study of single-agent lorlatinib in patients with advanced ALK-positive or advanced ROS1-positive NSCLC. The following reported most common adverse events are based on a data cutoff date of 15 March 2017. In Phase 1 (doses ranging from 10-200 mg QD and 35-100 mg BID), the most frequently reported all-causality AEs (>30% patients) included HYPERCHOLESTEROLEMIA (74.1%), EDEMA (63.0%), PERIPHERAL NEUROPATHY (57.4%), FATIGUE (48.1%), HYPERTRIGLYCERIDEMIA (42.6%), COGNITIVE EFFECTS (38.9%) and Anaemia (31.5%). Most events were Grades 1 and 2 in severity. In Phase 1, the most frequent treatment-related AEs (>30% patients) were HYPERCHOLESTEROLEMIA (72.2%), EDEMA (53.7%), HYPERTRIGLYCERIDEMIA (42.6%) and PERIPHERAL NEUROPATHY (40.7%). Grade 3 or 4 treatment-related AEs were reported in 18 (33.3%) patients. Treatment-related Grade 3 AEs were reported in 14 (25.9%) patients, with the most frequently reported (>5%) Grade 3 AEs being Lipase increased (7.4%), HYPERTRIGLYCERIDEMIA (7.4%), HYPERCHOLESTEROLEMIA (7.4%), and Weight increased (5.6%). Grade 4 AEs were reported in 4 (7.4%) patients, with the most frequently reported (>5%) Grade 4 AE being HYPERCHOLESTEROLEMIA (5.6%).

		In Phase 2 (100 mg QD starting dose), the most frequently reported (>20%) all-causality AEs were HYPERCHOLESTEROLEMIA (81.8%), HYPERTRIGLYCERIDEMIA (60.7%), EDEMA (51.3%), PERIPHERAL NEUROPATHY (43.3%), Dyspnoea 23.3%, COGNITIVE EFFECTS 22.5%, FATIGUE 22.2%, MOOD EFFECTS 21.8% and Weight increased 20.7%. In Phase 2, the most frequent (>20%) treatment-related AEs were HYPERCHOLESTEROLEMIA (81.5%), HYPERTRIGLYCERIDEMIA (60.4%), EDEMA (43.3%) and PERIPHERAL NEUROPATHY (29.8%). Grade 3 and Grade 4 treatment-related AEs were reported in 101 (36.7%) and 13 (4.7) patients, respectively. The most frequently (≥10%) reported all-causality Grade 3 AEs were HYPERCHOLESTEROLEMIA (14.2%) and HYPERTRIGLYCERIDEMIA (13.1%). The most frequently reported (>2%) treatment-related Grade 4 AE was HYPERTRIGLYCERIDEMIA (2.5%). As described above, the dose-escalation (Phase 1 portion) explored the safety and tolerability of lorlatinib administered in 21-day cycles. One Cycle 1 dose limiting toxicity (DLT) was reported in a patient treated at 200 mg QD lorlatinib. This patient did not receive at least 16 of the planned 21 doses of lorlatinib during Cycle 1 due to toxicities attributed to lorlatinib, which met the protocol definition of a DLT. This patient experienced Grade 1 and Grade 2 CNS effects during Cycle 1, including Grade 2 Aphasia and Cognitive disorder, as well as Grade 1 visual impairment and abnormal dreams. As a result, lorlatinib was temporarily discontinued. The CNS effects resolved within 7 days. Lorlatinib was reduced to a dose of 150 mg QD during Cycle 2. Additionally, for the 150 and 200 mg QD cohorts, the majority (66.7-100%) of patients had treatment-related AEs resulting in temporary discontinuation and/or dose reduction. As a result, it was agreed upon by the Sponsor and the Phase 1 investigators to evaluate doses lower than 200 mg QD and consider an alternative dosing regimen. BID dosing was evaluated to potentially modulate these CNS-related AEs, but patients did not tolerate either the 75 mg BID or 100 mg BID dosing regimen. The 100 mg QD dose was a well-tolerated dose. At the time of the recommended Phase 2 dose (R2PD) selection, none of the patients at 100 mg QD required a dose reduction. Temporary discontinuations did occur, but the temporary discontinuations were not attributed to CNS effects, but rather to HYPERCHOLESTEROLEMIA or HYPERTRIGLYCERIDEMIA, or to disease-related events. Therefore, while the MTD was not formally identified, 100 mg QD (in 21 day cycles) was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.
Maximum dose tested	Single Dose	Maximum single dose tested: 200 mg
	Multiple Dose	Maximum multiple dose tested: 200 mg QD 200 mg QD (n=3) Mean duration of treatment: 25.68 months (range 16.82-30.12 months) 100 mg BID (n=4) Mean duration of treatment: 17.32 months (range 0.85-24.18

		months)
Exposures Achieved at Maximum Tested Dose	Single Dose	200 mg Geometric Mean C_{max} (%CV): 1201 (19) ng/mL Geometric Mean AUC_{inf} (%CV): 18340 (61) ng·h/mL
	Multiple Dose	200 mg QD Range of parameters provided since PK data available from only n=2. Geometric Mean C_{max} : (760, 1430) ng/mL Geometric Mean AUC_{tau} : (4480, 12900) ng·h/mL
Range of linear PK	After single dose administration, lorlatinib AUC_{inf} and C_{max} increased in a dose-proportional manner over the dose range of 10 mg to 200 mg. After QD dose administration, lorlatinib C_{max} increased in a dose-proportional manner over the dose range of 10 mg to 200 mg QD. Lorlatinib AUC_{tau} increased slightly less than dose-proportionally over the dose range of 10 mg to 200 mg QD.	
Accumulation at steady state	After 100 mg QD administration of lorlatinib, the mean observed accumulation ratio R_{ac} ($AUC_{tau,ss}$ /$AUC_{tau,\ single\ dose}$) was 1.1. An observed accumulation ratio of approximately 2.0 was predicted for lorlatinib with a plasma half-life of ~24 hours administered once a day. The arithmetic mean R_{ss} ($AUC_{tau,ss}$ /$AUC_{inf,\ single\ dose}$) was 0.66, less than 1. Both R_{ac} and R_{ss} values suggest a net auto-induction effect of lorlatinib metabolism, after 100 mg QD dosing.	
Metabolites	Following administration of a single oral 100 mg dose of lorlatinib containing [^{14}C]lorlatinib to healthy subjects (Study B7461004), 47.7% of the radioactive dose was recovered in urine and 40.9% was recovered in feces, with overall mean total recovery of 88.6%. In circulation, lorlatinib was the primary drug-related material accounting for 44.4% of the plasma radioactivity. A benzoic acid metabolite resulting from cleavage of the amide and aromatic ether bonds (M8, PF-06895751) was observed as the most abundant metabolite, accounting for 21.0% of the circulating radioactivity. In addition, the pyridine N-glucuronide (M1a, PF-06924938; 8.0%), pyridine N-oxide (M6, PF-06923710; 4.5%), and pyrazole N desmethyl metabolite (M2a, PF-06648706; 2.3%) were also observed in plasma. All other metabolites in plasma individually accounted for <2% of circulating radioactivity. In urine, the pyridine N-oxide (M6, PF-06923710) and pyridine N-glucuronide (M1a, PF-06924938) were the most abundant metabolites, accounting for 16.3% and 10.9% of dose, respectively. The metabolite involving oxidative cleavage (M8, PF-06895751) and pyrazole N-desmethyl metabolite (M2a, PF-06648706) accounted for 5.1% and 2.3% of dose, respectively. The lactone form of M8 (M9) was detected at 0.5% of dose. The urinary excretion of unchanged lorlatinib was found to be a minor route of elimination with less than 1% of the administered parent drug. In feces, lorlatinib is the major drug-related component, accounting for 9.1% of dose. The pyrazole N-desmethyl metabolite (M2a) was the major metabolite, accounting for 6.4% of dose, while a product of aliphatic hydroxylation (M5)	

	accounted for 2.4% of dose. The pyridine N-glucuronide (M1a, PF-06924938) was only detected at significant levels in the fecal samples from 1 subject, accounting for 13.6% of dose. An uncharacterized conjugate of lorlatinib (M15) was only detected in the fecal samples of 1 subject, accounting for 7.2% of dose. Based on the results from in vitro potency assays against ALK and ROS1, the most abundant human circulating metabolite, PF-06895751 (M8), is considered pharmacologically inactive. The activity of the other minor human oxidative circulating metabolites (M6 and M2a) was not tested since they individually accounted for < 5% of circulating radioactivity.	
Absorption	Absolute/Relative Bioavailability	The absolute oral BA of lorlatinib in healthy subjects: 80.8% (90% CI: 75.7, 86.2).
	Tmax	• Lorlatinib parent: C_{max} occurs within 4 hours after oral dosing: (T_{max} range: 1.0-2.0 hours. • Most abundant human circulating metabolite (PF-06895751): Following single oral 100 mg lorlatinib administration, the median T_{max} values of PF-06895751ranged from 24.0 to 30.1 hours
Distribution	Vd/F or Vd	The geometric mean steady-state volume of distribution for lorlatinib (V_{ss}) is 305 L (geometric %CV: 28) following 50 mg intravenous (IV) dosing of lorlatinib to healthy subjects.
	% bound	Binding of lorlatinib to plasma proteins is 66% in humans.
Elimination	Route	Following administration of a single oral 100 mg dose of lorlatinib containing [^{14}C]lorlatinib to healthy subjects (Study B7461004), 47.7% of the radioactive dose was recovered in urine and 40.9% was recovered in feces, with overall mean total recovery of 88.6%. The urinary excretion of unchanged lorlatinib was found to be a minor route of elimination with <1% of the administered parent drug recovered in urine. The geometric mean CLr was 0.094 L/hr. Following administration of 100 mg QD lorlatinib in patients with ALK-positive or ROS1-positive NSCLC (Study B7461001), <0.5% of the dose was recovered unchanged in urine. The geometric mean CLr was 0.061 L/hr.
	Terminal $t_{½}$	• Lorlatinib parent: The plasma elimination half-life of lorlatinib after a single dose of 100 mg in patients ranges from 20.9 to 25.5 hours. • Most abundant human circulating metabolite (PF-06895751): Following single oral 100 mg dose lorlatinib administration, the geometric mean half-life of PF-06895751 ranged from 29.1 to 32.8 hours.
	CL/F or CL	The lorlatinib mean systemic clearance is 9.7 L/h (geometric %CV: 30) following 50 mg IV lorlatinib administration to healthy subjects.
Intrinsic Factors	Age Sex Race	Population PK analysis of the pooled PK data from 95 healthy subjects in 6 healthy subject studies (Studies B7461004, B7461005, B7461007, B7461008, B7461011

		and B7461016) and 330 patients with ALK-positive ROS1-positive NSCLC in Study B7461001, indicate that there are no clinically relevant effects of age, sex, and race on lorlatinib PK.
	Hepatic & Renal Impairment	Formal hepatic and renal impairment studies with lorlatinib have not been conducted. Population PK analyses (n=392 total subjects) have shown that lorlatinib steady-state exposure was not altered in patients with mild hepatic impairment (n=41 and n=9 for NCI criteria mild B1 and mild B2, respectively). Lorlatinib has not been studied in patients with moderate or severe hepatic impairment. Population PK analyses (n=392 subjects) have shown that lorlatinib steady-state exposure was not clinically meaningfully altered in subjects with mild (CrCL 60-89 mL/min, n=103) or moderate renal impairment (CrCL 30-59 mL/min, n=41). There was a slight trend of decreasing lorlatinib clearance (both single dose and steady state clearance), with worsening renal impairment. The range of individual estimates of lorlatinib clearance for patients with mild or moderate renal impairment, however were largely within the range of the patients with normal renal function. Information for lorlatinib use in patients with severe renal impairment (CrCL <30 mL/min) is limited (n=1).

Lorlatinib Single-dose and Steady State Clearance Summarized by Baseline Renal Function with K/DOQI Classification at 100 mg QD

Baseline Renal Function Stage (CrCL range)	Single-Dose Lorlatinib Clearance (L/hr)			Steady-State Lorlatinib Clearance[a] (L/hr)		
	n	Median (Range)	Mean ± SD	n	Median (Range)	Mean ± SD
Normal (≥90)	226	9.80 (6.35-17.09)	9.84 . 1.63	133	15.17 (10.15-23.09)	15.21 . 2.52
Mild impairment (60-89)	120	8.04 (5.84-11.42)	8.17 ± 1.17	103	12.70 (9.33-18.25)	12.90 ± 1.80
Moderate impairment (30-59)	45	7.22 (5.38-9.87)	7.16 ± 1.01	41	11.61 (8.60-15.77)	11.50 ± 1.66
Severe impairment (15-29)	1	4.81	4.81	1	7.68	7.68

		CrCL=Cockcroft-Gault calculated creatinine clearance; hr=hour; n=number of patients; K/DOQI=Kidney Disease Outcome Quality Initiative; QD=once daily; SD=standard deviation. a. The lorlatinib steady state clearance reported are the individual clearance estimates for each patient in Study 1001 at Cycle 1 Day 15, after multiple dosing.
Extrinsic Factors	Drug interactions	B7461012 DDI Study with itraconazole in healthy subjects: indicated an increase in mean lorlatinib AUC_{inf} of 42% and mean C_{max} of 24%. B7461011 DDI Study with rifampin in healthy subjects: indicated a decrease in mean lorlatinib AUC_{inf} of 85% and decreased mean C_{max} of 76%. B7461008 DDI Study with rabeprazole in healthy subjects: indicated an increase in mean lorlatinib AUC_{inf} of 0.87% and decrease in mean C_{max} of 29%.
	Food Effects	B7461008 Food Effect Study in healthy subjects: A High fat, high calorie meal:associated with mean lorlatinib AUC_{inf} increased by 5% and mean C_{max} decreased by 9%
Expected High Clinical Exposure Scenario	Lorlatinib is a substrate of CYP3A and in the DDI study with lorlatinib 100 mg single dose and strong CYP3A inhibitor itraconazole, there was an increase in mean lorlatinib AUC_{inf} by 42% and increase in mean C_{max} by 24%. Additionally population PK analyses indicated lack of clinically significant effect of mild/moderate renal impairment and mild hepatic impairment on lorlatinib exposures. Formal hepatic and renal impairment studies are pending. Based on the available data at the current time, the "worse case scenario" for high lorlatinib exposures, would be that observed with strong CYP3A inhibitionand associated with a 42% increase in lorlatinib AUC_{inf} and 24% increase in C_{max}. The highest doses administered clinically has been 200 mg QD / 100 mg BID. The observed high lorlatinib exposures with strong metabolic inhibition is hence covered by the higher lorlatinib doses previously administered to patients.	
Preclinical Cardiac Safety	Lorlatinib was evaluated in in vitro, ex vivo, and/or in vivo safety pharmacology studies to identify potential effects on the cardiovascular system. Lorlatinib was identified as a weak inhibitor of the hERG potassium channel and L-type calcium channels, and also increased late sodium currents. Lorlatinib increased PR and QRS intervals ex vivo and/or in vivo and induced changes in blood pressure and heart rate in vivo. Nonadverse histological changes in the heart and increases in heart weight were also observed after administration of lorlatinib for ≥4 weeks to rats. Lorlatinib was tested in in vitro and ex vivo assays to assess effects on hERG potassium channel, L-type calcium and sodium channels, vasoconstriction, and cardiac function in a guinea pig isolated Langendorff-perfused heart model. Lorlatinib inhibited the hERG potassium and L-type calcium channels with IC50 values of 203.1 μM and 44.0 μM, respectively, and increased the late sodium currents at 100 μM (310.5%). Lorlatinib did not cause vasoconstriction in rat isolated aortic rings at ≤30 μM. Lorlatinib increased PR intervals in a dose-	

	dependent manner from 1 to 30 μM, with maximum increases at 30 μM (46.9%), in the guinea pig isolated heart model. Cardiovascular effects (changes in blood pressure and heart rate and associated secondary effects on cardiac parameters) of lorlatinib were identified in telemetered rats and dogs in single- and/or repeat-dose studies. In rats, single-dose administration of lorlatinib at 10 or 30 mg/kg caused dose-dependent increases in blood pressure (systolic, diastolic, and mean) with maximum increases of +37 mmHg at 2-3 hours postdose (HPD). Heart rate was altered at ≥10 mg/kg in rats, characterized by a biphasic response, with an initial decrease of up to -36 bpm at 1-2 HPD and subsequently increased to up to +32 bpm at 12-21 HPD. Echocardiography in rats following 2 weeks of lorlatinib administration identified dose-dependent increases in end diastolic volume, diastolic area, wall thickness, stroke volume, and E and A velocity at ≥20 mg/kg/day, with no changes in functional measurements. These changes were suggestive of increased left ventricular lumen size, increased wall thickness, and an overall increased heart size. Higher absolute heart weights with no microscopic correlates were observed in rats at ≥8/4 mg/kg/day after 4 weeks of lorlatinib administration; higher absolute heart weights associated with minimally increased cellularity of Anichkov cells were identified at 15 mg/kg/day after 13 weeks of dosing. The increased heart size and weight likely reflects a compensatory response to hemodynamic changes and not a direct effect on cardiac tissue. The differences in cardiovascular profiles between rats and dogs for both blood pressure and heart rate parameters may reflect a species-specific response to lorlatinib. In dogs, lorlatinib administration at ≥15 mg/kg/day for 12 or 14 days resulted in decreased systolic blood pressure up to -37 mmHg and increased heart rate up to +17 bpm particularly during 12-22 HPD, increased PR interval (up to +9 msec), QRS interval (up to +3 msec), and fractional shortening (4%) as well as decreased QT (-16 msec) intervals. Increases in PR interval are considered a direct effect of lorlatinib, supported by the effects seen in the guinea pig isolated heart model, while decreases in QT interval and increases in fractional shortening are considered secondary to increases in heart rate. There was no effect on electrocardiogram parameters in dogs at ≤25 mg/kg/day following 13 weeks of lorlatinib administration. Reversibility of the effects on blood pressure, heart rate, and electrocardiogram intervals was demonstrated following a 5-day recovery period in dogs after 12 days of lorlatinib administration. Increases in heart weight and/or cellularity of Anichkov cells were reversible in rats following a 4-week recovery phase after 4 or 13 weeks of lorlatinib administration. Recovery was not assessed for blood pressure, heart rate, or echocardiography changes in the telemetered rat. A NOAEL for cardiovascular effects (blood pressure and heart rate) was not determined in the rat; the LOAEL was considered to be 10 mg/kg with an unbound C_{max} of 524 ng/mL and associated margin of 2.2x the unbound human steady-state C_{max} exposure of 236 ng/mL at the recommended dose of 100 mg QD. The NOAEL for cardiovascular effects (blood pressure, heart rate, and ECG changes) was considered to be 2 mg/kg/day in the 12-day dog study, with an

	unbound C_{max} of 67.7 ng/mL and associated margin of 0.3x the unbound human steady-state C_{max} exposure of 236 ng/mL at the recommended dose of 100 mg QD. In the 13-week study in rats, the NOAEL for heart effects was identified as 8/4 (M/F) mg/kg/day with associated unbound AUC_{24} exposures of 6240/7820 ng•h/mL. The NOAEL provides margins of 3.3x (male)/4.1x (female) the unbound human steady-state AUC exposure of 1920 ng•h/mL at the recommended dose of 100 mg QD.
Clinical Cardiac Safety	The total number of clinical trials and number of patients at different doses are provided in the table below. The requested summarization of safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths) by dose and overall, is provided separately in Appendix A. The safety events are provided for the B7461001 study (in patients with ALK-positive or ROS1-positive advanced NSCLC) with multiple dosing of lorlatinib and does not include data from the single-dose lorlatinib studies in healthy subjects.

List of Clinical Studies of Lorlatinib

Study Number	Study Design	Study Population	Actual or Planned Number who Received Lorlatinib[a]	Status[b]
B7461001	Phase 1/2 patient safety and efficacy study Midazolam DDI substudy	Patients with ALK-or ROS1-positive NSCLC	Phase 1: 54[f,g] Phase 2: 275[f] (100 mg QD)	Completed[c]
B7461004	Mass balance study	Healthy volunteers	6 (100 mg single dose)	Completed[c]
B7461005	Relative bioavailability study	Healthy volunteers	20 (100 mg single doses)	Completed[c]
B7461006	Phase 3 randomized, controlled safety and efficacy study of lorlatinib and crizotinib	Patients with ALK-positive NSCLC who are treatment-naive	140 (100 mg QD)	Enrolling
B7461007	Absolute bioavailability study	Healthy volunteers	11 (100 mg single oral dose; 50 mg single intravenous dose)	Completed[c]
B7461008	Food effect, PPI interaction study	Healthy volunteers	27 (100 mg single doses)	Completed[c]

B7461009	Hepatic impairment study	Patients with solid tumors	38[d]	Planned
B7461010	Renal impairment study	Otherwise healthy renal impairment subjects	32[e]	Planned
B7461011	Rifampin DDI study	Healthy volunteers	12 (100 mg single doses)	Completed[c]
B7461012	Itraconazole DDI study	Healthy volunteers	16 (50 mg, 75 mg and 100 mg single doses)	Completed[c]
B7461016	Bioequivalence study	Healthy volunteers	20 (100 mg single doses)	Completed[c]
B7461017	Mass balance study	Healthy volunteers	6 (100 mg single dose)	Ongoing
B7461020	Expanded Access Protocol	Patients with ALK-or ROS1-positive NSCLC	100 (100 mg QD)	Ongoing

ALK = anaplastic lymphoma kinase; CSR = clinical study report; DDI = drug-drug interaction; NDA = new drug application; NSCLC = non-small cell lung cancer; PPI = proton pump inhibitor; ROS1 = c-ros oncogene 1.

a. For status completed, it is the actual number, and for all others, it is the planned number.

b. Completed status denotes clinical study report is available.

c. Included in the NDA.

d. Approximately 8 mild, 8 moderate, 6 severe hepatic impairment, and 16 normal hepatic function. All numbers refer to evaluable subjects.

e. Approximately 8 mild, 8 moderate, 8 severe renal impairment and 8 normal renal function. All numbers refer to evaluable subjects.

f. As of the data cutoff date of 15 March 2017.

g. A total of 55 Phase 1 patients were assigned to treatment with lorlatinib: 3 patients each in the 10, 25, 50, 150, and 200 mg QD cohorts, 13 patients in the 75 mg QD cohort, 17 patients in the 100 mg QD cohort, 3 patients in the 35 and 75 mg BID dosing cohorts, and 4 patients in the 100 mg BID cohort. All patients received lorlatinib except for 1 patient in the 75 mg QD cohort who was enrolled but was never treated with lorlatinib

Appendix A: Safety events per ICH E14 guidance

Study B7461001 (Phase 1 part):

PF-06463922 Protocol B7461001 (Date of Data Cutoff: 15MAR2017 and Date of Data Snapshot: 09May2017)
Summary of Treatment-Emergent Cardiac Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade
(All Causalities, All Cycles) (Phase 1) - Safety Analysis Set

	10 mg QD (N=3)											
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	1	(33.3)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(66.7)
Electrocardiogram QT prolonged	1	(33.3)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(66.7)

	25 mg QD (N=3)													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)
Seizure	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)

	150 mg QD (N=3)													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	0	(0.0)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)
Electrocardiogram QT prolonged	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)
Seizure	0	(0.0)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(33.3)

	100 mg BID (N=4)													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	1	(25.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(50.0)
Electrocardiogram QT prolonged	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)
Seizure	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)

	Total (N=54)													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	3	(5.6)	3	(5.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(11.1)
Electrocardiogram QT prolonged	3	(5.6)	1	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(7.4)
Seizure	1	(1.9)	2	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(5.6)

Study B7461001 (Phase 2 part):

PF-06463922 Protocol B7461001 (Date of Data Cutoff: 15MAR2017 and Date of Data Snapshot: 09May2017)
Summary of Treatment-Emergent Cardiac Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade
(All Causalities, All Cycles) (Phase 2) - Safety Analysis Set

	100 mg QD (N=275)													
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	8	(2.9)	10	(3.6)	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	21	(7.6)
Electrocardiogram QT prolonged	8	(2.9)	10	(3.6)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	19	(6.9)
Syncope	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)

The preferred term of QT Prolongation is Electrocardiogram QT Prolonged in MedDRA (v20.0).

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/

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Date: April 16, 2018

From: Wendy Wu, Ph.D., Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: James Weaver Ph.D., Consult Lead and David Strauss M.D., Ph.D., Director; DARS/OCP

To: Devi Kozeli, CDER/DCRP/QT-IRT Team

Subject; Review of electrophysiology data from NDA 201868 for Lorlatinib

Executive Summary

Lorlatinib or PF-0463922 is an investigational drug developed by Pfizer for use in patients with ALK+ metastatic non-small cell lung cancer who have progressed on 1 or more ALK tyrosine kinase inhibitors (TKIs). The NDA for lorlatinib (NDA 210868) was granted priority review status by the FDA following its breakthrough therapy designation award. The QT-IRT team has conflicting evidence suggesting that lorlatinib shortens QT_C interval in one study and prolongs QT_C interval in another clinical study. Thus, DARS received a consult request from QT-IRT to evaluate 4 non-clinical study reports submitted by the sponsor that examined the effects of lorlatinib and its major metabolite PF-06895751 on cardiac Na^+ (lorlatinib data only), Ca^{2+} (lorlatinib data only), and hERG K^+ channels (lorlatinib and PF-06895751data) acquired using patch clamp electrophysiology technique. The goal of this consult is to determine whether the ion channel results from the study reports are believable, and whether the results support the reported ECG changes in the two clinical studies.

In vitro electrophysiology studies show that Lorlatinib does not affect peak Na^+ current at 100 μM. It suppressed hERG current with an IC_{50} of 203.1 μM, L-type Ca^{2+} current (at 0 mV) with an IC_{50} of 44.0 μM, and increased a standing current at -40 mV (100 μM, 310.5 ± 130.4% increase) that could reflect either late Na^+ current or L-type Ca^{2+} current. Lorlatinib's major metabolite, PF-06895751-02, marginally affected hERG current (300 μM, 11.8% suppression). Whether PF-06895751-02 affects other cardiac ion channels of concern for proarrhythmia propensity was not addressed.

Considering that lorlatinib's unbound human clinical exposure level at 100 mg QD is ~0.58 μM (C_{max} = 695 ng/mL or 1.7 μM), effects of lorlatinib on cardiac Ca^{2+}, Na^+, and hERG channels cannot explain lorlatinib's effect on QT_C, either shortening or prolongation. If the electrophysiology mechanism of QT_C effects is necessary for safety evaluation or drug labeling, then DARS recommends requesting for L-type Ca^{2+} and late Na^+ current analysis of lorlatinib's major metabolite(s). These experiments can be done using recombinant cell lines or isolated ventricular myocytes as long as the identity of the current measured is confirmed with appropriate positive controls.

Background.

Lorlatinib or PF-0463922 is an investigational drug developed by Pfizer for use in patients with ALK+ metastatic non-small cell lung cancer who have progressed on 1 or more ALK tyrosine kinase inhibitors (TKIs). The NDA for lorlatinib (NDA 210868) was granted priority review status by the FDA following its breakthrough therapy designation award.

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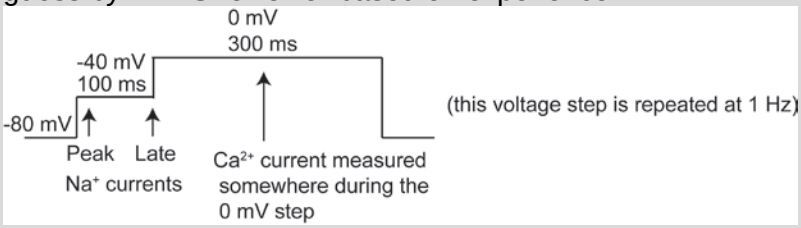
The QT-IRT has received conflicting evidence suggesting that lorlatinib shortens QT_C in one clinical study and prolongs QT_C in another clinical study. In an open label phase 1 study from 12 healthy volunteers, lorlatinib caused ~15 ms QT_C shortening and ~10 ms PR prolongation. However, in a phase 2 study with 275 subjects, categorical analysis showed 2 patients with QT_C > 500 ms and 5 patients with > 60 ms QT_C prolongation. Because drug-induced QT_C change often results from drugs acting on cardiac ion channels, QT-IRT would like to understand the electrophysiology effects of lorlatinib on cardiac ion channels to help determine how this drug is likely to affect QT_C. Thus, DARS received a consult request from QT-IRT to evaluate 4 non-clinical study reports (*study number 17GR038, 13GR078, 170207.QHJ, and 170313.QHJ*) submitted by Pfizer describing the effects of lorlatinib and its major metabolite PF-06895751 on cardiac Na^+ (lorlatinib data only), Ca^{2+} (lorlatinib data only), and hERG K^+ channels (lorlatinib and PF-06895751data) acquired using patch clamp electrophysiology technique. The goal of this consult is to determine whether the ion channel results from the study reports are believable, and how these results relate to the QT_C changes in the two clinical studies.

Evaluation

Study number 17GR038. This is a study conducted by Pfizer to evaluate the effects of lorlatinib on L-type Ca^{2+} current and Na^+ current (peak and late) measured using whole cell voltage clamp method performed at room temperature in isolated guinea pig ventricular myocytes. Ca^{2+} and Na^+ currents were evoked with a single voltage step shown below, at a frequency of 1Hz. Drug effects on Na^+ currents (peak and late) were measured at the -40 mV step, and on Ca^{2+} current at the 0 mV step. The study did not describe where during the voltage steps drug effects were measured. The arrows below hence reflect educated guess by DARS reviewer based on experience.



In these experiments, each cell was first perfused with vehicle control (0.1% DMSO) for one minute, followed by 3 ascending concentrations of lorlatinib (10, 30, and 100 μM). Each drug concentration was perfused for 2 minutes, and drug effect was measured at the end of each perfusion period. The sponsor quantified drug effect by calculating % current suppression (100 - (current values recorded in drug / current value recorded in DMSO vehicle control)*100). The results showed the following: 1) lorlatinib suppressed Ca^{2+} current with an IC_{50} of 44.0 ± 4.9 μM (no Hill coefficient given, presumably constrained to 1); 2) lorlatinib did not significantly affect peak Na^+ current at 100 μM (11.0 ± 4.9% current suppression); and 3) lorlatinib enhanced the current at the end of the -40 mV step (10 μM, 46.9 ± 25.5% increase; 30 μM, 103.4 ± 41.7% increase, and 100 μM, 310.5 ± 130.4% increase). The sponsor stated that this is the late Na^+ current. DARS reviewer thinks the current identity is not definitive.

These experiments are straightforward. While the original electrophysiology records were not available, the sponsor did provide time-matched control recording values from cells exposed to only DMSO vehicle control, suggesting that the drug effects were real. A major limitation in this study, hence interpretation of drug effect on a particular ionic current, is the lack of positive controls for Ca^{2+} and Na^+ channels (verapamil and TTX, respectively) to verify that the identity of the currents measured in this study. This is not critical for peak inward current at the -40 mV step and the current at the 0 mV, since they are predominantly mediated by peak Na^+ and L-type Ca^{2+} currents using the solutions in the current study.

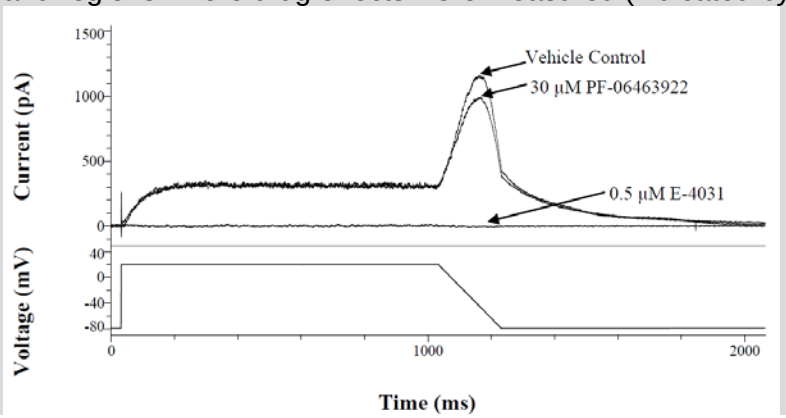
The identity of the current at the end of the -40 mV step is questionable, hence sponsor's interpretation that lorlatinib is a late Na^+ current agonist. As this voltage is close to the foot of activation for L-type Ca^{2+} channels, a drug that shifts voltage-dependence of Ca^{2+} channel activation to the left could also produce an increase in the current at the end of the -40 mV step. Note that this possibility and that lorlatinib reduces Ca^{2+} current at the 0 mV are not mutually exclusive, and can arise from a drug's shift of voltage dependence of Ca^{2+} channel gating. The sponsor also examined lorlatinib's effects on $Na_V1.5$ channels expressed in CHO cells (study number 13GR078; reviewed below). Further analysis of the 4 cells in that study as recommended by DARS reviewer could help to determine whether lorlatinib enhances late Na^+ current or L-type Ca^{2+} current.

In conclusion, lorlatinib reduced L-type Ca^{2+} current measured at 0 mV step with an IC_{50} of 44 μM, did not affect peak Na^+ current, and augments an standing inward current at end of the -40 mV step that could be mediated by Na^+ or Ca^{2+} channels.

Study number 13GR078. This is a study conducted by Pfizer using CHO cells stably expressing the human $Na_V1.5$ proteins. The effect of lorlatinib on $Na_V1.5$ current was measured using automated Qpatch HT platform operating in whole cell planar patch clamp mode at 23°C. Na^+ current was activated with a voltage step from -80 to -20mV for 30 ms at 1 Hz. Each cell was tested with 3 ascending concentrations of lorlatinib (10, 30, and 100 μM), and exposure to each drug lasted 5 minutes. Drug effects were determined by calculating % current suppression (100 - (current values recorded in drug / current value recorded in DMSO vehicle control)*100). Lorlatinib did not suppress peak $Na_V1.5$ current at any concentration tested (values not significantly different from 0). As a positive control, the sponsor tested the effect of propafenone and obtained an IC_{50} of 0.5 μM, which is within the range of reported values in the literature.

Study number 13GR078 ($Na_V1.5$ - CHO cells) and 17GR078 (guinea pig ventricular myocytes) show that lorlatinib does not affect peak Na^+ current. The 4 cells in this study report could be further analyzed to determine whether lorlatinib augments Ca^{2+} or late Na^+ current. If lorlatinib increases late Na^+ current, then the $Na_V1.5$ current at the end of the 30 ms long, -20 mV step should show an increase in the presence of this drug. If this information is important for safety evaluation, the DARS recommends obtaining it from the sponsor.

Study report 170207.QHJ. This study was conducted by ChanTest to examine the effect of lorlatinib on hERG current using an overexpression cell line and manual whole cell voltage clamp method at 33-35°C. The figure below shows the voltage protocol (repeated at 5 s interval) used to evoke the hERG current and regions where drug effects were measured (indicated by arrows).



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The concentrations of lorlatinib tested were 10, 30, 100, and 300 μM. A steady state hERG current was measured for at least 4 sweeps (20 s) before lorlatinib or positive control E-4031 (500 nM) was bath applied. During drug application, the peak hERG current was continuously recorded until a new steady state was achieved (steady state was defined as "linear time dependence", and current rundown with time was not corrected). % hERG current suppression by lorlatinib was calculated as 100 - (current values recorded in drug / current value recorded in DMSO vehicle control)*100. The results showed an IC_{50} of 203.1 μM for lorlatinib against hERG channels and a Hill coefficient of 1.1.

The data looked reasonable without outliers. Terfenadine at 60 nM produced 76.7 % inhibition on hERG current. This value is close to what DARS electrophysiologists obtained in-house (66% block), giving some confidence in the study results.

Effect of PF-06895751-02, the major metabolite of lorlatinib, on hERG channels expressed in HEK293 cells was examined by ChanTest at 33-35°C using manual whole cell voltage clamp method. PF-06895751-02 was tested at 30 and 300 μM, and the method of recording, drug application, and data analysis were the same as those used for study report 170207.QHJ above. 300 μM PF-06895751-02 caused 11.8 ± 0.9% hERG current suppression. Terfenadine at 60 nM suppressed hERG current by 74.2%, consistent DARS' in-house data and giving some confidence in the study results.

In conclusion, lorlatinib does not affect peak Na^+ current at 100 μM. It suppressed hERG current with an IC_{50} of 203.1 μM, L-type Ca^{2+} current (at 0 mV) with an IC_{50} of 44.0 μM, and increased a standing current at -40 mV (100 μM, 310.5 ± 130.4% increase) that could reflect either late Na^+ current or L-type Ca^{2+} current. If identity of this standing current is of safety concern, the DARS recommends the sponsor to analyze the $Na_V1.5$-CHO cell data in study number 13GR078 to verify. Lorlatinib's major metabolite, PF-06895751-02, marginally affected hERG current (300 μM, 11.8% suppression). Whether PF-06895751-02 affects other cardiac ion channels of concern for proarrhythmia propensity was not addressed.

Summary and Conclusions

DARS reviewer analyzed the following non-clinical study reports submitted by Pfizer that evaluated the effects of lorlatinib or its major metabolite on selective cardiac ion channels:

1) Effect of lorlatinib on hERG channels expressed in recombinant cells – manual whole cell patch clamp studies at 33-35°C performed by ChanTest. (1702.07.QHJ)
2) Effect of lorlatinib's major metabolite PF-06895751-02 on hERG channels expressed in recombinant cells – manual whole cell patch clamp studies at 33-35°C performed by ChanTest. (170313.QHJ)
3) Effect of lorlatinib on Ca^{2+} and Na^+ channels using isolated guinea pig ventricular myocytes – manual whole cell voltage clamp studies at room temperature performed by Pfizer. (17GR038)
4) Effect of lorlatinib on $Na_V1.5$ channels expressed in recombinant cells – automated patch clamp studies at room temperature performed by Pfizer. (13GR078)

The results showed that lorlatinib does not affect peak Na^+ current at concentration as high as 100 μM. It suppressed hERG current with an IC_{50} of 203.1 μM , L-type Ca^{2+} current (at 0 mV) with an IC_{50} of 44.0 μM, and increased a standing current at -40 mV (100 μM, 310.5 ± 130.4% increase) that could reflect either late Na^+ current or L-type Ca^{2+} current. PF-06895751-02, marginally affected hERG current (300 μM, 11.8% suppression). Whether PF-06895751-02 affects other cardiac ion channels of concern for proarrhythmia propensity was not addressed.

Lorlatinib shortens QT_C interval in one clinical study and seems to prolong QT_C interval in a small number of patients from another clinical study. Considering that this drug's unbound human clinical exposure level at 100 mg QD is ~0.58 μM (C_{max} = 695 ng/mL or 1.7 μM), much lower than the tens and hundreds of μM level required to affect the studied cardiac Na^+, Ca^{2+}, and hERG channels, its mechanism(s) on affecting QT_C (and PR) remains unclear. Additional studies examining the metabolites' effects on cardiac late Na^+ and Ca^{2+} currents, or action potential waveforms from acutely isolated myocytes are warranted if there is a safety concern of this drug.

References and Supporting Documents

Reports from NDA 210868*: 17GR038, 13GR078, 170207.QHJ, and 170313.QHJ*

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CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11723

Consultant Reviewer:	Gregory M. Dubitsky, MD Medical Officer Division of Psychiatry Products
Consultation Requestor:	Shubhangi Mehta, PharmD Senior Regulatory Project Manager Division of Oncology Products-2
Subject of Request:	NDA 210868/Lorlatinib
Date of Request:	May 22, 2018
Date Received:	May 22, 2018
Desired Completion Date:	June 20, 2018

I. Background

Lorlatinib (PF-06463922) is a next-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) that has been shown to be highly active in preclinical lung cancer models with chromosomal rearrangements of both ALK and ROS1 genes. Alterations in either the ALK gene or the ROS1 gene contribute to tumor development and are seen in 3% to 5% and approximately 1% of patients with non-small cell lung cancer (NSCLC), respectively. Because of tumor complexity and development of treatment resistance, disease progression is a challenge in patients with ALK-positive metastatic NSCLC. The brain is a common site for metastatic progression of NSCLC. Lorlatinib was specifically designed to inhibit tumor mutations that produce resistance to other ALK inhibitors and to penetrate the blood brain barrier.[1]

Pfizer has submitted NDA 210868 which is intended to support the use of lorlatinib in the treatment of patients with NSCLC who were previously treated with one or more ALK TKIs. Pfizer claims that lorlatinib addresses mechanisms of resistance following treatment with other ALK inhibitors, such as crizotinib.

Clinical data from Study B7461001 form the basis of this submission. This is an ongoing Phase 1/2 trial in patients with ALK-positive or ROS1-positive advanced NSCLC, with a cutoff date of March 15, 2017, for this submission. Assessments of cognitive function, mood, and suicidal ideation and behavior during Phase 2 of this trial were added to the original study protocol by amendment on July 22, 2015. (b) (4) a central vendor, then analyzed these data.

[1] From: https://www.pfizer.com/files/news/asco/Lorlatinib_Fact_Sheet.pdf.

The Division of Oncology Products-2 (DOP2) has requested consultation with the Division of Psychiatry Products (DPP) to address the validity of the instruments used to assess depressive symptoms (the Beck Depression Inventory-II or BDI-II) and suicidal ideation and behavior (the Columbia-Suicide Severity Rating Scale or C-SSRS) and to comment on the clinical significance of the reported findings.[2]

II. Material Reviewed

I referred to the (b) (4) Statistical Analysis Report in the Interim Clinical Study Report for Study B7461001.[3] This report pertains to the use of and findings from the assessments of mood and suicidal ideation and behavior from Phase 2 of this trial.[4]

Most of this review is based on my own analyses using the following datasets for Phase 2 of this trial:

- adqsbd.xpt (BDI-II data).
- adqscs.xpt (C-SSRS data).
- advers.xpt (adverse events).
- prevdi.xpt (previous diagnoses).
- cnmed.xpt (concomitant medication).
- cntrt.xpt (concomitant non-drug treatment).
- bldsr.xpt (baseline disease state).

III. Review of Clinical Data

A. Trial Design

Study B7461001 is a multi-national study with sites in the U.S., Europe, Asia, and Australia. It consists of two portions, Phase 1 and Phase 2. Phase 1 evaluated increasing doses of lorlatinib (10 mg/day to 400 mg/day) in adult patients with advanced NSCLC to estimate the maximum tolerated dose and select a dose for Phase 2 of the trial. Phase 2 of this study evaluated the overall and intracranial anti-tumor activity of lorlatinib at the dose identified from Phase 1 in multiple subpopulations of adult patients with advanced NSCLC. Assessments of mood and suicidal ideation and behavior were performed in Phase 2 only. Therefore, only data from Phase 2 are addressed in this review.

Phase 2 of the trial was open label and uncontrolled. Patients self-administered lorlatinib 100 mg once daily as outpatients in cycles of 21 days of continuous

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[2] DOP2 has requested consultation with the Division of Neurology Products to evaluate the instruments for cognitive assessment and the findings from those assessments.
[3] (b) (4) prepared this report for Pfizer that described findings on various measures of cognition as well as depression and suicidal thoughts and behavior.
[4] Located at: \\CDSESUB1\evsprod\NDA210868\0001.

dosing for up to 26 cycles. Lorlatinib was supplied as 100 mg tablets. In case of toxicity, the dose could be withheld or reduced to 75, 50, or 25 mg/day. Treatment was discontinued for patients who did not recover from toxicity within six weeks.

B. Patient Sample

A total of 213 patients (of the 275 patients in the safety sample for Phase 2 of this trial) were included in the (b) (4) Evaluable Analysis Set, defined as all enrolled patients who received study treatment, had a baseline assessment, and had at least one on-drug assessment.[5] However, the numbers of patients with evaluable BDI-II and C-SSRS data were less (N=196 and 200, respectively). Patients with a severe, acute or chronic psychiatric condition, including suicidal ideation or behavior within the past year, were excluded from the study.

The study enrolled patients from six subpopulations, based on mutation status and prior therapy. There were no clear differences in terms of psychiatric safety findings across the above subpopulations. For this reason and to more clearly elucidate the psychiatric safety profile of lorlatinib, I have presented the findings only from the pool of these groups.

C. Assessments of Mood and Suicidal Ideation and Behavior

Mood was assessed using the BDI-II. This is a 21-item, self-report scale with each item rated from the previous two-week period on a four-point scale from 0 to 3, with higher total scores indicating more severe depressive symptomatology. Standardized cutoffs for the BDI-II total score are:

- 0 to 13: minimal depression.
- 14 to 19: mild depression.
- 20 to 28: moderate depression.
- 29 to 63: severe depression.

Suicidal ideation and behavior was assessed using the C-SSRS. The C-SSRS is available in two versions:

1. the Baseline version rates the type and intensity of suicidal ideation and characterizes suicidal behavior prior to study treatment. The recall period for the baseline assessment in this study was one year.
2. the Since Last Visit (SLV) version rates suicidal ideation and behavior that emerged since the last assessment.

[5] My analyses of the BDI-II and C-SSRS datasets included only patients in the evaluable set, denoted by the variable EVLFL = Y.

Higher counts indicate more intense and frequent suicidal ideation and behavior. The BDI-II and C-SSRS were assessed prior to dosing on Day 1 of Cycles 1 through 6, then on Day 1 of every other cycle thereafter. Baseline was defined as the test score on Day 1 of Cycle 1.

D. Psychiatric Safety Findings

BDI-II Findings
The BDI-II evaluable analysis set consisted of 196 patients.

At baseline, the mean BDI-II total score was 8.8, indicating minimal depression on average. But, the range of baseline scores was 0 to 32. The distribution of total scores at baseline by overall symptom severity was:

- Minimal (0 to13) N=149
- Mild (14 to 19) N= 29
- Moderate (20 to 28) N=16
- Severe (29-63) N=2

Although most patients had minimal depressive symptomatology at baseline, 18 patients had scores in the moderate or severe range.

The mean change from baseline in the BDI-II total score for all assessments was -2.8, indicating improved depressive symptoms on average. However, the range of changes was -32 to +38, with 13 patients having an increase in the total score ≥ 10 on at least one assessment. An increase of 10 points suggests a potentially clinically significant increase in overall depressive symptoms. For these 13 patients, I examined the changes from baseline over time as a way of gauging the clinical significance of these findings. In nine of these patients, an increase ≥10 was observed at a single visit. In the remaining four patients, an increase ≥10 was seen at multiple visits, as summarized in Table 1 below.

All four patients had minimal depressive symptoms at baseline and none had a documented previous history of depression.

One of these patients (b) (6) reported suicidal ideation on the Suicidal Thoughts or Wishes item of the BDI-II, indicating that he would kill himself if he had the chance at the Cycle 10 assessment. At Cycles 4, 5, and 12, he had endorsed suicidal thoughts but no intent to carry them out. At other visits, including the EOT visit, he denied any suicidal thoughts.

Patient (b) (6) also reported emotional lability as well as auditory and visual hallucinations that resulted in discontinuation of lorlatinib.

Table 1: Patients with an Increase in BDI-II Total Score ≥ 10 on Multiple Occasions	
Subject ID	**Summary of Changes from Baseline**
(b) (6)	Baseline score=5. Changes from baseline were consistently ≥+11 for Cycles 2 through 26 (range +11 to +38).
	Baseline score=1. Six of eight on treatment assessments revealed changes from baseline ≥+10, with a maximum change=+33 at EOT.
	Baseline score=7. Six of nine on treatment scores showed changes from baseline ≥+10, with a maximum change=+32. However, the change at EOT was -7, indicating improvement.
	Baseline score=3. Three of six on treatment changes from baseline were ≥+10, with a maximum change=+25.

Curiously, none of the 13 patients with a change in the BDI-II total score ≥10 had a documented adverse event of depression or depressed mood. However, 13 other patients did report depression as a treatment-emergent adverse event.[6] The median duration of depressive events was about 9 weeks with a range of 2 weeks to 56 weeks. The adverse event maximum grade was 1 (mild) for nine patients, 2 (moderate) for three patients, and 3 (severe) for one patient.[7] None of the depression adverse events was considered serious or led to dropout from the study. Five of these patients received concomitant medication for depressive symptoms and none received non-drug treatment, such as psychotherapy. Four of these 13 patients had a previous diagnosis of depression and ten had brain metastases at baseline.

C-SSRS Findings

The C-SSRS evaluable analysis set consisted of 200 patients.

At baseline, six patients reported suicidal ideation within the last year on the C-SSRS. All six endorsed item 1 of the C-SSRS, i.e., a wish to be dead but no thoughts of acting on that wish. Four of these patients reported no suicidal ideation during study treatment.

The other two patients and five others reported suicidal ideation at some point during study treatment. In six of these seven cases, there was a wish to be dead but no thought of acting on it that was recorded at only one assessment.

[6] The mean on-treatment BDI-II total score for the 13 patients who reported depression as an adverse event was 6.1 (range 0 to 32); the mean change from baseline was -3.7 (range -16 to +7), indicating slight improvement on average.

[7] Adverse events were graded by the investigator according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

In the remaining patient [redacted] (b) (6) a wish to be dead was reported at Cycles 5, 6, 8, and 12. In addition, at Cycle 5, this patient indicated active thoughts of suicide but without a plan or intention to attempt suicide. The patient reported no suicidal ideation at Cycles 10 and 14. This patient did have a pre-study diagnosis of depression. At baseline, this patient had borderline moderate depression on the BDI-II total score (20) but changes from baseline during treatment were all ≤+6, with improvement relative to baseline at Cycles 2, 3, 4, 8, and 10.

No patient engaged in suicidal behavior during treatment.[8]

Other Psychiatric Adverse Events

I evaluated the occurrence of other treatment-emergent psychiatric adverse events in Phase 2 of Study B74611001 to further assess the lorlatinib safety experience from a psychiatric perspective.[9] The adverse event dataset (advers.xpt) was examined to determine the accuracy of the coding of investigator-reported adverse event terms to MedDRA Preferred Terms (PTs) for psychiatric events and to combine PTs for closely related psychiatric events. I combined the following adverse event PTs under common terms for purposes of analysis.

Table 2: Combined Adverse Event Preferred Terms

Combined PTs	Common Term
Hallucinations, Hallucinations auditory, Hallucinations visual	Hallucination
Abnormal dreams, Insomnia, Nightmare, Sleep disorder, Sleeptalking, Somnambulism	Sleep Disturbance
Aggression, Agitation, Impulse control disorder	Aggression
Affective lability, Mood swings	Mood swings

The proportion of patients who reported these adverse events during Phase 2 (from the safety analysis set of 275 patients) are shown in Table 3 below. My exploration of the reporting rates of these adverse events across the six subpopulations defined by genetic mutations and prior chemotherapy revealed no discernible relationship between adverse event incidence and subpopulation.

Among the 18 patients who experienced hallucinations, none of these events was considered serious or resulted in dropout and none of these patients

[redacted] (b) (4)

Evaluation of cognition-related adverse events, e.g., events coded to MedDRA Preferred Terms memory impairment, cognitive disorder, amnesia, confusional state, disturbance in attention, delirium, mental impairment, attention deficit/hyperactivity disorder, dementia, and reading disorder are deferred to DNP.

received concomitant antipsychotic medication. The median duration of this event was 59 days (range of one to 264 days). The maximum CTCAE grade for hallucinations in these patients was 1 (mild) in 11 patients, 2 (moderate) in five patients, and 3 (severe) in two patients. None had a pre-study diagnosis of psychotic illness but six patients had metastatic disease in the brain at baseline. Seven of these patients had other adverse events suggestive of an organic brain disorder (e.g., memory impairment, slow speech, and personality change).

Table 3: Percentage of Patients with Treatment-Emergent Psychiatric Adverse Events[10]	
PT/Common Term	**n (%)**
Sleep Disturbance	27 (10%)
Hallucination	18 (7%)
Irritability	16 (6%)
Anxiety	15 (5%)
Confusion	10 (4%)
Mood Swings	10 (4%)
Aggression	5 (2%)

An enumeration of patients with the other psychiatric adverse events in Table 3 by maximum CTCAE grade is shown in Table 4. In general, these adverse events were mild but there were appreciable numbers of patients with moderate and severe events, although none that were life-threatening (Grade 4) or fatal (Grade 5). However, for most patients with confusion (7/10), this event was rated as moderate or severe.

Table 4: Patients with Other Psychiatric Adverse Events by Severity			
	CTCAE Grade		
	1	**2**	**3**
Sleep Disturbance	20	7	0
Irritability	13	1	2
Anxiety	11	3	1
Mood Swings	9	1	0
Aggression	4	0	1

Among all patients who reported any psychiatric adverse event, four patients had events classified as serious (three with unspecified mental status changes and one with a confusional state who was hospitalized). Three patients were withdrawn from the study because of a psychiatric adverse event (one each for affect lability, anxiety, and non-serious mental status changes).

[10] This table excludes adverse events reported by only one patient (bradyphrenia, euphoric mood, mania, restlessness, and suicidal ideation) as well as events coded to PTs that are too vague to be clinically meaningful (affective disorder, mental status changes, mood altered, personality change, abnormal behavior, and eating disorder).

IV. Conclusions and Recommendations

Below are the questions posed by DOP2 followed by the DPP responses.

Question #1: Please comment on whether these assessment tools are validated to assess changes in mood and suicidality.

DPP Response: Yes, the BDI-II and C-SSRS are valid instruments to monitor for changes in mood and emergent suicidal ideation and behavior, respectively, in non-psychiatric clinical trials. The BDI-II has been in use since 1996 and is generally considered to be a cost-effective, valid, and reliable instrument for measuring depression severity, with wide applicability for research and clinical practice worldwide.[11] The C-SSRS has demonstrated validity, sensitivity to change, sensitivity and specificity for suicidal behavior, internal consistency, and interrater reliability.[12] It has been widely used in trials of both psychiatric and non-psychiatric drugs and is accepted by DPP as a valid method of monitoring for suicidal ideation and behavior.[13]

A limitation of the BDI-II analyses is the fact that the BDI-II rates symptoms from the previous two-week period. Thus, symptoms that were experienced earlier than two weeks prior to the assessment but since the last assessment would not have been rated. This issue is more concerning after the first six cycles of treatment, when assessments were performed only every other cycle, i.e., about six weeks apart.

Question #2: Please comment on whether the reported findings are clinically meaningful for patients treated with lorlatinib.

DPP Response: Safety findings were similar across subpopulations and, therefore, I have presented data pooled across these groups. Most patients who participated in Phase 2 of Study B7461001 experienced no or mild treatment-emergent symptoms of depression and, on average, symptoms of depression improved to a small extent. Among patients who experienced substantial increases in depressive symptomatology based on the BDI-II, symptom exacerbation was generally transient. Nonetheless, a few patients (4/196 or 2%) experienced more persistent, substantial depressive symptoms. For unclear reasons, patients with significant changes in the BDI-II did not report depression as an adverse event but a number of other patients did report depression that was documented as adverse experience. Most of these patients experienced

[11] Wang Y and Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Revista Brasileira de Psiquiatria 2013;35:416-431.
[12] Posner K, et al. The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. Am J Psychiatry 2011;168(12):1266-1277.
[13] See the Guidance for Industry - Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials at: https://www.fda.gov/downloads/drugs/guidances/ucm225130.pdf.

mild symptomatology but a few had moderate or severe symptoms. None of these events was serious or led to study dropout. Ten of 13 patients who reported depression had brain lesions at baseline.

Seven of 200 patients endorsed suicidal ideation on the C-SSRS. Six of these patients experienced a low level of ideation (a wish to be dead but no active thoughts of acting on the wish) and on only a single occasion. Only one patient (0.5%), who had a previous history of depression and moderate depressive symptomatology at baseline, had low level suicidal ideation on multiple occasions and active suicidal thoughts on one occasion. No suicidal behavior was reported among the 200 patients with evaluable C-SSRS data although it is remarkable that two patients were “erroneously” reported as having committed suicide.

Other psychiatric adverse events reported during Phase 2 of this trial included sleep disturbance (most commonly insomnia), hallucinations, irritability, anxiety, confusion, mood swings, and aggression. Most reports of confusion were graded as moderate or severe and one patient was hospitalized because of a confusional state, which was classified as serious. Most of the other psychiatric events were mild, non-serious, and did not lead to withdrawal from the trial.

In sum, the findings from the BDI-II, C-SSRS, and evaluation of psychiatric adverse events from Phase 2 of this study indicate that most patients had no or a minimal level of depression, suicidal ideation, and most other psychiatric adverse events. Nonetheless, a small fraction of patients (1% to 2%) had a more significant level of psychiatric symptomatology, as described above.

You may wish to consider adding other common psychiatric adverse events, such as insomnia, hallucinations, anxiety, aggression, and irritability, to labeling in Section 5.2 Central Nervous System Effects, which currently mentions changes in cognitive function, mood, and speech as events reported by patients receiving lorlatinib.

Limitations of these analyses are:

- the extent to which these findings are attributable to drug as opposed to other causes (such as reactions to disability or a shortened life span or brain metastasis) cannot be reasonably determined because there was no placebo control group in this trial.
- patients with severe psychiatric illness were excluded from this trial. Such patients may be more vulnerable to developing psychiatric adverse events than those in this study.
- Limitations of assessment tools such as inability to predict or prevent suicidal behavior in all cases.
- DPP advises CSSR assessment per our protocol at every visit, which did not occur in this trial. This leaves the possibility that some instances of suicidal ideation or behavior may have been undetected.

Thank you for your consultation request. Please do not hesitate to contact DPP if you have any further questions.

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/s/

GREGORY M DUBITSKY
06/20/2018
Corrected version.

MITCHELL V Mathis
06/20/2018

Clinical Inspection Summary

Date	5/18/2018
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Shubhangi Mehta, PharmD., Regulatory Project Manager Nicole Drezner, M.D., Clinical Reviewer Erin Larkins, M.D., Cross Discipline Team Leader Division of Oncology Products 2
NDA #	210868
Applicant	Pfizer Inc.
Drug	Lorlatinib
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive (b) (4) metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors.
Consultation Request Date	January 12, 2018
Summary Goal Date	May 18, 2018
Action Goal Date	August 5, 2018
PDUFA Date	August 5, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study B7461001 was submitted to FDA in support of a proposed indication for NDA 210868. This was a Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamics, and anti-cancer efficacy exploration study of lorlatinib as a single agent in patients with advanced ALK-positive or advanced ROS1-positive NSCLC. The data for Study B7461001 submitted by the Sponsor to the Agency in support of NDA 210868 appear reliable based on available information from the inspections of one domestic and two foreign clinical sites.

Three clinical sites were selected for audit: Dr. Alice Shaw, M.D. (Site 1002), Dr. Enriqueta Felip Font, M.D. (Site 1003), and Dr. Benjamin Besse, M.D. (Site 1005).

There were no significant inspectional observations for the clinical investigators, Dr. Alice Shaw, M.D., Dr. Enriqueta Felip Font, M.D., and Dr. Benjamin Besse, M.D., and the preliminary compliance classification for these inspections is No Action Indicated (NAI).

A Clinical Inspections Summary Addendum will be provided if the final classification of the inspection of the clinical investigators, Dr. Shaw, Dr. Felip Font, and Dr. Besse is significantly different following receipt and review of the Establishment Inspection Report (EIR).

II. BACKGROUND

Pfizer Inc., as sponsor of NDA 210868, seeks accelerated marketing approval for the use of lorlatinib for the treatment of patients with advanced ALK-positive NSCLC (b) (4) previously treated with one or more ALK tyrosine kinase inhibitors. Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive, brain-penetrant, small molecule inhibitor of ALK/ROS1 receptor tyrosine kinases that addresses mechanisms of resistance following previous treatment with ALK inhibitor therapy.

This clinical study consisted of 2 parts, Phase 1 and Phase 2. The Phase 1 portion of the study estimated the MTD (Maximum Tolerated Dose) for single-agent lorlatinib in dose escalation cohorts in patients with advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic central nervous system (CNS) metastases. The Phase 1 portion was also the basis for selecting the RP2D (Recommended Phase 2 Dose). The Phase 2 portion of the study employed single-agent lorlatinib at the RP2D identified in Phase 1 and was designed to evaluate the anti-cancer activity of lorlatinib in multiple subpopulations of patients with advanced ALK-positive NSCLC and in patients with advanced ROS1-positive NSCLC based on prior type and lines of therapy received. In all study parts, lorlatinib was administered orally QD (or BID dosing in Phase 1) continuously in 21-day cycles. Patients self-administered lorlatinib in the outpatient setting.

The primary efficacy outcome measure was Objective Response Rate (ORR) based on investigator assessment and confirmed by independent central review. ORR was defined as the percent of patients with best overall response as confirmed complete response (CR) or confirmed partial response (PR) based on RECIST v1.1 relative to the analysis subgroups. Confirmation of response was required at least 4 weeks after initial response was observed.

Study B7461001 was conducted at 47 centers in Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Singapore, Spain, Switzerland, Taiwan, and the United States. A total of 276 Phase 2 patients were assigned to selected cohorts and 275 patients received lorlatinib treatment in multiple cohorts. One patient died before the first dose. As of the data cutoff date (March 15, 2017), 157 patients were ongoing on treatment and 118 patients had permanently discontinued treatment from Phase 2. The primary reason for permanent discontinuation of treatment across all groups was objective progression or relapse.

GCP inspection was conducted at three clinical investigator (CI) sites. The CI sites for inspection were the highest enrolling sites for Study B7461001. Approximately 63% of patients enrolled were from foreign sites. Furthermore, Sites 1002 and 1005 had the highest number of protocol violations.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # # of Subjects	Inspection Dates	Classification
Alice Shaw, M.D. Site Number: 1002 Massachusetts General Hospital 55 Fruit St. Boston, MA 02115, U.S. Dana Farber Cancer Institute 450 Brookline Ave Boston, MA 02115, U.S.A.	Study: B7461001 Subjects Enrolled: 47	March 28-30 and April 2-4, 2018	*NAI
Enriqueta Felip Font, M.D. Site Number: 1003 Hospital Universitari Vall D'Hebron Planta Baja, UITM Servicio de Oncologia Passeig de la Vall D'Hebron 119-129 Barcelona 08035, Spain	Study: B7461001 Subjects Enrolled: 22	April 16-20, 2018	*NAI
Benjamin Besse, M.D. Site Number: 1005 Institut Gustave Roussy Department de Medecine 114 rue Edouard-Vaillant Villejuif Cedex 94805, France	Study: B7461001 Subjects Enrolled: 21	April 30 to May 4, 2018	*NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data may be unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Alice Shaw, M.D. (Site 1002)

The site screened 53 subjects and 47 were enrolled and randomized. At the time of the inspection, 14 subjects were on study treatment. Twenty-six (26) subjects completed the study. Subject (b) (6) enrolled and began treatment, but transferred to Site 2014 in California. Six (6) subjects withdrew from treatment. An audit of all enrolled subject's records was conducted with a focus on Phase 2 data review.

The inspection evaluated all subject informed consent forms, subject eligibility, concomitant medications, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and electronic Case Report Forms (eCRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, ORR, as defined by RECIST criteria, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1002 appear reliable based on available information.

2. Enriqueta Felip Font, M.D. (Site 1003)

The site screened 23 subjects and 22 were enrolled and randomized. At the time of the inspection, 9 subjects were on study treatment. Eleven (11) subjects completed the study. Subject (b) (6) enrolled and began treatment, but transferred to a different site. One subject withdrew from treatment. An audit of all enrolled subject's records was conducted with focus on Phase 2 data review.

The inspection evaluated all subject informed consent forms, subject eligibility, concomitant medications, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and electronic Case Report Forms (eCRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The primary efficacy endpoint data, ORR, as defined by RECIST criteria, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1003 appear reliable based on available information.

3. Benjamin Besse, M.D. (Site 1005)

The site screened 25 subjects and 21 were enrolled and randomized. At the time of the inspection, 12 subjects were on study treatment. Five (5) subjects completed the study. Four (4) subjects withdrew from treatment. An audit of all enrolled subject's records was conducted with focus on Phase 2 data review.

The inspection evaluated all subject informed consent forms, subject eligibility, concomitant medications, source documents, primary endpoint, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and electronic Case Report Forms (eCRF) and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional

Observations, was issued. The primary efficacy endpoint data, ORR, as defined by RECIST criteria, were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1005 appear reliable based on available information.

{See appended electronic signature page}

Navid Homayouni, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.
Review Division /Division Director/Patricia Keegan
Review Division /Medical Team Leader/Erin Larkins
Review Division/Medical Officer/Nicole Drezner
Review Division /Project Manager/Shubhangi Mehta
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Navid Homayouni
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

NAVID R HOMAYOUNI
05/18/2018

SUSAN D THOMPSON
05/18/2018

KASSA AYALEW
05/18/2018

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

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

Memorandum

Date: May 11, 2018

To: Shubhangi Mehta, PharmD
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Lorbrena (lorlatinib), for oral use**
NDA 210868

Office of Prescription Drug Promotion comments on proposed prescribing information (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for Lorbrena (lorlatinib) tablets, for oral use (Lorbrena) as requested by Division of Oncology Products (DOP2) in consult dated January, 09, 2018.

OPDP's review of the proposed PI is based on the draft PI titled, "NDA 210868 Label to Pfizer 042718" send by electronic mail on April 27, 2018 to OPDP (Nazia Fatima) from DOP2 (Shubhangi Mehta). OPDP comments are listed on the attached PI.

Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Patient Package Insert (PPI) were provided under a separate cover on May 11, 2018. OPDP's comments on Carton/Container Labeling will be provided under a separate cover.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
05/13/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	May 11, 2018
Requesting Office or Division:	Division of Oncology Products (DOP2)
Application Type and Number:	NDA 210868
Product Name and Strength:	Lorbrena (lorlatinib) Tablets, 25 mg and 100 mg
Applicant Name:	Pfizer Inc.
FDA Received Date:	May 9, 2018
OSE RCM #:	2017-2473-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

DOP2 requested that we review the revised container labels for Lorbrena (Appendix A) to determine if they are 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 revised container labels for Lorbrena are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Stewart J. Label and Labeling Review for Lorbrena (lorlatinib) NDA 210868. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 30. RCM No.: 2017-2473.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 9, 2018

Container labels

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/s/

JANINE A STEWART
05/11/2018

CHI-MING TU
05/14/2018

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:	May 10, 2018
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LORBRENA (lorlatinib)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 210868
Applicant:	Pfizer

1 INTRODUCTION

On December 5, 2017, Pfizer, submitted for the Agency's review an original New Drug Application (NDA) for LORBRENA (lorlatinib) tablets, for oral use, for the proposed indication of use for the treatment of patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).

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 Oncology Products 2 (DOP2) on December 19, 2017 and January 9, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LORBRENA (lorlatinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft LORBRENA (lorlatinib) PPI received on December 5, 2017, and received by DMPP and OPDP on April 27, 2018.
- Draft LORBRENA (lorlatinib) Prescribing Information (PI) received on December 5, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 27, 2018.

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.

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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/s/

SHAWNA L HUTCHINS
05/10/2018

NAZIA FATIMA
05/10/2018

LASHAWN M GRIFFITHS
05/10/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: April 20, 2018 **Date Consulted:** January 12, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Shubhangi Mehta, PharmD, Regulatory Project Manager (RPM)
Division of Oncology Products (DOP2)

Drug: lorlatinib

NDA: 210868

Indication: Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors

Applicant: Pfizer

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 210868 submitted on December 5, 2017
- Prior DPMH review for ceritinib by Tamara Johnson, MD, dated May 18, 2017
- Prior DPMH review for alectinib by Suchitra Balakrishnan, MD, dated October 3, 2015

Consult Question: **"**PLLR labeling review of New Molecular Entity; labeling indicates can cause embryo-fetal harm when administered during pregnancy"

INTRODUCTION

On December 5, 2017, Pfizer submitted a new NDA 210868 via the 505 (b) (1) regulatory pathway for the New Molecular Entity (NME) lorlatinib. The proposed indication for lorlatinib is the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors.

On January 12, 2018, DOP2 consulted DPMH to provide input on the labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR). This consult provides pregnancy and lactation labeling recommendations to DOP2 for the lorlatinib labeling.

REGULATORY HISTORY

- Orphan Drug Designation was granted on June 6, 2015, for the treatment of ALK-positive or ROS1 positive NSCLC.
- Breakthrough Therapy Designation was granted on April 26, 2017, for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK tyrosine kinase inhibitors (TKIs).

BACKGROUND

Lorlatinib Drug Characteristics[1]

- *Drug Class:* (b) (4) Kinase Inhibitor (TKI)
- *Mechanism of action*: (b) (4) inhibitor of ALK and ROS1 (b) (4)
- *Dosage and Administration:* 100 mg oral tablet taken once daily (b) (4). (b) (4)
- *Major Metabolite:* a benzoic acid metabolite of lorlatinib was observed in plasma.
- *Molecular weight:* 406 Daltons
- *Half-life:* (b) (4) hours
- (b) (4)
- *Bioavailability:* (b) (4) %
- *Serious Adverse reactions:* (b) (4), Atrioventricular Block, Hyperlipidemia
- *Common Adverse reactions:* Hypercholesterolemia, Hypertriglyceridemia, Edema, Peripheral Neuropathy, Fatigue, Cognitive (b) (4) Mood (b) (4) and Weight gain.
- (b) (4) *Drug Interactions:* lorlatinib decreases the concentration of CYP3A substrates (b) (4) which may reduce efficacy of these drugs.

[1] Lorlatinib (NDA 210868) proposed package insert

Pregnancy Considerations: Non-Small Cell Lung Cancer (NSCLC)

- *Prevalence:* Lung cancer in pregnancy is rare. Approximately 1:1000 pregnancies are complicated by maternal malignancy.[2]

- *Diagnosis:* Pregnant women with NSCLC tend to be diagnosed at an advanced stage which is attributed to the masking of symptoms by pregnancy, reluctance to perform radiological investigations, postponement of invasive diagnostic procedures, and low level of suspicion by providers.[2] Even with early diagnosis, the management plan must consider the potential risk of treatment to the fetus during organogenesis.[3]

- *Current Treatment:* The standard of care for treating lung cancer in pregnancy is chemotherapy in the second and third trimester, but the prognosis remains poor.[3]

- *Targeted Treatment:* Since the use of routine molecular genotyping in NSCLC, there have been several reports of successful use of EGFR tyrosine kinase inhibitors (TKIs) during pregnancy (erlotinib and gefitinib). However, little is known about the safety of these targeted agents in pregnancy.[3] There are no reports of ALK tyrosine kinase inhibitor use in pregnancy, but there are 2 published cases of postpartum treatment with crizotinib in which disease progression had occurred while receiving chemotherapy.[3]

- *Pregnancy Outcomes:* Maternal outcomes of NSCLC diagnosed during pregnancy are historically dismal with the majority of patients dying within 1 year.[4] However, in a recent retrospective analysis of women with NSCLC diagnosed during pregnancy or peripartum at Massachusetts General Hospital between 2009 and 2015, improved survival outcomes were reported in 8 women treated postpartum with genotype specific agents (crizotinib, ceritinib, alectinib, gefitinib, erlotinib) compared to traditional chemotherapy.[3]

REVIEW

PREGNANCY

Nonclinical Experience

In preliminary embryo-fetal development studies in rats and rabbits, lorlatinib was administered orally during the period of organogenesis. Embryo-fetal toxicity was observed including lower embryo-fetal viability, reduced fetal body weights, and congenital malformations (rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate, and dilation of cerebral ventricles) at exposure multiples that were 1.1 and 0.6 times, respectively, the human exposure at the recommended dose, based on AUC. For further details, see the Nonclinical Review by Elizabeth Spehalski, PhD.

[2] S. Boussios et al. Lung cancer in pregnancy: report of nine cases from an international collaborative study. Lung Cancer 82 (2013) 499-505.
[3] Yongli Ji, MD et al. Successful Treatment of Non-Small Cell Lung Cancer with Erlotinib Throughout Pregnancy. JAMA Oncology. September 2015. Volume 1, Number 6. 838-839.
[4] Ibiayi Dagogo-Jack, MD et al. Clinicopathologic Features of NSCLC Diagnosed During Pregnancy or the Peripartum Period in the Era of Molecular Genotyping. J of Thoracic Oncology. Vol. 11 No. 9: 1522-1528.

Reviewer's Comment
The applicant stated in the Nonclinical Overview that developmental toxicity (including complete litter loss, embryo-fetal lethality, external and visceral malformations) appear to be a class effect for the ALK tyrosine kinase inhibitors (crizotinib, ceritinib, alectinib, brigatinib). This reviewer agrees with the applicant's conclusion and notes that class labeling includes a Warning and Precaution for Embryo-Fetal Toxicity which is also recommended for lorlatinib labeling.

Applicant's Review of Literature
As this application is for an NME, the Agency did not request a published literature review.

DPMH's Review of Literature
A search was performed in PubMed, Embase, Micromedex[5], TERIS,[6] Reprotox[7], and Briggs[8], using the terms "lorlatinib" AND "pregnancy," "pregnant women," "pregnancy and birth defects," "pregnancy and congenital malformations," "pregnancy and stillbirth," "spontaneous abortion," and "pregnancy and miscarriage." No reports of lorlatinib use during pregnancy were found in the published literature.

Review of the Pharmacovigilance Database
Pregnant and lactating women were excluded from the lorlatinib clinical trials. Patients of childbearing potential were required to maintain contraception. The applicant stated in the Integrated Summary of Safety (ISS) that there have been no known reports of pregnancy in the patients that received lorlatinib during the development program.

Summary
Although human data are not available, the animal data indicate a significant risk of developmental toxicity from lorlatinib exposure during organogenesis (abortion, embryo-fetal lethality, external and visceral malformations). Therefore, DPMH and the Nonclinical Team agree that a "Warning and Precaution for Embryo-Fetal Toxicity" should be included in the lorlatinib labeling with recommendations to avoid use in pregnancy.

In addition, lorlatinib can decrease the concentration of hormonal contraceptives rendering them less effective. Thus, females of reproductive potential should use an effective non-hormonal contraceptive method during therapy and for 6 months after the final dose.[9] Males with female partners of reproductive potential should use an effective non-hormonal contraceptive method during therapy and for 3 months after the final dose.

LACTATION
Nonclinical Experience
Per ICH S9 guidelines, a pre-and postnatal development study was not conducted with lorlatinib. No lactation studies have been conducted with lorlatinib.

[5]Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/14/18.
[6]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 3/14/18.
[7]Reprotox® Website: www.Reprotox.org. Accessed 3/14/18.
[8]Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[9]FDA Guidance for Industry "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations." September 2017.

Applicant's Review of Literature
As this application is for an NME, the Agency did not request a published literature review.

DPMH's Review of Literature
A search was performed in *Medications and Mother's Milk*[10], LactMed[11], Micromedex[5], PubMed, and Embase using the terms lorlatinib AND "lactation" and "breastfeeding." No reports of lorlatinib use in lactation were identified.

Review of Pharmacovigilance Database
The applicant reported that no infants were exposed to lorlatinib through breastfeeding.

Summary
There are no data on the presence of lorlatinib or its metabolite in either human or animal milk, its effects on the breastfed infant or on milk production. Considering the drug's mechanism of action and the adverse reactions observed in adults during clinical trials (e.g., cognitive disorder, atrioventricular block, leukopenia, peripheral neuropathy, and severe hyperlipidemia), DPMH recommends lorlatinib labeling advise lactating women not to breastfeed. Breastfeeding should be discontinued during treatment and for 7 days after the last dose (at least 6 half-lives). This recommendation is consistent with class labeling for the other ALK tyrosine kinase inhibitor approved products (crizotinib, ceritinib, alectinib, and brigatinib).

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Findings in male reproductive organs from repeat dose toxicity studies included testicular tubular degeneration/atrophy associated with mild oligo/aspermia in dogs and rats at clinically relevant exposures (1.6 and 3.6-times the recommended human dose based on AUC). In genotoxicity studies, lorlatinib was identified as an aneugen (defined as a substance that causes a daughter cell to have an abnormal number of chromosomes or aneuploidy), but not a mutagen or clastogen.

Fertility, early embryonic development, and carcinogenicity studies were not conducted with lorlatinib given the intended treatment of patients with advanced cancer in accordance with ICH S9 guidelines. For more information, see the Nonclinical Review by Elizabeth Spehalski, PhD.

Applicant's Review of Literature
As this application is for an NME, the Agency did not request a published literature review.

DPMH's Review of Literature
A search was performed in PubMed, Embase, and Reprotox[7] using the terms "lorlatinib" AND "fertility," "contraception," "oral contraceptives," and "infertility." No reports were found in the published literature related to lorlatinib and fertility or interactions with hormonal contraceptives.

[10]Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.
[11]http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. Accessed 3/14/18.

Summary

There are no human data regarding the effects of lorlatinib on fertility. However, animal data from genotoxicity studies indicate a risk for aneugenicity. In addition, repeat dose toxicity studies indicated an adverse effect on male reproductive organs (testicular tubular degeneration/atrophy associated with oligo/aspermia).

Based on mechanism of action, embryofetal toxicity demonstrated in animal studies, and drug-drug interactions with hormonal contraceptives, DPMH recommends subsection 8.3 of lorlatinib labeling include a contraceptive heading which advises females of reproductive potential to use an effective non-hormonal contraceptive method during therapy and for 6 months after the final dose. Considering the aneugenic potential of lorlatinib, males with female partners of reproductive potential should be advised to use effective contraception during therapy and for 3 months after the final dose.[9] These recommendations are consistent with labeling for the other ALK tyrosine kinase inhibitor drugs in class.

DPMH also recommends subsection 8.3 of lorlatinib labeling include an infertility heading with cross reference to Nonclinical Toxicity 13.1, advising males that lorlatinib may cause reduced fertility based on findings in male reproductive organs in animal studies. DPMH discussed these findings with the Nonclinical Review Team which noted the infertility effects were fully or partially reversible. Finally, a pregnancy testing heading is recommended in subsection 8.3 of lorlatinib labeling to recommend obtaining a pregnancy test prior to ALK tyrosine kinase inhibitor administration. Pregnancy testing is considered routine practice prior to the administration of oncology products in women of reproductive potential.

CONCLUSIONS

Developmental and reproductive toxicity were observed in animal studies indicating lorlatinib can cause fetal harm when administered during organogenesis. Therefore, DPMH and the Nonclinical Team recommend a pregnancy "Warning and Precaution for Embryo-Fetal Toxicity" be included in lorlatinib labeling. Because of the potential for serious adverse reactions in breastfed infants from exposure to lorlatinib, DPMH recommends labeling subsection 8.2 advise lactating women not to breastfeed during treatment and for 7 days after the final dose.

In addition, the Females and Males of Reproductive Potential subsection 8.3 of lorlatinib labeling should include a recommendation to verify pregnancy status prior to initiation of treatment. An effective non-hormonal contraceptive method in females of reproductive potential and males with female partners of reproductive potential should be used because lorlatinib can render hormonal contraceptives ineffective. Finally, considering the adverse effects of lorlatinib exposure on male reproductive organs in animals, an infertility section should be included in subsection 8.3.

The lorlatinib labeling subsections for *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Subsection 8.1**
  - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" and "Data" headings.
- **Lactation, Subsection 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: "Risk Summary" heading.
- **Females and Males of Reproductive Potential, Subsection 8.3**
  - The "Females and Males of Reproductive Potential" subsection of labeling was formatted in the PLLR format to include: "Pregnancy Testing", "Contraception", "Infertility" headings.
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to subsection 5.5, 8.1, 8.2, and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH reviewed Highlights, subsections 5.5, 8.1, 8.2, 8.3, and section 17 of labeling for compliance with the PLLR. The labeling recommendations include input from the Nonclinical and Clinical Review Team. DPMH discussed our labeling recommendations with the Division on March 28, 2018. DPMH refers to the final NDA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective non-hormonal method of contraception (5.5, 7.2, 8.1, 8.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.2 Testing Prior to TRADENAME Administration

Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with TRADENAME *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TRADENAME can cause fetal harm when administered to a pregnant woman. Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less

than the human exposure at the recommended dose of 100 mg once daily based on AUC. Verify pregnancy status of females of reproductive potential prior to initiating TRADENAME. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective non-hormonal method of contraception since TRADENAME can render hormonal contraceptives ineffective, during treatment with TRADENAME and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TRADENAME and for 3 months after the final dose *[see Drug Interactions (7.2), Use in Specific Populations (8.1), (8.3), Nonclinical Toxicology (13.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, TRADENAME can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on TRADENAME use in pregnant women. Administration of lorlatinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less than the human exposure at the recommended dose of 100mg once daily based on AUC *(see Data).* Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population in clinically recognized pregnancies is 2-4 % and 15-20%, respectively.

Data

Animal Data

Preliminary embryo-fetal development studies investigating the administration of lorlatinib during the period of organogenesis were conducted in rats and rabbits. In rabbits, lorlatinib administration resulted in abortion and total loss of pregnancy at doses of 15 mg/kg (approximately 1.6 times the human exposure at the 100 mg recommended dose) or greater. At a dose of 4 mg/kg (approximately 0.6 times the human exposure at the 100 mg recommended dose by AUC) toxicities included increased post-implantation loss and malformations including rotated limbs, malformed kidneys, domed head, high arched palate, and dilation of the cerebral ventricles. In rats, administration of lorlatinib resulted in total loss of pregnancy at doses of 4 mg/kg (approximately 5.2 times the human exposure at the 100 mg recommended dose) or greater. At a dose of 1 mg/kg (approximately 1.3 times the human exposure at the 100 mg recommended dose) there was increased post-implantation loss, decreased fetal body weight, and malformations including gastroschisis, rotated limbs, supernumerary digits, and vessel abnormalities.

8.2 Lactation

Risk Summary

There are no data on the presence of lorlatinib or its metabolites in either human or animal milk, or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants, advise a lactating woman not to breastfeed during treatment with TRADENAME and for 7 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with TRADENAME *[see Dosage and Administration (2.1), Warnings and Precautions (5.5), and Use in Specific Populations (8.1)]*.

Contraception

Females

TRADENAME can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with TRADENAME and for 6 months after the final dose. Counsel patients to use a non-hormonal method of contraception since TRADNAME can render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with TRADENAME and for at least 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on findings from animal studies, TRADENAME may transiently impair male fertility. *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use an effective non-hormonal contraception during treatment with TRADENAME and for at least 6 months after the final dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with TRADENAME and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise females not to breastfeed during treatment with TRADENAME and for 7 days after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that TRADENAME may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

PATIENT INFORMATION

Before you take TRADENAME, tell your healthcare provider if you:

- Are pregnant, or plan to become pregnant. TRADENAME can harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with TRADENAME or think you may be pregnant.
    - **Females** who are able to become pregnant should use an effective non-hormonal birth control during treatment with TRADENAME and for at least 6 months after the final dose of TRADENAME. Birth control methods that contain hormones (such as birth control pills, injections, or patches) may not work as well during treatment with TRADENAME. You should use another effective method of birth control during treatment with TRADENAME. Talk to your healthcare provider about birth control choices that are right for you during treatment with TRADENAME.
    - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with TRADENAME and for at least 3 months after the final dose of TRADENAME.
- are breastfeeding or plan to breastfeed. It is not known if TRADENAME passes into your breast milk. Do not breastfeed during treatment with TRADENAME and for 7 days after the final dose. Talk to your healthcare provider about the best way to feed your baby during this time.

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/s/

KRISTIE W BAISDEN
04/20/2018

TAMARA N JOHNSON
04/20/2018

LYNNE P YAO
04/20/2018

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:	March 30, 2018
Requesting Office or Division:	Division of Oncology Products (DOP2)
Application Type and Number:	NDA 210868
Product Name and Strength:	Lorbrena (lorlatinib) Tablets, 25 mg and 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	December 5, 2017 and February 15, 2018
OSE RCM #:	2017-2473
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of this NDA review, this review evaluates the proposed Lorbrena (lorlatinib) Tablets container labels and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS 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

Our review of materials found the proposed PI and container labels may be improved to promote the safe use of the proposed product, and we provide our recommendations in Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and container labels for Lorbrena (lorlatinib) Tablets can be improved to promote safe use.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. Consider adding instructions in the event vomiting occurs after lorlatinib administration in Section 2.1. We note Pfizer's Ibrance PI contains the following instructions to account for the event when a patient vomits: "If the patient vomits or misses a dose, an

additional dose should not be taken that day. The next prescribed dose should be taken at the usual time."

4.2 RECOMMENDATIONS FOR [redacted] (b) (4).

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

A. Container Labels
   1. Replace "TRADENAME" with the conditionally accepted proprietary name, Lorbrena.

   2. Although the proposed 25 mg and 100 mg strength container labels are already color differentiated (purple vs. blue), consider adjusting the blue and purple colors (e.g. lighter shade of purple vs. blue) or use another color (visually brighter or lighter colors like pink, or yellow) to further provide color differentiation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lorbrena received on February 15, 2018 from Pfizer Inc.

Table 2. Relevant Product Information for Lorbrena

Initial Approval Date	N/A
Active Ingredient	lorlatinib
Indication	For the treatment of patients with anaplastic lymphoma kinase (ALK)- positive non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors.
Route of Administration	Oral
Dosage Form	Tablets
Strength	25 mg and 100 mg
Dose and Frequency	Lorbrena is administered once daily until disease progression or (b) (4) Maximum daily dose is 100 mg. Dose Levels / Dose: Recommended dose: 100 mg once daily 1st dose reduction: 75 mg once daily 2nd dose reduction: 50 mg once daily
How Supplied	25 mg • 30 count bottles 100 mg • 30 count bottles
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure	Proposed commercial packaging is a (b) (4) high-density polyethylene (HDPE) bottle containing (b) (4) desiccant and (b) (4) closures with heat induction seal liners.

APPENDIX G. LABELS AND LABELING

G.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 Lorbrena labels and labeling submitted by Pfizer Inc.

- Container labels submitted December 5, 2017
- Prescribing Information submitted February 15, 2018

G.2 Label and Labeling Images

(b) (4)

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

Container Label: 100 mg

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/s/

JANINE A STEWART
03/30/2018

CHI-MING TU
03/30/2018