# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210868Orig1s000

# MULTI-DISCIPLINE REVIEW

**Summary Review**
**Office Director**
**Cross Discipline Team Leader Review**
**Clinical Review**
**Non-Clinical Review**
**Statistical Review**
**Clinical Pharmacology Review**

# NDA/BLA Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| **Application Type** | NDA |
| **Application Number(s)** | 210868 |
| **Priority or Standard** | Priority |
| **Submit Date(s)** | December 5, 2017 |
| **Received Date(s)** | December 5, 2017 |
| **PDUFA Goal Date** | November 5, 2018 |
| **Division/Office** | OHOP/DOP2 |
| **Review Completion Date** | November 2, 2018 |
| **Established Name** | Lorlatinib |
| **(Proposed) Trade Name** | LORBRENA |
| **Pharmacologic Class** | Kinase inhibitor |
| **Code name** | PF-06463922 |
| **Applicant** | Pfizer, Inc. |
| **Formulation(s)** | 100 mg and 25 mg tablets |
| **Dosing Regimen** | 100 mg orally once daily |
| **Applicant Proposed Indication(s)/Population(s)** | 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). |
| **Recommendation on Regulatory Action** | Accelerated Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small celling cancer (NSCLC) whose disease has progressed on:<br>• crizotinib and at least one other ALK inhibitor for metastatic disease; or<br>• alectinib as the first ALK inhibitor therapy for metastatic disease; or<br>• ceritinib as the first ALK inhibitor therapy for metastatic disease |



Reference ID: 4344794

**Table of Contents**

Reviewers of Multi-Disciplinary Review and Evaluation ..... 13

Additional Reviewers of Application ..... 13

Glossary ..... 14

1 Executive Summary ..... 17
- 1.1. Product Introduction ..... 17
- 1.2. Conclusions on the Substantial Evidence of Effectiveness ..... 17
- 1.3. Benefit-Risk Assessment ..... 18
- 1.4. Patient Experience Data ..... 25
- Section 19.6, Additional Clinical Outcome Assessment Analyses ..... 25

2 Therapeutic Context ..... 27
- 2.1. Analysis of Condition ..... 27
- 2.2. Analysis of Current Treatment Options ..... 28

3 Regulatory Background ..... 35
- 3.1. U.S. Regulatory Actions and Marketing History ..... 35
- 3.2. Summary of Presubmission/Submission Regulatory ..... 35
- ActivityFollowing the receipt of final written responses for a Type B pre-IND meeting on June 14, 2013, regarding the design of the first-in-patient trial of lorlatinib (PF-06463922) under IND 118296, the original IND was filed on August 15, 2013. A list outlining the pertinent regulatory history for lorlatinib is included in the table below. ..... 35

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety ..... 38
- 4.1. Office of Scientific Investigations (OSI) ..... 38
- 4.2. Product Quality ..... 39
- 4.3. Clinical Microbiology ..... 39
- 4.4. Devices and Companion Diagnostic Issues ..... 39

5 Nonclinical Pharmacology/Toxicology ..... 40
- 5.1. Executive Summary ..... 40
- 5.2. Referenced NDAs, BLAs, DMFs ..... 42
- 5.3. Pharmacology ..... 43



Reference ID: 4344794

5.4. ADME/PK ..... 52
5.5. Toxicology ..... 56
5.5.1. General Toxicology ..... 56
5.5.2. Genetic Toxicology ..... 66
5.5.3. Carcinogenicity ..... 68
5.5.4. Reproductive and Developmental Toxicology ..... 68
5.5.5. Other Toxicology Studies ..... 73

6 Clinical Pharmacology ..... 74
6.1. Executive Summary ..... 74
6.2. Summary of Clinical Pharmacology Assessment ..... 77
6.2.1. Pharmacology and Clinical Pharmacokinetics ..... 77
6.2.2. General Dosing and Therapeutic Individualization ..... 78
6.3. Comprehensive Clinical Pharmacology Review ..... 80
6.3.1. General Pharmacology and Pharmacokinetic Characteristics ..... 80
6.3.2. Clinical Pharmacology Questions ..... 84

7 Sources of Clinical Data and Review Strategy ..... 105
7.1. Table of Clinical Studies ..... 105
7.2. Review Strategy ..... 107

8 Statistical and Clinical and Evaluation ..... 108
8.1. Review of Relevant Individual Trials Used to Support Efficacy ..... 108
8.1.1. Study B761001 ..... 108
8.1.2. Study Results ..... 131
8.1.3. Assessment of Efficacy Across Trials ..... 149
8.2. Review of Safety ..... 152
8.2.1. Safety Review Approach ..... 152
8.2.2. Review of the Safety Database ..... 152
8.2.3. Adequacy of Applicant's Clinical Safety Assessments ..... 155
8.2.4. Safety Results ..... 158
8.2.5. Analysis of Submission-Specific Safety Issues ..... 177
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability ..... 202
8.2.7. Safety Analyses by Demographic Subgroups ..... 202



Reference ID: 4344794

8.2.8. Specific Safety Studies/Clinical Trials ..... 205
8.2.9. Additional Safety Explorations ..... 205
8.2.10. Safety in the Postmarket Setting ..... 207
8.2.11. Integrated Assessment of Safety ..... 207

SUMMARY AND CONCLUSIONS ..... 208
8.3. Statistical Issues ..... 208
8.4. Conclusions and Recommendations ..... 208

9 Advisory Committee Meeting and Other External Consultations ..... 210

10 Pediatrics ..... 211

11 Labeling Recommendations ..... 212
11.1. Prescription Drug Labeling ..... 212

12 Risk Evaluation and Mitigation Strategies (REMS) ..... 216

13 Postmarketing Requirements and Commitment ..... 217

14 Division Director (DHOT) ..... 219

15 Division Director (OCP) ..... 220

16 Division Director (OB) ..... 221

17 Division Director (Clinical) ..... 222

18 Office Director (or designated signatory authority) ..... 223

19 Appendices ..... 224
19.1. References ..... 224
19.2. Financial Disclosure ..... 226
19.3. Nonclinical Pharmacology/Toxicology ..... 226
19.4. OCP Appendices (Technical documents supporting OCP recommendations) ..... 227
19.4.1. Summary of Bioanalytical Method Validation and Performance ..... 227
19.4.2. Applicant's population pharmacokinetic analysis ..... 248
19.4.3. Applicant's Exposure-Response Analysis for Efficacy ..... 259
19.4.4. Applicant's Exposure-Response Analysis for Safety ..... 268
19.5. Statistical Appendices ..... 280



Reference ID: 4344794

19.6. Additional Clinical Outcome Assessment Analyses ..... 284



Reference ID: 4344794

**Table of Tables**

Table 1: Summary of treatment armamentarium relevant to proposed indication ..... 31
Table 2: Regulatory history for lorlatinib ..... 35
Table 3 Inspection results by site (from Clinical Inspection Summary Review) ..... 38
Table 4: $K_i$ of PF-06463922 for target kinases in biochemical assays ..... 43
Table 5: Activity of PF-06463922 in enzyme and cell-based assays ..... 44
Table 6: PF-06463922 activity against ALK fusion variants and ALK fusion mutations in cell-based assays ..... 45
Table 7: PF-06463922 activity against ROS1 fusion phosphorylation in cell-based assays..... 46
Table 8: Statistically significant effects of PF-06463922 on cardiovascular parameters by time period ..... 51
Table 9: Selected histopathology findings in rats ..... 59
Table 10: Selected histopathology in dogs ..... 64
Table 11: In Vitro Micronucleus Findings ..... 67
Table 12: In Vivo Wistar Han rat Micronucleus Findings ..... 67
Table 13 Individual Lorlatinib Steady State CL Estimates Summarized by Renal Impairment Groups ..... 87
Table 14 ICR-assessed best overall response in previously treated ALK-positive NSCLC patients with ALK kinase domain mutations detected in tumor tissue (N=40) ..... 88
Table 15 PK Parameters of a single dose of lorlatinib after a high-fat meal as compared with fasted state ..... 90
Table 16 PK Parameters of a single dose of lorlatinib after concomitant with rabeprazole as compared with fasted state ..... 90
Table 17 PK Parameters of a single dose of lorlatinib oral solution vs. anhydrous free-base tablets under fasting condition ..... 91
Table 18 PK Parameters of a single dose of lorlatinib anhydrous free base tablet vs. lorlatinib (b) (4) tablet ..... 92
Table 19 PK Parameters of a single dose of lorlatinib (b) (4) tablet vs. lorlatinib (b) (4) tablet ..... 92
Table 20 PK Parameters of a single dose of lorlatinib commercial tablet vs. lorlatinib clinical anhydrous free base tablet ..... 93
Table 21 Geometric mean ratios of a single dose of lorlatinib commercial tablet vs. lorlatinib clinical anhydrous free base tablet ..... 93
Table 22 PK Parameters [Geometric Mean (%CV)] of a single dose of midazolam before and after repeated doses of lorlatinib ..... 94
Table 23 Geometric mean ratios of a single dose of midazolam before and after repeated doses of lorlatinib ..... 94
Table 24 PK Parameters of a single dose of lorlatinib with or without concomitant itraconazole ..... 95
Table 25 PK Parameters of lorlatinib with or without concomitant rifampicin ..... 96
Table 26 PK Parameters of M8 (main lorlatinib metabolite) with or without concomitant rifampicin ..... 97



Reference ID: 4344794

Table 27 PK Parameters of rifampicin and deacetyl rifampicin on day 9 of the concomitant rifampicin and lorlatinib ..... 98
Table 28 Qualitative assessment of the level of lorlatinib (PF-06463922) and its metabolites on Day 1 (Period 1) and Day 9 (Period 2) ..... 98
Table 29 Levels of lorlatinib (PF-06463922) and its metabolites with or out without rifampicin induction in human hepatocytes ..... 99
Table 30 Lorlatinib induction of mRNA and activity level (fold change) of CYP enzymes from 1 human hepatocyte lot (Lot HC7-4) ..... 101
Table 31 Calculated R1 values for lorlatinib inhibition of CYP activities in Human Liver Microsomes ..... 101
Table 32 Calculated R1 values for M8 or PF-06895751 inhibition of CYP activities in Human Liver Microsomes ..... 102
Table 33 Calculated R1 values for lorlatinib inhibition of UGT activities in Human Liver Microsomes ..... 102
Table 34 Calculated R1 values for M8 or PF-06895751 inhibition of UGT activities in Human Liver Microsomes ..... 102
Table 35 Calculated R1 and R2 values for lorlatinib inhibition of transporter activities ..... 103
Table 36 Calculated R1 and R2 values for M8 or PF-06895751 inhibition of transporter activities ..... 103
Table 37 Listing of clinical trials relevant to this NDA ..... 106
Table 38 Lorlatinib dose modification guidelines (Applicant tables) ..... 118
Table 39 Lorlatinib dose level reductions (Applicant tables) ..... 121
Table 40 Study calendars for Study B7461001 (Applicant table) ..... 123
Table 41: Summary of Protocol Amendments ..... 129
Table 42 List of Studies (Reviewer Table) ..... 132
Table 43 Patient disposition (dose escalation portion) - full analysis population from Study B7461001 (Reviewer table) ..... 133
Table 44 Patient disposition (dose expansion phase and Japanese lead-in cohort) - full analysis population from Study B7461001 (Reviewer table) ..... 134
Table 45: Disposition of Patients in the Primary Efficacy Population ..... 134
Table 46 Summary demographics of patients in the primary safety populations in Study B7461001 ..... 136
Table 47: Demographic Characteristics of Patients in the Primary Efficacy Population ..... 137
Table 48: Other Baseline Characteristics in the Primary Efficacy Population ..... 138
Table 49: Important Dates in the Central Imaging Read Process ..... 140
Table 50: Reasons for Change in Reader after the CSR Cutoff ..... 141
Table 51: Confirmed ORR and IC-ORR per IRC in the Primary Efficacy Population ..... 142
Table 52: Duration of Response per IRC for Responders in the Primary Efficacy Population ..... 142
Table 53: Updated Confirmed ORR and IC-ORR per IRC in the Primary Efficacy Population ..... 143
Table 54: Confirmed ORR and IC-ORR per INV in the Primary Efficacy Population ..... 144
Table 55: Duration of Response per INV for Responders in the Primary Efficacy Population ..... 144
Table 56: Confirmed ORR per IRC in Patients Who Had Previously Received Alectinib as Their Only ALK TKI ..... 145



Reference ID: 4344794

Table 57: Confirmed ORR per IRC in Patients Who Had Previously Received Ceritinib as Their Only ALK TKI ..... 146
Table 58: Confirmed ORR per IRC in Patients Who Had Previously Received Crizotinib and at Least One Other ALK TKI ..... 146
Table 59: Confirmed IC-ORR per IRC in Patients with Measurable Intracranial Disease per IRC in the Primary Efficacy Population ..... 147
Table 60: Duration of Response per IRC in the Primary Efficacy Population ..... 147
Table 61: Updated Confirmed IC-ORR per IRC in Patients with Measurable Disease per IRC in the Primary Efficacy Population ..... 148
Table 62: Number of Patients Whose Intracranial Response Data Was Different at the Safety Update Cutoff than the CSR Cutoff ..... 148
Table 63: Number of Patients Whose Overall Response Data Was Different at the Safety Update Cutoff than the CSR Cutoff ..... 149
Table 64: Confirmed ORR per IRC by Age, Sex, and Race ..... 150
Table 65: Confirmed ORR per IRC by Prior Therapy Cohorts Defined in Protocol ..... 150
Table 66: Confirmed IC-ORR per IRC by Age, Sex, and Race ..... 151
Table 67: Confirmed IC-ORR per IRC by Prior Therapy Cohorts Defined in Protocol ..... 151
Table 68: IC-ORR per IRC by Prior Brain Radiation Therapy ..... 152
Table 69 Dosing cohorts in the dose expansion portion of Study B7461001 (Reviewer table) . 153
Table 70 Exposure for Study B7461001, 100 mg QD pooled group (Reviewer table) ..... 153
Table 71 Safety population (Reviewer table) ..... 153
Table 72 Patient characteristics of the safety population (Reviewer table) ..... 154
Table 73 Baseline disease characteristics of the safety population (Reviewer table) ..... 154
Table 74 Serious adverse events occurring in >2 patients (Reviewer table) ..... 162
Table 75 Adverse events leading to discontinuation of lorlatinib (n=295) (Reviewer table) ..... 164
Table 76 Adverse events leading to dose reduction of lorlatinib in > 1% of patients (n=295) (Reviewer table) ..... 165
Table 77 Adverse events leading to dose interruption of lorlatinib in >1% of patients (n=295) (Reviewer table) ..... 166
Table 78 Treatment-emergent adverse events occurring in > 10% (all Grades) or > 2% (Grades 3-5) of patients receiving lorlatinib 100 mg QD (n=295) (Reviewer table) ..... 170
Table 79 Worsening laboratory values occurring in >20% of patients (n=295) (Reviewer table) ..... 171
Table 80 Liver function testing for patient (b) (6) (Reviewer table) ..... 172
Table 81 Liver function testing for patient (b) (6) (Reviewer table) ..... 174
Table 82 Liver function testing in Study B7461011 (Reviewer table) ..... 178
Table 83 Hepatic function testing during co-administration of lorlatinib and modafinil, patient (b) (6) (Applicant table) ..... 180
Table 84 Hepatic function testing during co-administration of lorlatinib and modafinil, patient (b) (6) (Applicant table) ..... 181
Table 85 Preferred terms included as CNS effects (Reviewer table) ..... 184
Table 86: Patients with an increase in BDI-II total score ≥ 10 on multiple study visits (DPP Reviewer table) ..... 187



Reference ID: 4344794

Table 87 Patients with suicidal ideation in Study B7461001 (Reviewer table) ..... 190
Table 88 Time to start of medication to lower cholesterol and/or triglycerides (Reviewer table) ..... 197
Table 89 Mean cholesterol and triglyceride levels preceding adverse event ..... 198
Table 90 Comparison of treatment-emergent adverse events by age in Study B7461001 (Reviewer table) ..... 203
Table 91 Comparison of treatment-emergent adverse events by gender in Study B7461001 (Reviewer table) ..... 204
Table 92 Comparison of treatment-emergent adverse events by race in Study B7461001 (Reviewer table) ..... 205
Table 93 Summary of the Validated Analytical Methods for Lorlatinib, Midazolam, Rifampicin, and Desacetyl Rifampicin ..... 228
Table 94 Summary of Bioanalytical Assay Performance ..... 229
Table 95 Summary of Bioanalytical Assay Performance for PF-06895751 ..... 229
Table 96 Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following a Single Oral Dose of Lorlatinib ..... 230
Table 97 Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following Multiple Oral Doses of Lorlatinib ..... 231
Table 98 Comparison of lorlatinib pharmacokinetic parameters between observed values[a] and predicted values from PBPK model following a single 50 mg IV or 100 mg SD or MD oral administration ..... 237
Table 99 Comparison of mean accumulation ratio ($R_{ac}$) and steady state accumulation ratio ($R_{ss}$) between observed and predicted values ..... 239
Table 100 Observed and simulated lorlatinib exposure following a single dose of lorlatinib with multiple daily doses of itraconazole, a strong CYP3A inhibitor, or rifampicin, a strong CYP3A inducer ..... 240
Table 101 Observed and simulated midazolam exposure following a single dose of midazolam, a CYP3A index substrate, with multiple daily doses of lorlatinib ..... 240
Table 102 Steady state exposure of lorlatinib with (+) or without (-) CYP3A inhibitor itraconazole (200 mg QD) and relative exposure ratios ..... 241
Table 103 Lorlatinib PBPK model input parameters (Simcyp, v16, release 1) ..... 242
Table 104 Enzyme Kinetic Parameters for the metabolism of lorlatinib in pooled liver microsomes[a] ..... 245
Table 105 M2a formation rates and prediction of fraction metabolic contribution determined from lorlatinib metabolism in rhCYPs ..... 247
Table 106 Metabolite formation rates of M1a from lorlatinib metabolism in rhUGTs[a] ..... 247
Table 107 Clinical Studies Included in Population PK Analysis ..... 249
Table 108 Summary of Continuous Covariates ..... 251
Table 109 Summary of Categorical Covariates ..... 254
Table 110 Final PK Model Parameter Estimates ..... 255
Table 111 Summary of Patients with Advanced NSCLC Enrolled in Study B7461001 ..... 260
Table 112 Potential Predictors of Response (i.e. Covariates) ..... 261
Table 113 Summary of Patient Categorical Covariate Characteristics ..... 262



Reference ID: 4344794

Table 114 Summary of Patient Continuous Covariate Characteristics ..... 263
Table 115 Univariate Analysis Results for Lorlatinib Exposure Metrics: ORR ≥1 Prior ALK-Inhibitors ..... 265
Table 116 Univariate Analysis Results for Lorlatinib Exposure Metrics: IC-ORR ≥1 Prior ALK-Inhibitors ..... 266
Table 117 Final Model for Exposure Response Analysis: IC-ORR ≥1 Prior ALK-Inhibitors ..... 267
Table 118 Potential Predictors of Covariate Analysis ..... 270
Table 119 Continuous Covariates ..... 270
Table 120 Categorical Covariates ..... 271
Table 121 Incidence of Safety Endpoints ..... 273
Table 122 Logistic Regression Analysis Results for Grade ≥ 3 Hypercholesterolemia ..... 275
Table 123 Hosmer-Lemeshow Goodness of Fit Test Results for Grade ≥ 3 Hypercholesterolemia ..... 276
Table 124 Logistic Regression Analysis Results for Grade ≥ 3 TEAEs ..... 277
Table 125 Hosmer-Lemeshow Goodness of Fit Test Results for Grade ≥ 3 TEAEs ..... 279
Table 126: Disposition by Pre-Specified Cohort of Patients in the Primary Efficacy Population 280
Table 127: Demographic Characteristics by Pre-Specified Cohort of Patients in the Primary Efficacy Population ..... 280
Table 128: Other Baseline Characteristics by Pre-Specified Cohort in the Primary Efficacy Population ..... 281
Table 129: PFS per IRC and OS for the Primary Efficacy Population ..... 282
Table 130: Summary of CNS Disease Discordance for Patients in the Primary Efficacy Population ..... 282
Table 131: Summary of Overall Response Discordance for Patients in the Primary Efficacy Population ..... 282
Table 132: Summary of Intracranial Response Discordance for Patients in the Primary Efficacy Population ..... 283
Table 133: Summary of Intracranial Response Discordance for Patients in the Primary Efficacy Population ..... 283
Table 134: PRO Completion Rates During the First 24 Cycles of Treatments for Patients in the Primary Efficacy Population ..... 284



Reference ID: 4344794

**Table of Figures**

Figure 1: Inhibition of EML4-ALKv1$^{G1202R}$ tumor growth by PF-06463922 in a NSCLC model ..... 46
Figure 2: Inhibition of ALK and ALK I1171T by lorlatinib and crizotinib ..... 47
Figure 3: Inhibition of EML4-ALKL1196M (left) and ROS1 (right) tumor growth following treatment with PF-06463922 in mouse models of NSCLC ..... 47
Figure 4: Effects of PF-06463922 on cognitive performance parameters..... 49
Figure 5 Simulated Body Weight Effect on Lorlatinib Pharmacokinetics ..... 86
Figure 6 Time course of the increase in plasma ALT and AST liver over the treatment period of all 12 healthy subjects. ..... 96
Figure 7: Study Schemas of B761001..... 110
Figure 8 Lorlatinib dose levels (Applicant figure) ..... 116
Figure 9 eDISH analysis for patient (b) (6)(Applicant figure)..... 173
Figure 10 eDISH analysis for patient (b) (6)(Applicant figure)..... 175
Figure 11 The observed and simulated concentration-time profiles of a single (A) 50 mg IV and (B) 100 mg oral administration of lorlatinib in healthy subjects. Blue circles with standard derivation denoted the observed mean values obtained from Study B7461007; Black solid line denoted the simulated concentrations from PBPK model with 95$^{th}$ percentile highlighted by gray shadow and red dash lines..... 235
Figure 12 The observed and simulated concentration-time profiles of 100 mg QD doses of lorlatinib in NSCLC patients. Color circles denoted the individual observed values obtained from Study B7461001; Black solid line denoted the simulated concentrations from PBPK model with 95$^{th}$ percentile highlighted by gray shadow and red dash lines. ..... 237
Figure 13 Dose proportionality between dose and exposure ($C_{max}$ and AUC) and the calculated R ratio. ..... 238
Figure 14 Simulated lorlatinib concentration-time profiles with (multiple doses of lorlatinib and itraconazole) or without itraconazole under steady state condition using PBPK modeling..... 241
Figure 15 Eadie-Hofstee, Michaelis-Menten, and Lineweaver-Burk plots for M6 formation from lorlatinib (Source: Preclinical Report 123802; Figures 8.2 and 6.1 on Page 22) ..... 246
Figure 16 Goodness-of-fit Plots of the Final Model..... 256
Figure 17 Prediction- and Variability- Corrected Visual Predictive Check..... 257
Figure 18 Predicted Probability of Achieving IC-ORR Stratified by Significant Predictor Variable: IC-ORR ≥1 Prior ALK-Inhibitors..... 267
Figure 19 Predicted Probability of Grade ≥ 3 Hypercholesterolemia Versus Cmax Prior to the AE with Fixed Time to Event Stratified by Baseline Cholesterol Level ..... 275
Figure 20 Hosmer-Lemeshow Goodness of Fit Calibration Plot for Grade ≥ 3 Hypercholesterolemia..... 276
Figure 21 Predicted Probability of Grade ≥ 3 TEAEs Versus CAUCcomplete with Fixed Time to Event Stratified by Age, Concomitant Narcotics, and Concomitant Steroids..... 278
Figure 22 Hosmer-Lemeshow Goodness of Fit Calibration Plot for Grade ≥ 3 TEAEs..... 279
Figure 23: Mean EORTC QLQ-C30 QoL Score by Visit..... 285
Figure 24: Mean Change from Baseline EORTC QLQ-C30 QoL Score by Visit ..... 286
Figure 25: Mean EORTC QLQ-LC13 Scores by Category and Visit ..... 287



Reference ID: 4344794

Figure 26: Mean Change from Baseline EORTC QLQ-LC13 Scores by Category and Visit ..... 288



Reference ID: 4344794

## Reviewers of Multi-Disciplinary Review and Evaluation

| | |
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| | |
|---|---|
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| **OPDP** | Nazia Fatima |
| **OSI** | Navid Homayouni/Susan Thompson |
| **OSE/DEPI** | Carolyn McCloskey/Steven Bird |
| **OSE/DMEPA** | Janine Stewart/Alice Tu |
| **OSE/DRISK** | Ingrid Chapman/Elizabeth Everhart |
| **Other** | |

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management



Reference ID: 4344794

## Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CMC | chemistry, manufacturing, and controls |
| CNS | central nervous system |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CR | complete response |
| CRF | case report form |
| CRM | continual reassessment model |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DHOT | Division of Hematology Oncology Toxicology |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCTD | electronic common technical document |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GLP | good laboratory practice |
| GRMP | good review management practice |
| ICH | International Conference on Harmonization |
| ICR | independent central radiology |



Reference ID: 4344794

| | |
|---|---|
| IC-ORR | intracranial overall response rate |
| IND | Investigational New Drug |
| INV | investigator |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| LIC | lead-in cohort |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| MTD | maximum tolerated dose |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NSCLC | non-small cell lung cancer |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| ORR | overall response rate |
| OS | overall survival |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PFS | progression-free survival |
| PI | prescribing information |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PR | partial response |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| QoL | quality of life |
| REMS | risk evaluation and mitigation strategy |
| RP2D | recommended phase II dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDTM | study data tabulation model |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |



Reference ID: 4344794

| | |
|---|---|
| TKI | tyrosine kinase inhibitor |



Reference ID: 4344794

# 1 Executive Summary

## 1.1. Product Introduction

Lorlatinib (proposed proprietary name LORBRENA) is a new molecular entity (NME), tyrosine kinase inhibitor with in vitro activity against multiple kinases, including ALK and ROS1. In vivo studies of lorlatinib in mice implanted with tumor cell lines expressing ALK gene fusion mutations, including EML4-ALK v1L1196M and EML4-ALK v1G1202R which have been associated with resistance to crizotinib, demonstrated tumor growth inhibition and prolonged survival in both the subcutaneous and intracranial mouse implantation models. The proposed dosing regimen is 100 mg once daily until disease progression or unacceptable toxicity. Pfizer's proposed indication for lorlatinib is "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)".

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval according to 21 CFR 314.510 Subpart H is based on the results from a subgroup of patients enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter trial (Study B7461001) that demonstrated a durable 48% overall response rate (ORR) per Independent Review Committee-assessment in 215 patients with ALK-positive metastatic NSCLC who had been previously treated with one or more ALK inhibitors and who received the lorlatinib dose proposed in product labeling. For NSCLC, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). Responses were observed across study sites and across various subgroups defined by number of prior therapies and by specific prior treatment. Based on these findings, FDA expects that lorlatinib will have, as described in section 505(d) of the Act, "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."



Reference ID: 4344794

## 1.3. Benefit-Risk Assessment

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Reference ID: 4344794

**Benefit-Risk Summary and Assessment**

Metastatic ALK-positive lung cancer is a fatal, incurable disease, despite advances made in the development of first- and later generation ALK inhibitors including alectinib, ceritinib, and brigatinib. Ceritinib and alectinib, which were first approved under the provisions of accelerated approval for the treatment of patients with metastatic ALK-positive NSCLC who progressed on or were intolerant to crizotinib, received regular approval for the treatment of patients with metastatic ALK-positive NSCLC in May and November 2017, respectively. Brigatinib is approved under the provisions of accelerated approval for the treatment of patients with ALK-positive NSCLC with progression on or after prior treatment with crizotinib. Thus, brigatinib is not considered available therapy because FDA recognizes, as a general matter, that it is preferable to have more than one treatment approved under the provisions of accelerated approval (21 CFR 314 Subpart H) because of the possibility that clinical benefit may not be verified in post-approval confirmatory trials. Responses to cytotoxic chemotherapy, the treatment modality that would most commonly be used after targeted therapy options are exhausted, are in the range of 15-45% (unselected NSCLC) and are generally of less than 6 months duration. Therefore, an unmet need exists for patients with ALK-positive NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease. An unmet need also exists for patients with disease progression on alectinib or ceritinib as initial ALK inhibitor therapy as there are no data demonstrating that treatment with any FDA-approved ALK inhibitor would achieve the same or better results in patients initially treated with alectinib or ceritinib.

Lorlatinib is a tyrosine kinase inhibitor that targets ALK and ROS1 genetic aberrations. Pfizer's proposed indication for lorlatinib is: "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)". Pfizer is seeking accelerated approval based on overall response rates and durations of response observed in a subgroup of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter clinical trial, Study B7461001.

The independent review assessed overall response rate with lorlatinib was 48% (95% CI 42, 55) among 215 patients with metastatic ALK-positive NSCLC who had received treatment with at least one prior ALK inhibitor, with or without prior chemotherapy, enrolled on Study B7461001. The median duration of response was 12.5 months (95% CI 8.4, 23.7), indicating that the responses were durable. In 89 patients with measurable intracranial metastases at baseline (e.g. study entry), the intracranial response rate was 60% (95% CI 49, 70) with a median duration of response of 19.5 months (95% CI 12.4, NR). In exploratory analyses conducted in subgroups defined by prior therapy, the response rates were 39% in patients who received crizotinib and at least one other ALK inhibitor (with or without chemotherapy), 31% in patients who received alectinib as the only ALK inhibitor (with or without prior chemotherapy, and 46% in patients who received ceritinib as the only ALK inhibitor (with or without chemotherapy). These response rates, coupled with the durability of the responses observed, indicate that lorlatinib confers a clinically meaningful benefit in patients whose disease has progressed on prior ALK inhibitor therapy.



Reference ID: 4344794

Lorlatinib is contraindicated in patients taking strong CYP3A4 inducers due to hepatotoxicity. The adverse reactions of lorlatinib appear to be manageable with supportive care, dose modification, and/or the addition of lipid-lowering therapy. These adverse reactions include the risks described in the Warnings and Precautions section of the US prescribing information, specifically, hepatoxicity (liver toxicity) with the concomitant use of strong CYP3A inducers for which lorlatinib is contraindicated, central nervous system (CNS) effects, hyperlipidemia, atrioventricular block, and interstitial lung disease (ILD)/pneumonitis. Pfizer will conduct additional studies to further characterize the risk for hepa toxicity when lorlatinib is administered concurrently with drugs that are CYP3A inducers and to further characterize the pharmacokinetics of lorlatinib in patients with pre-existing hepatic or renal impairment.

Of significance is the large proportion of patients (approximately half) treated on Study B7461001 who experienced one of a wide-ranging group of CNS effects, which included mood effects (including thoughts of suicide), cognitive effects, speech effects, sleep effects, seizures, and hallucinations. The most common (≥ 20% of patients) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. The most common adverse reactions that led to dose reductions of lorlatinib were edema (6%), peripheral neuropathy (4.7%), cognitive effects (4.1%), and mood effects (3.1%); and the most common adverse reactions that led to interruption of therapy with lorlatinib were edema (7%), hypertriglyceridemia (6%), peripheral neuropathy (5%), and cognitive effects (4.4%).

Although lorlatinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Contraindications, Warnings and Precautions, and Dosage and Administration sections in product labeling. Lorlatinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use by either the clinical review team or the Division of Medication Error and Prevention Analysis (DMEPA).

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for accelerated approval. Due to the limited efficacy data available for lorlatinib and the clinically significant toxicity involving the central nervous system and hepatotoxicity of lorlatinib compared to the toxicity profiles for other FDA-approved therapies in its class, the most appropriate indication was determined to be for use following prior treatment with alectinib or ceritinib, which are approved for the first-line treatment of ALK-positive NSCLC [since alectinib and ceritinib were initially approved for use following crizotinib and are available treatment options for this patient population] or following crizotinib and at least one other ALK inhibitor. Lorlatinib has a favorable risk-benefit profile in the indicated population in the agreed-upon labeling based on the high response rate and durable responses observed in a patient population with a life-threatening disease and an unmet medical need. The potential for clinical benefit in the indicated population outweighs the risks of lorlatinib identified during the review of this NDA.



Reference ID: 4344794

The review team's regulatory recommendation is to grant lorlatinib accelerated approval for the following indication: "For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on: crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease." This recommendation for accelerated approval is based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. The confirmatory trial is currently ongoing, comparing the safety and efficacy of lorlatinib with crizotinib as first-line treatment in patients with advanced ALK-positive NSCLC.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Metastatic ALK-positive non-small cell lung cancer (NSCLC) is a serious and life-threatening disease.<br>• Approximately 3-7% of patients with NSCLC have a rearrangement in the anaplastic lymphoma kinase (ALK) gene. Brain metastases have been reported to occur in approximately 1/3 of patients without brain metastases at baseline who receive crizotinib for ALK-positive metastatic NSCLC. | Metastatic ALK-positive NSCLC is a fatal, incurable disease and for patients whose disease has progressed following prior ALK inhibitor therapy there are few treatment options. |
| Current Treatment Options | • Prior to the approvals of later generation kinase inhibitors that target ALK, most patients with metastatic ALK-positive NSCLC would die within two years of treatment; treatment options included crizotinib (an approved first generation ALK inhibitor) or cytotoxic chemotherapy.<br>• Since the approval of crizotinib, later generation ALK inhibitors have been developed to address the problems of crizotinib resistance and brain metastasis; these include alectinib, ceritinib, and brigatinib.<br>• Responses to cytotoxic chemotherapy, the treatment modality most commonly used after targeted therapy options are exhausted, are in the range of 15-45% (unselected NSCLC) and are generally of short | There is an unmet medical need for patients with ALK-positive metastatic NSCLC who experience disease progression on ALK inhibitor therapy. This conclusion is based on the observed response rates and duration of response / progression-free survival reported for therapies currently used in clinical practice for the treatment of this patient population. |



Reference ID: 4344794

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | duration. | |
| **Benefit** | • The benefits of lorlatinib were determined in a subgroup of 215 patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors enrolled in a non-randomized, dose-ranging and activity-estimating, multi-cohort, multicenter clinical trial, Study B7461001, that enrolled patients with locally advanced or metastatic ALK- or ROS1-positive NSCLC.<br>• The ORR was 48% among patients with metastatic ALK-positive NSCLC who had received treatment with at least one prior ALK inhibitor, with or without chemotherapy, who received lorlatinib at the recommended dosing regimen, with a median duration of response of 12.5 months.<br>• The intracranial response rate was 60% in 89 patients with measurable intracranial metastases at baseline, with a median duration of response of 19.5 months.<br>• Response rates in patients with ALK-positive NSCLC who received prior therapy with crizotinib and one other ALK inhibitor, alectinib as the only prior ALK inhibitor, or ceritinib as the only prior ALK inhibitor (with or without prior chemotherapy) ranged from 31-46% in exploratory analyses.<br>• This recommendation for accelerated approval is based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Such a confirmatory trial is currently ongoing, assessing lorlatinib versus crizotinib as first-line | The submitted data in this NDA meets the statutory standards for accelerated approval. For NSCLC, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics).<br><br>The observed response rate, coupled with the durability of the responses observed, are consistent with a clinically meaningful benefit in patients whose disease has progressed on prior ALK inhibitor therapy and suggest lorlatinib may provide a meaningful advantage over available therapy.<br><br>Due to the limited efficacy data available for lorlatinib and the toxicity profile of lorlatinib compared to the other FDA-approved therapies in its class, the most appropriate indication was determined to be for use following prior treatment with alectinib or ceritinib, which are approved for the first-line |



Reference ID: 4344794

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | treatment in patients with advanced ALK-positive NSCLC. | treatment of ALK-positive NSCLC, or following crizotinib and at least one other ALK inhibitor, since alectinib and ceritinib were initially approved for use following crizotinib and are available treatment options for this patient population. |
| **Risk and Risk Management** | • The most common (≥ 20% of patients) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea.<br>• The most common adverse reactions that led to dose reductions of lorlatinib were edema (6%), peripheral neuropathy (4.7%), cognitive effects (4.1%), and mood effects (3.1%); and the most common adverse reactions that led to interruption of therapy with lorlatinib were edema (7%), hypertriglyceridemia (6%), peripheral neuropathy (5%), and cognitive effects (4.4%).<br>• Of particular significance is the large proportion of patients (approximately half) treated on Study B7461001 who experienced one of a wide-ranging group of CNS effects, which included mood effects (including thoughts of suicide), cognitive effects, speech effects, sleep effects, seizures, and hallucinations.<br>• The adverse reactions observed with lorlatinib appear to be manageable with supportive care, dose modification, or the addition of lipid-lowering therapy. These include the risks described in the Warnings and Precautions section of the US prescribing information, specifically, hepatoxicity (liver toxicity) with the concomitant use of strong CYP3A inducers, central nervous system (CNS) effects, hyperlipidemia, atrioventricular block, and interstitial lung disease (ILD)/pneumonitis. Pfizer will conduct additional studies in the post- | While lorlatinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. Lorlatinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). |



Reference ID: 4344794

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | market setting to assess the risk for liver toxicity when lorlatinib is given at the same time as drugs that are CYP3A inducers. | |



Reference ID: 4344794

## 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | | |
|---|---|---|---|---|---|
| x | The patient experience data that was submitted as part of the application, include: | | | | Section 8.1.2, Efficacy Results – Secondary or exploratory COA (PRO) endpoints |
| | x | Clinical outcome assessment (COA) data, such as | | | |
| | | | x | Patient reported outcome (PRO) | Section 19.6, Additional Clinical Outcome Assessment Analyses |
| | | | □ | Observer reported outcome (ObsRO) | |
| | | | □ | Clinician reported outcome (ClinRO) | |
| | | | x | Performance outcome (PerfO) | Section 19.6, Additional Clinical Outcome Assessment Analyses |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | | |
| | □ | Observational survey studies designed to capture patient experience data | | | |
| | □ | Natural history studies | | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | | |
| | □ | Other: (Please specify) | | | |
| □ | Patient experience data that was not submitted in the application, but was considered in this review. | | | | |



Reference ID: 4344794

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Erin Larkins, Cross-Disciplinary Team Leader



Reference ID: 4344794

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Lung cancer is the leading cause of cancer death in the United States (U.S.) with more than 80% of all lung cancer cases classified as NSCLC. In 2018, an estimated 234,030 new cases of lung and bronchial cancer will be diagnosed in the US, with 154,050 deaths estimated to occur due to this disease[1]; lung cancer accounted for approximately 27% of cancer deaths in 2014.[2] Eight-five percent of cases are diagnosed at later stages, and for patients with distant metastasis, the 5-year relative survival rate is less than 5%.[2]

The ALK gene was first identified as a lung adenocarcinoma oncogene in 2007 when a small number of NSCLC cells were found to have a small inversion within chromosome 2p resulting in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK gene (referred to hereafter as ALK rearrangement).[3] This EML4-ALK fusion transcript results in a constitutively active tyrosine kinase that promotes angiogenesis, cell survival, and cell cycle progression.[4] Preclinical and clinical studies demonstrated that cancer cells harboring an ALK rearrangement are sensitive to ALK inhibition.[5]

The estimated incidence of ALK rearrangements in NSCLC is 2-7%. Clinical characteristics of patients with ALK rearrangements include adenocarcinoma histology, never or light smokers, more likely to be men, and younger age. In these populations, approximately 30% of patients will have ALK rearrangements.[6]

Crizotinib, the first FDA-approved ALK kinase inhibitor (hereafter referred to as ALK inhibitor), was approved in 2011 for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive (i.e., positive for ALK rearrangement). The initial approval of crizotinib was based on the results from two multicenter single arm studies of crizotinib in 255 patients with advanced NSCLC demonstrating overall response rates (ORRs) of 50% and 61%. The majority of patients in these studies had metastatic disease (95%) and had received prior systemic treatment for locally advanced or metastatic disease (94%).[7] In 2013, the crizotinib USPI was updated with the results of a randomized trial comparing crizotinib to chemotherapy (pemetrexed or docetaxel) in 347 patients with metastatic ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen, which demonstrated an improvement in median progression-free survival (PFS) for patients treated with crizotinib (7.7 months vs 3.0 months; hazard ratio [HR] 0.49 [95% confidence interval {CI} 0.37, 0.64]).[8] The crizotinib USPI was further updated in 2015 with results from a randomized trial of crizotinib compared to pemetrexed-platinum combination chemotherapy in 343 patients with ALK-positive non-squamous NSCLC who had not received any previous systemic therapy for



Reference ID: 4344794

advanced NSCLC. There was a significant improvement in median PFS for patients in the crizotinib arm (10.9 months vs 7.0 months; HR 0.45 [95% CI 0.35, 0.60]).[9]

Development of resistance to crizotinib is possible, and in approximately 28% of patients progressing on crizotinib, secondary mutations distributed throughout the ALK domain, including resistance mutations located in the solvent-exposed region of the adenosine triphosphate (ATP)-binding pocket have been identified; amplification of the ALK fusion gene is also a mode of resistance.[10] Furthermore, approximately one-third of patients treated with crizotinib develop brain metastases within the first year of treatment, with the central nervous system (CNS) representing the most common site of progression.[11] Since the approval of crizotinib, later generation ALK inhibitors, discussed in Section 2.2 below, have been developed to address the problems of crizotinib resistance and/or CNS metastasis.

## 2.2. Analysis of Current Treatment Options

Ceritinib and alectinib were granted accelerated approval for the treatment of patients with ALK-positive metastatic NSCLC who progressed on or were intolerant to crizotinib in 2014 and 2015, respectively. Regular approval for the treatment of patients with ALK-positive metastatic NSCLC was granted to both ceritinib and alectinib in 2017, after confirmatory trials demonstrated benefit (a large, clinically meaningful and statistically robust improvement in progression-free survival) in the first-line setting. Brigatinib is the only FDA-approved ALK inhibitor with an indication limited to the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Brigatinib is not considered available therapy, as defined in the FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, because it is approved under the provisions of accelerated approval.

Ceritinib was received accelerated approval in 2014 based on the results of a multicenter, single arm study in 163 patients with metastatic ALK-positive NSCLC who progressed on or were intolerant to crizotinib. The results demonstrated an ORR of 44% (95% CI 47%, 62%) as assessed by Blinded Independent Central Review Committee (BICR) with a median duration of response (DOR) of 7.4 months (95% CI 5.4, 10.1). Approximately 60% of patients initiating treatment with ceritinib at the recommended dose of 750 mg daily required at least one dose reduction, and dose modification related to gastrointestinal toxicities of nausea, vomiting, diarrhea or abdominal pain occurred in 38% of patients.[12] The USPI was updated in May 2017 with the conversion to regular approval based on the results of an open-label, randomized, active-controlled, multicenter study of ceritinib versus chemotherapy (pemetrexed with cisplatin or carboplatin). The median PFS in the ceritinib arm was 16.6 months (95% CI 12.6, 27.2) versus 8.1 months (95% CI 5.8, 11.1) in the chemotherapy arm, with a HR of 0.55 (95% CI 0.42, 0.73).[13]

Alectinib was granted accelerated approval in 2015 based on the results of two single-arm multicenter studies in 225 patients who had progressed on or were intolerant to crizotinib.



Reference ID: 4344794

Results included ORRs of 38% (95% CI 28%, 49%) and 44% (95% CI 36%, 53%) as assessed by Independent Central Review (IRC). Median DOR was 7.5 months (95% CI 4.9, not estimable [NE]) and 11.2 months (95% CI 9.6, NE).[14] The USPI was updated in November 2017 with the conversion to regular approval based on the results of an open-label, randomized, active-controlled, multicenter study in 303 patients who were randomized to receive alectinib or crizotinib. The median PFS in alectinib-treated patients was 25.7 months (95% CI 19.1, not estimable [NE]) compared to 10.4 months (95% CI 7.7, 14.6) in crizotinib-treated patients. Permanent discontinuation of alectinib for adverse reactions occurred in 11% of patients. Adverse drug reactions that led to discontinuation of alectinib were renal impairment (2.0%), hyperbilirubinemia (1.3%), increased ALT (1.3%), and increased AST (1.3%). Dose reductions and drug interruption due to adverse reactions occurred in 16% and 19% of patients, respectively, in the alectinib arm. The most frequent adverse reactions that led to dose modifications in the alectinib arm were hyperbilirubinemia (6%), increased aspartate aminotransferase (AST) (5%), increased alanine aminotransferase (ALT) (4.6%), and pneumonia (3.3%).[15]

Other classes of therapy that are available for the treatment of patients with ALK-positive metastatic NSCLC with progression on a prior ALK inhibitor include anti-programmed cell death (PD-1)/programmed cell death ligand (PD-L1) monoclonal antibodies and chemotherapy. Pembrolizumab, an anti-PD-1 antibody, was granted accelerated approval in October 2015 for the treatment of patients with metastatic NSCLC that has progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay.[16] In October 2016, regular approval was granted based on results from a randomized, multicenter, open-label study in which 1033 patients whose tumors had PD-L1 expression of 1% or greater were randomized 1:1:1 to receive one of two doses of pembrolizumab or docetaxel. The results demonstrated an improvement in median overall survival (OS) in pembrolizumab-treated patients who received 2 mg/kg every 3 weeks (10.4 months vs 8.5 months; HR 0.71 (95% CI 0.58, 0.88). The ORR of pembrolizumab in patients with a PD-L1 tumor proportion score of ≥ 1% was 18% (95% CI: 14, 23) in the 2 mg/kg arm compared to 19% (95% CI: 15, 23) in the 10 mg/kg arm. Pembrolizumab was discontinued due to adverse reactions in 14% of patients. The primary toxicities of concern are related to the class of drug and include immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and infusion-related reactions.[17]

Initially approved for metastatic NSCLC with squamous histology only, nivolumab, an anti-PD-1 monoclonal antibody, was subsequently approved for patients with any histology NSCLC and progression on or after platinum-based chemotherapy, including those with EGFR or ALK genomic tumor aberrations after progression on FDA-approved therapy for these aberrations, in October 2015. The approval was based on the results of a randomized open-label multicenter trial in which 582 patients received either nivolumab or docetaxel. The ORR of nivolumab for second-line treatment of metastatic non-squamous NSCLC was 19% (95% CI: 15, 24) compared to 12% (95% CI: 9,17) in the docetaxel arm. Median OS demonstrated an improvement in nivolumab-treated patients (12.2 months vs 9.4 months; HR 0.73 (95% CI 0.60, 0.89). Nivolumab was discontinued in 13% of patients for an adverse reaction.[18]



Reference ID: 4344794

Atezolizumab, an anti-PD-L1 monoclonal antibody, was approved for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy, including those with EGFR or ALK genomic tumor aberrations after progression on FDA-approved therapy for these aberrations, in October 2016. The approval was based on the results of a randomized, open-label multicenter trial in which 1137 patients received either atezolizumab or docetaxel. The ORR observed in the first 850 patients randomized to receive atezolizumab for the second-line treatment of metastatic NSCLC in the OAK trial was 14% (95% CI: 11, 17), with a median duration of response of 16.3 months (95% CI 10, NE) in the atezolizumab arm (n=450). The median OS observed amongst all 1225 randomized patients was 13.3 months (95% CI 11.3, 14.9) in the atezolizumab arm (n=613) and 9.8 months (95% CI 8.9, 11.3) in the docetaxel arm (n=612).[19]

The primary toxicities of concern for nivolumab and atezolizumab, as for all anti-PD-1/anti-PD-L1 directed antibodies are immune-related adverse reactions, as described above for pembrolizumab.

Finally, chemotherapy (including platinum-based doublets) in patients who are chemotherapy-naïve is another option for patients with ALK-positive NSCLC with progression of disease following treatment with an ALK inhibitor. Median OS observed for first-line treatment with platinum-based combination chemotherapy in earlier studies, which included patients with NSCLC regardless of histology, ranged from approximately 8 to 11 months with response rates of 15% to 32%.[20] A subsequent randomized study comparing cisplatin plus pemetrexed to cisplatin plus gemcitabine for the first-line treatment of NSCLC demonstrated response rates close to 30% in both arms; this study included a pre-specified analysis of OS by histology, and the median OS for the subset of patients with adenocarcinoma histology receiving cisplatin plus pemetrexed was 12.6 months.[21] In a randomized trial comparing crizotinib to platinum-based combination chemotherapy for the first-line treatment of advanced ALK-positive NSCLC, the ORR observed in the chemotherapy arm was 45% with a median duration of response of less than 6 months and median progression-free survival (PFS) of 7.0 months.[22] These findings were in patients who had received no prior systemic therapy for advanced NSCLC. Another study randomized patients with ALK-positive NSCLC who had already received one prior platinum-based regimen to treatment with crizotinib versus either pemetrexed or docetaxel and demonstrated an ORR of 20% in the chemotherapy arm.[23] There is insufficient data available to determine the potential impact of prior treatment with an ALK inhibitor on response to treatment with platinum-based combination chemotherapy. The major toxicities of chemotherapy regimens most commonly used for NSCLC include hematologic toxicities (e.g., cytopenias), gastrointestinal toxicities (e.g., nausea, vomiting), and neurotoxicity (e.g., peripheral neuropathy with taxanes, ototoxicity with cisplatin).



Reference ID: 4344794

**Table 1: Summary of treatment armamentarium relevant to proposed indication**

APPEARS THIS WAY ON ORIGINAL



Reference ID: 4344794

| Product (s) Name | Relevant Indication | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| FDA Approved Treatments | | | | | | |
| Ceritinib | Advanced ALK-positive NSCLC with progression on crizotinib | Accelerated approval: 2014 | 750 mg PO daily | ORR 44% (95% CI 36, 52)<br>mDOR 7.1 months (95% CI 5.6, NE)[b] | GI toxicity, hepatotoxicity, ILD, QT interval prolongation, hypergylcemia, bradycardia | |
| Alectinib | Advanced ALK-positive NSCLC with progression on crizotinib | Accelerated approval: 2015 | 600 mg PO BID | ORRs 38% (95% CI 28, 49) and 44% (36, 53)<br>mDORs 7.5 months (95% CI 4.9, NE) and 11.2 months (95% CI 9.6, NE)[c] | Hepatotoxicity, ILD, renal impairment, bradycardia, severe myalgia and CPK elevation | |
| Brigatinib | Advanced ALK-positive NSCLC with progression on crizotinib | Accelerated approval: 2017 | 90 mg → 180 mg PO daily | ORR 53% (95% CI 43, 62)<br>mDOR 13.8 months (95% CI 9.3, NE)[d] | ILD, hypertension, bradycardia, visual disturbance, CPK elevation, pancreatic enzyme elevation, hyperglycemia | |
| Pembrolizumab | Metastatic NSCLC with PD-L1 expression TPS ≥ 50% with prior platinum-containing therapy and targeted therapy for EGFR or ALK | Regular approval: 2016 | 2 mg/kg IV every 2 weeks | TPS ≥ 50%:<br>ORR 30% (95% CI 23, 39)<br>mDOR NR (range 0.7+, 16.8+ months)<br>All randomized patients:<br>ORR 18% (95% CI 14, 23)<br>mDOR NR (range 0.7+, 20.1+ months)[e] | Immune-mediated pneumonitis, hepatitis, colitis, nephritis, endocrinopathy, infusion-related reactions | |



Reference ID: 4344794

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| Nivolumab | Metastatic NSCLC with progression on or after prior platinum-based therapy and on FDA-approved therapy for ALK genomic tumor aberrations if present | Regular approval: 2015 | 3 mg/kg IV every 2 weeks | ORR 19% (95% CI 15, 24)<br>mDOR 17 months (95% CI 8.4 months, NR)[f] | Immune-mediated pneumonitis, hepatitis, colitis, nephritis, endocrinopathy, infusion-related reactions | |
| Atezolizumab | Metastatic NSCLC with progression on or after prior platinum-based therapy and on FDA-approved therapy for ALK genomic tumor aberrations if present | Regular approval: 2016 | 1200 mg IV every 3 weeks | ORR 14% (95% CI 11, 17)<br>mDOR 16.3 months (95% CI 10 months, NE)[g] | Immune-mediated pneumonitis, hepatitis, colitis, nephritis, endocrinopathy, infusion-related reactions | |
| Platinum-based chemotherapy (pemetrexed plus carboplatin/cisplatin) | Advanced ALK-positive non-squamous NSCLC with no prior systemic therapy for advanced disease | Regular approval for pemetrexed in combination with cisplatin: 2008 | Cisplatin 75 mg/m$^2$ or carboplatin AUC 5-6 with pemetrexed 500 mg/m$^2$ | ORR 45% (95% CI 37, 53)<br>mDOR 5.3 months (95% CI 4.1, 5.8)[h] | Neutropenia, anemia | Chemotherapy was given as first-line treatment in an open-label randomized trial vs. crizotinib. |



Reference ID: 4344794

| | | | | | | |
|---|---|---|---|---|---|---|
| Platinum-based chemotherapy | Metastatic NSCLC | N/A | Various regimens | Range 15-32%[i] | Myelosuppression, peripheral neuropathy, nephrotoxicity, ototoxicity | Given as first-line treatment in patients with metastatic NSCLC without targetable mutations or aberrations; however, the ORRs are likely similar in the first-line setting to those observed in patients with ALK-positive NSCLC who receive platinum-based chemotherapy after progression on a prior ALK inhibitor. |

a: PROFILE 1007; USPI crizotinib 2013
b: ASCEND-1; USPI ceritinib 2014
c: NP28761 and NP28673; USPI alectinib 2015
d: ALTA, USPI brigatinib 2017
e: KEYNOTE-010; USPI pembrolizumab 2016
f: CheckMate-057; USPI nivolumab 2015
g: OAK; USPI atezolizumab 2016
h: Mok, et al 2014
i: Ramalingam, et al 2008



Reference ID: 4344794

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Lorlatinib is a new molecular entity (NME) and is not currently marketed in the U.S.

## 3.2. Summary of Presubmission/Submission Regulatory

ActivityFollowing the receipt of final written responses for a Type B pre-IND meeting on June 14, 2013, regarding the design of the first-in-patient trial of lorlatinib (PF-06463922) under IND 118296, the original IND was filed on August 15, 2013. A list outlining the pertinent regulatory history for lorlatinib is included in the table below.

**Table 2: Regulatory history for lorlatinib**

| Date | Description |
|---|---|
| June 14, 2013 | Pre-IND/written response only (WRO) meeting to discuss the development program for lorlatinib and the proposed initial open-label, multicenter, multiple-dose study in advanced ALK or ROS1-positive NSCLC (Study B7461001) |
| September 13, 2013 | New IND containing study B7461001 allowed to proceed |
| June 23, 2015 | Orphan Drug Designation granted for the treatment of ALK or ROS1-positive NSCLC |
| December 18, 2015 | Type B EOP1/pre-phase 3 meeting to discuss the clinical development program for lorlatinib, evidence that would support a request for breakthrough therapy designation (BTD) and advice on proposed revisions to Study B7461001 to support a request for the accelerated approval of lorlatinib |
| April 26, 2017 | BTD granted for the development of lorlatinib for the treatment of ALK-positive NSCLC previously treated with one or more ALK inhibitors |
| August 30, 2017 | Type B pre-NDA meeting to discuss and reach agreement on the content and format of an NDA for lorlatinib for the proposed indication of the treatment of patients with ALK-positive NSCLC previously treated with one or more ALK inhibitors |
| February 12, 2018 | Priority review granted for NDA 210868 for lorlatinib |

During the December 18, 2015 Type B EOP1/pre-phase 3 meeting, FDA agreed that the demonstration of an ORR that is clinically meaningful in magnitude and durability in approximately 160 planned patients with ALK-positive NSCLC who have been treated with prior



Reference ID: 4344794

crizotinib or other ALK inhibitor(s) with or without prior chemotherapy, enrolled in four cohorts in Study B7461001 could support the filing of a marketing application seeking accelerated approval for the indication of the treatment of patients with ALK-positive NSCLC with disease progression following crizotinib. The ability of such data to support accelerated approval would be contingent upon there being no available therapies for the indication at the time of the NDA submission or demonstration of significant improvement over any available therapies. FDA recommended that Pfizer consider providing data in populations not covered by drugs such as alectinib or ceritinib, such as patients who received more than one prior ALK inhibitor or specific ALK mutations where lorlatinib may have superior efficacy. FDA agreed that a subset of 80 patients with two or more prior lines of therapy with an ALK inhibitor could represent the primary analysis population, supported by the results from 160 patients. FDA further stated that the analysis of ORR should be conducted in the intent-to-treat (ITT) population based on independent review committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

FDA also agreed that pooled analyses of estimated intracranial ORR and DOR per RECIST v1.1, as determined by independent radiology assessment, in a subgroup of patients with CNS metastases at baseline across cohorts 1-5 in Study B7461001 may support inclusion of CNS ORR results in product labeling. FDA also stated that the clinical significance of a “time to intracranial progression” endpoint cannot be interpreted in a single arm study and would not be included in product labeling.

During the August 30, 2017 pre-NDA meeting, FDA agreed that the study results from Study B7461001 proposed for inclusion in an NDA submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) may provide sufficient clinical evidence to characterize the benefit and risks of lorlatinib in patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors. FDA stated that the safety population should include all 275 patients treated in the dose expansion portion of Study B7461001 and all 54 patients from the dose escalation portion of the study, and that separate safety analyses should be performed and provided for the 292 patients across both parts of Study B7461001 who received lorlatinib at the recommended phase 2 dose (RP2D) of 100 mg daily. FDA also stated that the proposed ITT population should include all patients in expansion cohorts 2-5 (patients with ALK-positive NSCLC previously treated with one or more ALK inhibitors) who received at least one dose of lorlatinib, including one patient enrolled in cohort EXP-3 for whom ALK positivity was not confirmed. Pfizer agreed to provide analyses of ORR and DOR in the following populations: all patients with documented ALK mutation enrolled in the dose expansion portion of the study, all patients with documented ALK mutation receiving lorlatinib 100 mg across the entire study, all patients enrolled in the dose expansion portion of the study purported to be ALK positive and who received prior treatment, and all patients receiving lorlatinib 100 mg across the entire study purported to be ALK positive and who received prior treatment. The results to be presented in the product labeling will be determined during review of the application. Overall, agreement was reached regarding the contents of a complete application.



Reference ID: 4344794

On October 25, 2017, Pfizer submitted a clarification to the Type B meeting minutes from the August 30, 2017 Type B pre-NDA meeting. Pfizer stated that a total of three Japanese patients were enrolled in the Japanese lead-in cohort (LIC), which was not part of the dose escalation or dose expansion portions of the study but was described in the protocol for Study B7461001. Pfizer believed that since these patients received lorlatinib 100 mg daily, they should be included in the pooled analyses of safety and efficacy; specifically, the Pfizer proposed that all three patients be included in the pooled analyses of safety and two patients who had ALK-positive NSCLC be included in the pooled analyses of efficacy. The addition of these patients would bring the total numbers of patients to 295 and 215, respectively, for the pooled analyses of safety and efficacy in patients receiving lorlatinib 100 mg daily. FDA responded with their acknowledgment that the Japanese LIC patients were included in the analyses.



Reference ID: 4344794

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

For full details, see the Clinical Inspection Summary by Navid Homayouni, MD. Three clinical sites were selected for audit; these sites were selected based on the number of patients enrolled. Inspection results by site are listed in the following table.

**Table 3 Inspection results by site (from Clinical Inspection Summary Review)**

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

NAI: No deviation from regulations

The final classification of these sites remains NAI after review of the Establishment Inspection Report (EIR).



Reference ID: 4344794

## 4.2. Product Quality

See CMC review from the current NDA submission. The proposed "to be marketed" 25-mg and 100-mg immediate release (IR) tablets were the formulations evaluated in Study B7461001.

## 4.3. Clinical Microbiology

See CMC review from the current NDA submission; there were no Clinical Microbiology concerns.

## 4.4. Devices and Companion Diagnostic Issues

Eligibility for Study B7461001 included the requirement for documentation of ALK rearrangement in tumor tissue confirmed by an FDA-approved test [either the fluorescence in situ hybridization (FISH) assay (Abbott Molecular Inc.) or by immunohistochemistry (IHC) (Ventana, Inc.)]. There are no issues of concern related to the use of such tests to select patients appropriate for treatment with lorlatinib.



Reference ID: 4344794

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

Lorlatinib (PF-06463922) is a small molecule kinase inhibitor targeting anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1) as well as multiple ALK kinase domain point mutations (L1196M, G1269A, F1174L, C1156Y, L1152R, S1206Y, I1171T and 1151Tins) identified in the tumors of patients who have developed resistance to other ALK inhibitors with $K_i$ values of between 0.005 and 0.9 nM. Lorlatinib also inhibited phosphorylation of TYK1, FER, FPS, FAK2, ACK, FAK, TRKA, TRKB, TRKC, and PTK with $IC_{50}$ values of less than 25 nM, a concentration at least 19-fold lower than the average maximum serum concentration ($C_{max}$) of unbound lorlatinib, or ~197 n/mL (485 nM). This calculation is based on the total $C_{max}$ of lorlatinib at the recommended dose of 100 mg, 577 ng/mL, and protein binding of ~66%. Lorlatinib inhibited phosphorylation of $ALK^{L1196M}$ and brain-derived neurotrophic factor-activated TRKB in cell lines. Lorlatinib also reduced proliferation of cell lines harboring ALK fusion variants with or without crizotinib resistant ALK kinase domain mutations and ROS1 oncogenic fusion mutations. Pfizer evaluated the in vivo anti-tumor activity of lorlatinib in mice implanted with tumor cell lines expressing ROS-1 fusion variants or fusions with ALK mutations, including EML4-ALK $v1^{L1196M}$ and EML4-ALK $v1^{G1202R}$. In these studies, administration of lorlatinib resulted in tumor growth inhibition and prolonged survival in both subcutaneous and intracranial implantation models.

To assess the safety of lorlatinib, Pfizer conducted GLP-compliant toxicology studies of up to 13-weeks in rats and dogs. In both species, major target organs included the liver (bile duct hyperplasia, single cell necrosis and increased sinusoid cellularity with increases in AST, ALT, ALP, total bilirubin, and cholesterol) and skin (persistent findings of discoloration, swelling, inflammation, and lesions). In rats the hepatobiliary findings were accompanied by pancreatic findings of acinar atrophy and increased serum amylase. In both species animals at the high dose levels also displayed abdominal distention. The hepatobiliary findings coupled with significant increases in cholesterol (also seen clinically), abdominal distention, and skin findings suggest cholestasis and are included in the label, under Section 13.2.

In the 13-week rat study, animals received lorlatinib twice daily by oral gavage. Females received lower doses of lorlatinib due to higher plasma exposure values. Additional targets not described above included the kidney (tubular basophilia and hyaline cast with glomerulopathy and arterial degeneration), lymph nodes (increased cellularity and hematopoiesis), and sciatic nerve (minimal axonal degeneration). In high dose females, there were also findings of increased Anichkov cells in the heart, possibly consistent with the increase in cholesterol. Most of these findings were reversible within the recovery period.

In the 13- week dog study, animals received lorlatinib twice daily. Moribundity occurred at the high dose level; cause of death was attributed to pulmonary and mandibular bone



Reference ID: 4344794

inflammation. Observations in the remaining animals included decreased activity, decreased muscle tone, tremors, and abnormal gait (resembling the signs of peripheral neuropathy observed clinically), as well as emesis, liquid feces, warm to touch, increased incidence of skin reddening, swollen skin, dry skin, lesions, and thin fur cover. Other target organs of toxicity included the lymph nodes (minimal to mild medullary plasmacytosis, inflammation, and erythrocytosis), lungs (subacute inflammation at the mid and high doses). Decreased tidal volume also occurred in a safety pharmacology study in rats and pneumonitis occurs clinically. High dose males also exhibited GI tract toxicity, with villous atrophy, crypt hyperplasia and subacute inflammation of the ilium, duodenum, and jejunum. Toxicity of the testes (tubular atrophy), epididymides (cellular debris), and prostate (glandular atrophy) occurred in mid and high dose dogs in the 4-week study and was reversible during a 4-week recovery period.

There was a single significant metabolite of lorlatinib found clinically at levels of approximately 21% of the parent drug, M8 (PF-06895751). This metabolite was present in both rats and dogs, though at much lower levels than in humans. Pfizer conducted in vitro pharmacology studies showing that M8 did not have pharmacologic activity at clinically relevant levels, was not mutagenic in in vitro assays, and did not inhibit hERG signaling. Given this additional data and the fact that the metabolites were present at some level in animal studies, consistent with the principles in ICHS9, no additional animal toxicology studies to qualify this metabolite are warranted.

In a central nervous system (CNS) safety pharmacology study, oral administration of lorlatinib at doses ≥ 3 mg/kg in rats resulted in clear decreases in memory recall. Lorlatinib also demonstrated high penetrance in brain tissue, inhibition of TRKA, B, and C in biochemical assays, and inhibition of ligand-mediated TRKB phosphorylation in cells at clinically achievable concentrations. Decreases in TRKB have been associated with CNS disorders including schizophrenia and mood disorders.[24-26] Clinically, CNS effects including hallucinations, mood disorders, and seizures have occurred during treatment with lorlatinib.

There is a potential for lorlatinib to adversely affect the cardiovascular parameters. In vitro studies of lorlatinib and M8 did not predict QTc prolongation, by inhibition of the hERG channel at clinically relevant concentrations; lorlatinib itself also failed to inhibit L-type calcium channel, or Nav1.5 sodium current at clinically relevant concentrations. In an in vitro Langendorff-perfused paced heart model, there were no lorlatinib related changes to cardiac parameters such as left ventricular pressure, coronary perfusion pressure, QRS or QT intervals. There was, however, a lorlatinib related increase in PR interval at doses ≥1 µM and above, consistent with prolonged PR intervals reported clinically. In safety pharmacology studies in rats, oral administration of a single dose of ≥10 mg/kg lorlatinib was associated with increases in systolic, diastolic, and mean blood pressure. Conscious telemetered dogs receiving a 15 mg/kg lorlatinib dose for 12 consecutive days followed by a 5-day recovery period exhibited changes in systolic blood pressure, heart rate, PR, and QRS intervals, and in fractional shortening. Decreased systolic blood pressure as well as increased heart rate occurred on Days 12, 15 and 19. An increased PR interval was observed on Days 8 and 15, as was an increased QRS interval on Days



Reference ID: 4344794

8 and 19. Adverse cardiovascular findings were also noted in 14-day toxicology studies in rats and dogs.

Carcinogenicity studies were not conducted with lorlatinib and are not required to support the use of a drug intended to treat patients with advanced cancer. Lorlatinib was aneugenic in an in vitro micronucleus assay using TK6 cells and positive in an in vivo bone marrow micronucleus assay in rats. Lorlatinib was negative in the in vitro bacterial reverse mutation assay.

Dedicated studies to assess fertility were not conducted or required to support the development of a drug intended to treat patients with advanced cancer. Histopathological findings in male dogs suggest the potential for transient decreases in male fertility. There were also minimal histological findings in rats at high doses. Pfizer conducted embryo-fetal development studies in rats and rabbits. Rats received total daily lorlatinib doses of 1, 4, 15, 30 mg/kg/day on gestation days (GDs) 6-17. In pregnant rats, there was increased post-implantation loss at doses ≥1 mg/kg/day (approximately equal to the clinical lorlatinib exposure of 5650 ng*hr/mL at the 100 mg dose) and 100% loss at ≥4 mg/kg/day. Fetuses of dams dosed at 1 mg/kg showed external and visceral malformations including medially rotated hindlimbs, a supernumerary digit on the left forepaw, gastroschisis, and interrupted aortic arch. Rabbits received total daily doses of 1, 4, 15, 30 mg/kg/day on GDs 7-19. Abortions resulting in 100% litter loss occurred at doses ≥15 mg/kg/day (resulting in exposures approximately 3.5 times the clinical exposure). At 4 mg/kg/day (~ 0.6 times the clinical lorlatinib exposure) there was increased post-implantation loss, and malformations including domed head, medially malrotated forelimbs, hyperextended forepaws, high arched palate, dilation of the lateral and third ventricles of the brain, malpositioned and misshapen kidneys, and retroesophageal subclavian artery. In an investigative study in zebrafish, Pfizer showed that there was potential for developmental toxicity, but at concentrations that were above those seen clinically. Based on data from the embryo-fetal development studies and the drug's mechanism of action, a warning for embryo-fetal toxicity is included in the label for LORBRENA. Because the drug is genotoxic, females of reproductive potential are advised to use non-hormonal contraception (see Section Additional Safety Explorations) for at least 6 months after the last dose of LORBRENA; similarly, males with female partners of reproductive potential are advised to use contraception for at least 3 months after the final dose. No studies were conducted or required to investigate the presence of lorlatinib in milk. Because many drugs are secreted in milk, the label includes a warning not to breastfeed during treatment with LORBRENA for 7 days after the final dose, based on half-life. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of LORBRENA for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK tyrosine kinase inhibitors.

## 5.2. Referenced NDAs, BLAs, DMFs

IND 118,296, initial IND for PF-06463922



Reference ID: 4344794

## 5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

Pfizer evaluated the potency of PF-06463922 against ALK and ROS1, as well as a panel of ALK and ROS1 secondary kinase domain mutations identified in tumors that developed resistance to first and second line ALK inhibitors, such as crizotinib (Study #174542). Briefly, investigators engineered baculovirus constructs to express activated kinase domains from recombinant human wild type or mutant ALK, catalytic domains from wild type or fusion mutations of ROS1, and the kinase domains from several other tyrosine kinase receptors (RTRK2, TRKB) then incubated these constructs in the presence of ATP with the test compound (11-dose 3-fold serial dilutions), DMSO (negative control), or crizotinib (reference compound) for 1 hour at room temperature. Inhibition was determined after electrophoretic separation of fluorescently labeled peptide substrates and phosphorylated product. ROS1 and non-target kinases were assayed using a microfluidic mobility shift assay.

In the biochemical assays, PF-06463922 inhibited ALK and a panel of crizotinib resistant ALK mutants, including L1196M and G1269A, the most frequently identified resistance mutations found among crizotinib-resistant tumors in patients, with a potency of up to 24 times that of crizotinib (Table 4).

**Table 4: $K_i$ of PF-06463922 for target kinases in biochemical assays**

| Recombinant Enzyme Assays | Ki, GMean (GCI95)[a] | | | | | | Ki Ratio crizo/ PF3922 |
|---|---|---|---|---|---|---|---|
| | PF-06463922 | | | Crizotinib | | | |
| ALK and ALK mutants | nM | ng/mL | n | nM | ng/mL | n | |
| Recombinant human wild-type ALK kinase domain | <0.2 | <0.08 | 3 | 0.72 (0.65-0.80) | 0.3 | 127 | >4 |
| Recombinant human $ALK^{L1196M}$ kinase domain | 0.7 (0.4-1.3) | 0.3 | 3 | 8.1 (7.6-8.7) | 3.6 | 143 | 12 |
| Recombinant human $ALK^{G1269A}$ kinase domain | 0.9 (0.3-3.0) | 0.4 | 2 | 20.1 (17.6-23.1) | 9.1 | 4 | 22 |
| Recombinant human $ALK^{F1174L}$ kinase domain | <0.1 | <0.04 | 1 | 0.82 (0.74-0.90) | 0.4 | 3 | >8 |
| Recombinant human $ALK^{C1156Y}$ kinase domain | <0.1 | <0.04 | 1 | 0.6 (0.1-3.3) | 0.3 | 3 | >6 |
| Recombinant human $ALK^{L1152R}$ kinase domain | <0.1 | <0.04 | 1 | 2.2 (1.3-3.6) | 1 | 3 | >22 |
| Recombinant human $ALK^{I1151Tins}$ kinase domain | 0.1 | 0.04 | 1 | 2.2 | 1 | 1 | 22 |
| Recombinant human $ALK^{S1206Y}$ kinase domain | 0.2 | 0.08 | 1 | 1.3 | 0.6 | 1 | 7 |
| ROS1 Kinase | | | | | | | |
| Recombinant human wild-type ROS1 kinase domain | <0.005 | <0.002 | 2 | 0.12 (0.08-0.19) | 0.06 | 3 | >24 |
| [a]Ki values are geometric means with a geometric confidence 95% interval for n independent measurements. | | | | | | | |

*(Applicant Figure reproduced from Study 174542)*

PF-06463922 was further evaluated in biochemical kinase screening assays against a panel of 206 additional recombinant kinases. Pfizer selected 11 of these kinases as potentially relevant hits, based on the level of inhibition at 1 µM, and evaluated them in biochemical or cell-based assays using inhibition of $ALK^{L1196M}$ as a positive control. The results of these follow-up



Reference ID: 4344794

experiments are summarized in Table 5. Targets that were inhibited by PF-06463922 with an $IC_{50}$ below the $C_{max}$ of unbound lorlatinib of approximately 197 ng/mL (~485 nM) in patients treated at the once daily oral dose of 100 mg included TYK1, FER, FPS, FAK2, ACK, FAK, TRKA, TRKB, TRKC, and PTK.

**Table 5: Activity of PF-06463922 in enzyme and cell-based assays**

| In Vitro Enzyme Activity Against Non-Target Kinases | Enzyme IC50 (Ki)[a] | | Fold vs. $ALK^{L1196M}$ |
|---|---|---|---|
| | nM | ng/mL | |
| $ALK^{L1196M}$ | 0.7 (Ki) | 0.3 (Ki) | 1 |
| ROS1 | <0.005 (Ki) | <0.002 (Ki) | <0.01 |
| LTK (TYK1) | 2.7 | 1.1 | 4 |
| FER | 3.3 | 1.3 | 5 |
| FES (FPS) | 6 | 2.4 | 9 |
| PTK2B (FAK2) | 14 | 5.5 | 19 |
| TNK2 (ACK) | 17 | 6.7 | 24 |
| PTK2 (FAK) | 17 | 7.1 | 25 |
| NTRK2 (TRKB) | 23 (Ki) | 9.3 (Ki) | 33 |
| NTRK1 (TRKA) | 24 | 9.8 | 34 |
| NTRK3 (TRKC) | 46 | 19 | 66 |
| FRK (PTK5) | 53 | 22 | 76 |
| EGFR (ErbB1) T790M L858R | 56 | 23 | 80 |
| **In Vitro Cellular Activity Against Non-Target Kinases** | **Mean Cell IC50[b]** | | **Fold vs. $ALK^{L1196M}$** |
| | nM | ng/mL | |
| Engineered EML4-ALKv1 phosphorylation in 3T3-EML4-$ALK^{L1196M}$ cells | 21 | 8.5 | 1 |
| NGF-stimulated TrkA phosphorylation in TrkA-PAE cells | 10000 | 4064 | 477 |
| BDNF-stimulated TrkB phosphorylation in TrkB-PAE cells | 229 | 93 | 11 |
| EGF-stimulated wild-type EGFR phosphorylation in A549 cells | >10000 | >4064 | >477 |
| Endogenous $EGFR^{E746-A750\,Del}$ phosphorylation in PC9 cells | >10000 | >4064 | >477 |
| Endogenous $EGFR^{L858R}$ phosphorylation in NCI-H3255 cells | >10000 | >4064 | >477 |
| Endogenous $EGFR^{L858R/T790M}$ phosphorylation in NCI-H1975 cells | >10000 | >4064 | >477 |

[a]: Reported are either IC50 values at the Km-level of ATP or Ki (where shown).
[b]: RTK phosphorylation was determined by using ELISA capture methods.

*(Applicant Figure reproduced from Study 174542)*

In addition to the biochemical based assays, Pfizer investigated the activity of PF-06463922 in cellbased assays. NCI-H3122 and NCI-H2228 are two human lung adenocarcinoma cell lines harboring chromosomal inversion events resulting in expression of EML4-ALK fusion protein variant 1 (v1) and variant 3 (v3), respectively. To establish cell models expressing mutant ALK, human EML4-ALK $v1^{L1196M}$ and EML4-ALK $v1^{G1269A}$ were ectopically introduced into NCI-H3122 cells. Additionally, a panel of NIH3T3 cell lines was engineered to stably express ALK fusion variants (EML4-ALKv1, -ALKv2, -ALKv3a, -ALKv3b, and KIF5B-ALK) and crizotinib resistant EML4-ALK mutants that were identified in human tumors (L1196M, G1269A, F1174L, C1156Y, L1152R, G1202R, S1206Y and 1151Tins). Of note, the G1202R and I1171T mutations have been identified in human tumors that developed resistance to second line ALK inhibitors such as alectinib and brigatinib. Karpas 299 human anaplastic large cell lymphoma (ALCL) cells bearing the NPM-ALK fusion and NPM-ALK fusion amplification (t(2;5) chromosomal translocation and focal amplification) were also used to test the potency of PF-06463922. The cell lines were plated with dilutions of PF-06463922, crizotinib, or controls, and incubated for 72 hours. Table _ summarizes the activity of PF-06463922 against the ALK fusion variants and ALK fusion mutations. PF-06463922 inhibited ALK phosphorylation in all cell lines tested with $IC_{50}$s at



Reference ID: 4344794

clinically achievable concentrations; crizotinib inhibited ALK phosphorylation at higher concentrations (Table 6).

**Table 6: PF-06463922 activity against ALK fusion variants and ALK fusion mutations in cell-based assays**

| Cell-based ALK phosphorylation (Tyr 1604) ELISA Assay[a] | IC50 (Mean ± SEM) | | | | IC50 Ratio crizo/ PF3922 |
|---|---|---|---|---|---|
| | PF-06463922 | | Crizotinib | | |
| | nM | n | nM | n | |
| Endogenous EML4-ALKv1 phosphorylation in H3122 human NSCLC cells | 2.4 ± 0.3 | 3 | 87 ± 8.9 | 29 | 36 |
| Endogenous EML4-ALKv3a/b phosphorylation in H2228 human NSCLC cells | 1.3 ± 0.4 | 3 | 206 ± 41 | 3 | 158 |
| Endogenous NPM-ALK phosphorylation in Karpas 299 human ALCL cells | 1.2 ± 0.4 | 2 | 95 ± 7.4 | 2 | 79 |
| Engineered EML4-ALKv1 phosphorylation in H3122-ALK$^{L1196M}$ cells | 11 ± 0.3 | 7 | 535±73 | 6 | 49 |
| Engineered EML4-ALKv1 phosphorylation in H3122-ALK$^{G1269A}$ cells | 17 ± 1.9 | 3 | 504±135 | 3 | 30 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALKv1 cells | 1.5 ± 0.4 | 5 | 80 ±37 | 101 | 53 |
| Engineered EML4-ALKv2 phosphorylation in NIH3T3-EML4-ALKv2 cells | 1.4 ± 0.1 | 2 | 96 ± 3.7 | 2 | 69 |
| Engineered EML4-ALKv3a phosphorylation in NIH3T3-EML4-ALKv3a cells | 0.9 ± <0.1 | 2 | 55 ± 2.8 | 2 | 61 |
| Engineered EML4-ALKv3b phosphorylation in NIH3T3-EML4-ALKv3b cells | 1.0 ± <0.1 | 2 | 76 ± 13 | 2 | 76 |
| Engineered KIF5B-ALK phosphorylation in NIH3T3-KIF5B-ALK | 0.5 ± 0.2 | 3 | 29 ± 6.4 | 3 | 58 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{L1196M}$ | 21 ± 2.3 | 5 | 843 ± 382 | 101 | 40 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{G1269A}$ | 15 ± 8.5 | 2 | 605 ± 90 | 4 | 40 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{F1174L}$ | 0.2 ± <0.1 | 2 | 165 ± 36 | 4 | 825 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{C1156Y}$ | 1.6 ± 1.4 | 2 | 478 ± 153 | 4 | 299 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{L1152R}$ | 9 ± 7 | 2 | 1026 ± 71 | 4 | 114 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{G1202R}$ | 65 ± 23 | 4 | 1148 ± 471 | 4 | 18 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3-EML4-ALK$^{1151Tins}$ | 46 ± 0.7 | 2 | 3039 ± 39 | 2 | 66 |
| Engineered EML4-ALKv1 phosphorylation in NIH3T3/EML4-ALK$^{S1206Y}$ | 4.2 | 1 | 626 | 1 | 149 |

[a] The cells were treated with different concentrations of PF-06463922 or vehicle in the serum free media for one hour, and lysed by using the Cell Lysis Buffer (Cell Signaling Technologies). The ALK-tyrosine 1604 phosphorylation in cell lysates was determined utilizing a commercially available PathScan® Phospho-ALK Chemiluminescent Sandwich ELISA Kit (Cell Signaling Technologies). IC50 values were calculated by concentration-response curve fitting utilizing a four-parameter analytical method.

*(Applicant Figure reproduced from Study 174542)*

To examine the activity of PF-06463922 on ROS1 fusion proteins, Pfizer employed HCC78 NSCLC cells harboring chromosomal translocations that result in the expression of the constitutively active SLC34A2-ROS1(s/L) fusion proteins, NIH3T3 cells engineered to express various human oncogenic ROS1 fusion gene constructs identified in human cancers (SLC34A2-ROS1(L) (Se12;Re32), SLC34A2-ROS1(s), CD74-ROS1(s), Fig-ROS1(L) and Fig-ROS1(s)), and Ba/F3-CD74-ROS1(s) cells, engineered to express human CD74-ROS1(s) fusion. PF-06463922 inhibited the phosphorylation of ROS1 fusion variants, as summarized in **Table 7**.

**Table 7: PF-06463922 activity against ROS1 fusion phosphorylation in cell-based assays**

| Cell-based ROS1 phosphorylation ELISA Assay[a] | IC50 (Mean ± STD) | | | | IC50 Ratio crizo/ PF3922 |
|---|---|---|---|---|---|
| | PF-06463922 | | Crizotinib | | |
| | nM | n | nM | n | |
| Endogenous SLC34A2-ROS1(s/L) phosphorylation in HCC78 human NSCLC cells | 0.14±0.09 | 4 | 96 ± 55 | 10 | 686 |
| Engineered CD74-ROS1(s) phosphorylation in NIH3T3-CD74-ROS1(s) cells | 0.23±0.18 | 4 | 16 ± 6 | 6 | 70 |
| Engineered Fig-ROS1(s) phosphorylation in NIH3T3-Fig-ROS1(s) cells | 0.31±0.41 | 4 | 104 ± 48 | 6 | 335 |
| Engineered Fig-ROS1(L) phosphorylation in NIH3T3-Fig-ROS1(L) cells | 0.29±0.11 | 4 | 48 ± 25 | 5 | 166 |
| Engineered SLC34A2-ROS1(s) phosphorylation in NIH3T3-SLC34A2-ROS1(s) cells | 1.00±1.14 | 6 | 61 ± 44 | 7 | 61 |
| Engineered SLC34A2-ROS1(L) phosphorylation in NIH3T3-SLC34A2-ROS1(L) cells | 1.30±0.55 | 6 | 123 ± 42 | 6 | 95 |
| Engineered CD74-ROS1(s) phosphorylation in BaF3-CD74-ROS1(s) cells | 0.95±0.16 | 6 | 202 ± 63 | 12 | 213 |

[a] Cells were treated with designated concentrations of PF-06463922 for one hour, and cells were lysed for protein extraction. The total ROS1 phosphorylation in the cell lysate was determined utilizing a commercially available PathScan® Phospho-ROS1 Sandwich ELISA Kit (Cell Signaling Technologies). IC50 values were calculated by concentration-response curve fitting utilizing a four-parameter analytical method.

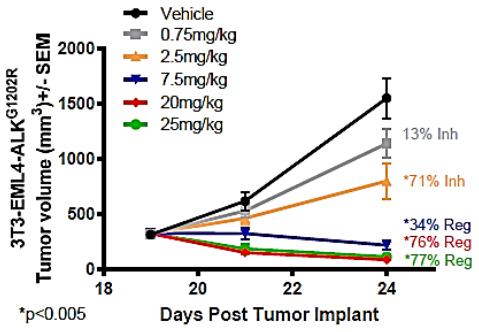
*(Applicant Figure reproduced from Study 174542)*

B. In Vivo Studies

Pfizer characterized the in vivo antitumor efficacy of PF-06463922 against the previously described ALK mutations in several xenograft mouse models. In Study #020236, NIH3T3 and Ba/F3 cells were engineered to express human EML4-ALKV1$^{G1202}$ and EML4- ALK$^{I1171T}$ respectively, via retroviral transduction. For both studies, cells were implanted subcutaneously into the hind flank of female athymic mice and allowed to grow to the size of 320 mm$^3$. Mice were then treated with either PF-06463922 at doses of 0.75, 2.5, 7.5, 20, or 25 mg/kg/day for 6 days via pump infusion (Study #020236) or with either PF-0646392 at doses of 0.3, 1, and 3 mg/kg/day or crizotinib at 30 mg/kg twice daily (BID) for 12 days (Study #055600). Tumor size was measured to calculate tumor growth inhibition as evidence of anti-tumor activity. Tumor ALK phosphorylation levels were assessed by ELISA.

PF-06463922 demonstrated a dose-dependent inhibition of EML4-ALKV1$^{G1202R}$ phosphorylation in the subcutaneous tumors, as well as dose-dependent tumor growth inhibition (Figure 1).

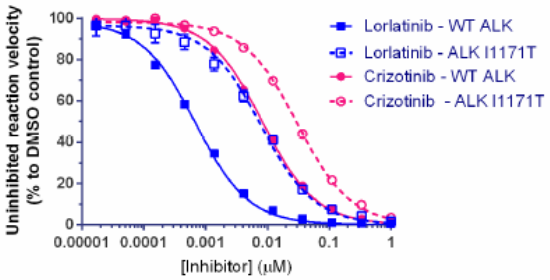
**Figure 1: Inhibition of EML4-ALKv1$^{G1202R}$ tumor growth by PF-06463922 in a NSCLC model**




*(Applicant Figure reproduced from Study 020236)*

To compare the ability of PF-06463922 and crizotinib to inhibit ALK and ALK mutations, Pfizer produced recombinant human wild-type and mutant ALK I1171T kinase domain proteins, pre-activated them via auto-phosphorylation, and treated them with increasing concentrations (0-1 µM) of each drug. PF-06463922 inhibited both wild-type ALK and mutant ALK at lower concentrations than crizotinib (Figure 2), with $IC_{50}$ values of 0.65 and 7.8 nM for wild-type ALK and $ALK^{I1171T}$, respectively vs. crizotinib $IC_{50}$ values of 8.3 and 30.4 nM.

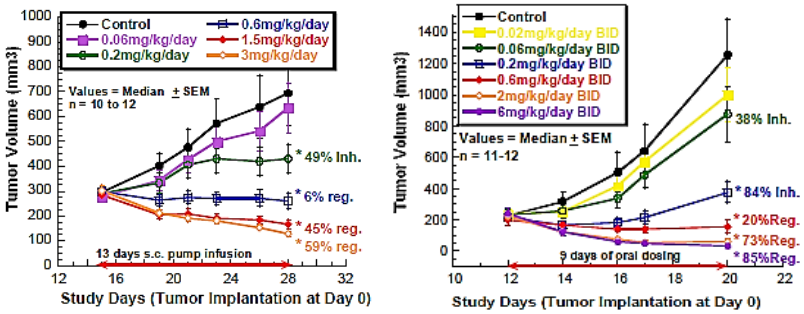
**Figure 2: Inhibition of ALK and ALK I1171T by lorlatinib and crizotinib**




*(Applicant Figure reproduced from Study 055600)*

Pfizer further characterized the anti-tumor activity of PF-06463922 by examining xenograft models using luciferase expressing ALK V1 and ROS fusion NSCLC cell lines that included examining brain penetration of the drug (Study #174736). Briefly, female nu/nu or scid/beige mice (5-8 weeks old) were implanted subcutaneously in the hind flank with 5 x $10^6$ cells in 100 µL supplemented with 50% Matrigel. Tumor size was determined by caliper measurement. A subset of animals was implanted intracranially with 3 x $10^5$ cells, and tumor size was measured by luciferase reporter activity. PF-06463922 was administered at 5 to 10 mL/kg orally or via subcutaneous pump infusion that administered a constant infusion rate to reflect dose levels of 0.06, 0.2, 0.6, 1.5 and 3 mg/kg/day for 13 days, while crizotinib was used as a reference compound at 80 mg/kg BID. PF-06463922 demonstrated dose-dependent anti-tumor activity in both the subcutaneous (Figure 3) and intracranial models (data not shown), suggesting that PF-06463922 is brain penetrant.

**Figure 3: Inhibition of EML4-ALKL1196M (left) and ROS1 (right) tumor growth following treatment with PF-06463922 in mouse models of NSCLC**




*(Applicant Figure reproduced from Study 174736)*

Secondary pharmacology

Pfizer screened PF-06463922 for activity against a broad panel of receptors, enzymes, transporters, and ion channels in a ligand profile screen at a concentration of 10 µM (Study #100001517). At the 10 µM concentration PF-06463922 showed less than 50% inhibition of binding or enzymatic activity against most profiled targets with the exceptions of the following enzymes: acetylcholinesterase (73.0% inhibition), AurA/Aur2 kinase (87.0% inhibition), EGFR (73.6% inhibition) and Lck (53.4% inhibition), with the $IC_{50}$ values for these activities determined to be 5.3 µM, 3.8 µM, 5 µM, and 0.7 µM, respectively.

Safety pharmacology

A. Central nervous system

Pfizer evaluated the effects of PF-06463922 on the CNS using rat hippocampal slices and in vitro screening. To examine the effects of PF-06463922 on long term potentiation (LTP), (Study #14GR133), adult male Sprague-Dawley rats were anesthetized, and brains were removed. Slices of the brain were perfused with artificial spinal fluid. Extracellular field excitatory postsynaptic potential (fEPSP) recordings were made from the CA1 region of the hippocampus using a multielectrode array recording system. After obtaining baseline, a vehicle control or PF-06463922 at concentrations of 0.1 and 1 µM were applied for 20 minutes followed by theta burst stimulation (TBS) at three 10 second intervals to induce LTP. The magnitude of LTP was expressed as a percentage of fEPSP amplitude from baseline. PF-06463922 did not impact long term potentiation (LTP) in the CA1 region at the concentration of 0.1 µM, but it did reduce LTP strength when tested at 1 µM, roughly twice the concentration that would be reached at the proposed human dose of 100 mg.

Pfizer also performed two in vitro screening studies that examined potential Nav 1.5 or $GABA_A$ receptor inhibition by PF-06463922 (Study #13GR078, 13GR081). Chinese hamster ovary (CHO) cells were stably transfected with either the human Nav1.5 gene or the human GABAα1, humanized rat GABAβ2 and human GABAγ2 genes. Cells were exposed to PF-06463922 at concentrations of 1-100 µM or a positive control (propafenone or gamma-aminobutyric acid), and inhibition was determined by whole cell patch clamp channel current readings. The $IC_{50}$ for Nav1.5 current inhibition by PF-06463922 was over 100 µM. PF-06463922 also showed no inhibition of the $GABA_A$ receptor in CHO cells at concentrations up to 100 µM (Study #13GR081).

In addition to activity against ALK, PF-06463922 was also able to inhibit TrkA and TrkB receptors, which are involved in attention and memory processes. Therefore, Pfizer examined the effects of PF-06463922 on cognitive function (Study 12GR137). Male Wistar rats were trained under the contextual renewal paradigm. The contextual renewal model is based on the premise that conditioning occurring in one context is recalled whenever the animal is

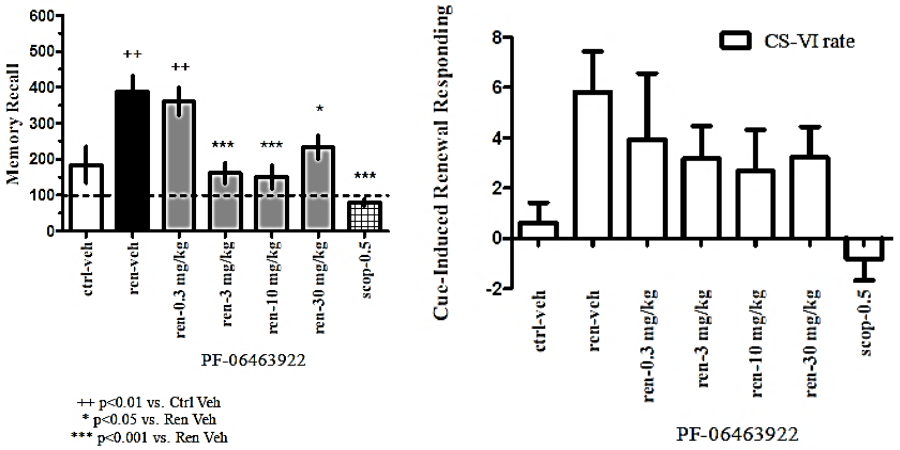


Reference ID: 4344794

returned to that context, but not when the animal is placed into an alternative context. The methods involve conditioning and extinction in two different contexts, and the renewal of conditioned behavior is induced by return to the conditioning context. Control groups remain in the same context during conditioning, extinction, and testing. During conditioning, rats learned to associate a cue light with food pellets. After extinction with light only presentations, animals were tested for renewal of responding to the light. Performance was assessed through the expression of the conditioned response, which included approach and activity directed at the food receptacle (nose pokes). Rats received PF-06463922 at doses of 0.3, 3, 10, and 30 mg/kg, a vehicle control, or scopolamine, a positive control known to reduce memory, at doses of 0.5 and 1 mg/kg. Animals were tested 1 hour post dose. Animals were then assessed for memory recall and cue-induced renewal responding, parameters considered to be measures of cognitive function.

Oral administration of PF-06463922 at doses ≥ 3 mg/kg resulted in clear decreases in memory recall and a trend in cue-induced renewal responding, parameters that are indicative of cognitive performance (Figure 4).

**Figure 4: Effects of PF-06463922 on cognitive performance parameters**




Memory recall = $\frac{\text{Percent cue light responding in test session for an individual rat}}{\text{Average percent cue light responding in prior extinction session for the entire dose}} \times 100$

Cue-induced renewal responding = Cue light to VI ratio during test session –Cue light to VI ratio during prior day's extinction session

*(Applicant Figure reproduced from Study 12GR137)*

B. Cardiovascular system

Pfizer examined the effects of PF-06463922 on cardiovascular parameters using several in vitro and in vivo safety pharmacology studies. HEK293 cells, were stably transfected to express human ether-a-go-go (hERG) potassium channels. Patch clamp testing was performed at a temperature of 33-35°C. Onset and steady state inhibition of hERG potassium current due to PF-06463922 were measured using a pulse pattern with fixed amplitudes repeated at 5 second



Reference ID: 4344794

intervals. PF-06463922 concentrations of 10, 30, 100 and 300 µM were applied. Terfenadine was used as a positive control. In the reported results, inhibition of hERG by PF-06463922 at 30, 100 and 300 µM was statistically significant ($P < 0.05$) when compared with the vehicle control values. The hERG inhibition of PF-06463922 at 10 µM was not statistically significant ($P < 0.05$) when compared with the vehicle control values. The $IC_{50}$ for the inhibitory effect of PF-06463922 on hERG potassium current was 203.1 µM.

In a similar patch clamp technique study assessing the effect of PF-06463922 on L-type calcium and sodium currents in isolated guinea pig ventricular myocytes (Study #17GR038), PF-06463922 showed inhibition ($p<0.01$) of L-type calcium currents at all concentrations tested (10, 30 and 100 µM) when compared with the time-matched controls, with an $IC_{50}$ of 44± 5 µM. PF-06463922 had no effects on peak sodium currents, but increased late sodium currents at 100 µM as compared to time-matched controls. The free lorlatinib plasma concentration predicted to be reached at the proposed human dose of 100 mg is approximately 0.5 µM, suggesting low potential for QT prolongation by this mechanism.

An ex vivo study was performed by Pfizer with the goal of examining the effect of PF-06463922 on cardiac function in the guinea pig isolated Langendorff-perfused paced heart model. Hearts were excised from anesthetized guinea pigs and placed in Tyrodes' solution. The hearts were cannulated via the aorta onto the Langendorff perfusion system. After a stabilization period, a baseline was recorded for 10 minutes. Hearts were then perfused with increasing concentrations (0.01 to 30 µM) of the test article or vehicle for 5 minutes each. Cardiac functional parameter effects were calculated as percent changes from baseline. There were no PF-06463922 related changes to cardiac contractility, left ventricular pressure, coronary perfusion pressure, QRS or QT intervals. There was a PF-06463922 related increase in PR interval at concentrations ≥ 1 µM.

Pfizer also performed non-GLP in vivo studies in rats (Study 12LJ029) and dogs (Study 12LJ083), examining the effects of PF-06463922 on cardiovascular function. Wistar rats were previously implanted with a blood pressure transmitter and baseline data were collected over 22 hours within 7 days prior to treatment and around 22 hours post-dose. Rats were orally administered 0, 10 or 30 mg/kg/day PF-06463922. Beagle dogs were treated with 2 mg/kg/day PF-06463922, administered orally BID with 7 hours between doses for 5 consecutive days. After a 2-day washout period, animals were then treated with 15 mg/kg/days on the same schedule for 12 consecutive days. Jacketed external telemetry data were obtained from each animal beginning 1 hour pre-dose through 22 hours post-dose. Echocardiography was collected around 2 hours post dose.

In rats, oral administration of PF-06463922 was associated with increases in systolic, diastolic and mean blood pressure, and a biphasic response (an initial decrease and later increase) in heart rate at ≥10 mg/kg (Table 8).



Reference ID: 4344794

**Table 8: Statistically significant effects of PF-06463922 on cardiovascular parameters by time period**

| Parameter | Dose (mg/kg) | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diastolic Blood Pressure (mmHg) | 10 | 15.0 | 18.1 | 19.8 | 18.8 | 16.8 | 14.3 | 16.4 | 9.6 | 7.9 | | |
| | 30 | 19.7 | 27.2 | 31.9 | 32.7 | 26.4 | 26.4 | 22.8 | 15.6 | 13.5 | 10.4 | 9.8 |
| Mean Blood Pressure (mmHg) | 10 | 15.9 | 19.1 | 21.8 | 20.9 | 18.5 | 16.5 | 18.6 | 12.0 | 10.3 | 8.9 | |
| | 30 | 22.3 | 30.0 | 35.3 | 35.4 | 29.0 | 29.3 | 26.2 | 19.2 | 16.7 | 13.6 | 12.7 |
| Systolic Blood Pressure (mmHg) | 10 | 15.8 | 19.1 | 22.0 | 21.0 | 18.8 | 17.5 | 19.8 | 13.7 | 12.2 | 10.6 | |
| | 30 | 23.5 | 31.3 | 36.7 | 36.6 | 30.0 | 30.8 | 28.5 | 22.1 | 19.2 | 16.1 | 15.0 |
| Heart Rate (bpm) | 10 | -24.8 | -35.7 | | | | -19.2 | | | 17.9 | 23.8 | 28.5 |
| | 30 | -32.7 | -20.6 | | | | | | | | 18.0 | 31.2 |

(Rounding of time bins occurs within SAS analysis process)
Blank = No significant treatment effect between treated and control groups.

*(Applicant Figure reproduced from Study 12LJ029)*

In dogs, oral dosing of PF-06463922 at 15 mg/kg/day resulted in decreases in systolic blood pressure and QT intervals, along with increases in heart rate, PR, and intervals, and fractional shortening during the dosing phase of the study. Pfizer reported that after a 5-day recovery period, effects observed during the dosing phase returned to baseline levels, indicating complete recovery from treatment-related effects.

C. Respiratory system

Pfizer evaluated the pulmonary effects of PF-06463922 administered as a single dose to male rats. Briefly, six male rats per dose group were given 10, 30, or 100 mg/kg PF-06463922 by oral gavage. Unrestrained animals were placed in a whole-body plethysmograph. Following acclimation, each animal was removed from the chamber, dosed, and returned to the chamber for the 240-minute collection period. The respiratory signals (tidal volume, respiratory rate, and minute volume) were collected every 5 seconds.

Oral administration of 30 and 100 mg/kg PF-06463922 resulted in decreases in mean tidal volumes at 60 minutes post-dose compared with vehicle control (-8%). In the 100 mg/kg group, this decrease became more pronounced (-15%) at 200 minutes and persisted up to 240 minutes post-dose. Oral administration of doses up to 100 mg/kg PF-06463922 did not significantly alter respiratory rate or minute volume.



Reference ID: 4344794

## 5.4. ADME/PK

APPEARST THIS WAY ON ORIGINAL



Reference ID: 4344794

| Type of Study | Major Findings |
|---|---|
| **Absorption** | |
| Study #120541: Single dose pharmacokinetics and oral bioavailability of PF-06463922 in rats following oral or intravenous administration<br><br>Study #121134: Single dose pharmacokinetics and oral bioavailability of PF-06463922 in dogs following oral or intravenous administration | • Following 1 mg/kg intravenous (IV) or 5 mg/kg oral administration in rats, the mean CL was 15.5 mL/min/kg and mean $V_d$ was 2.66 L/kg. The half-life ranged from 2.7 h (IV) to 3.6 h (oral).<br>• Oral bioavailability was approximately 100%.<br><br>• Following 1 mg/kg IV or 2 mg/kg oral administration in dogs, the mean CL was 9.05 mL/min/kg and mean $V_d$ was 2.80 L/kg. The half-life ranged from 4.6 h (IV) to 8 h (oral).<br>• Oral bioavailability was approximately 97 %. |
| **Distribution** | |



Reference ID: 4344794

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Study #092743: Protein binding of PF-06463922 in mouse and rabbit plasma<br><br>Study #ADME2012-001-0027: Protein binding of PF-06463922 in human, rat, and dog plasma<br>Study #104704: Protein binding of PF-06463922 in human serum albumin and alpha-1-acid<br><br>Study #114157: Plasma, CSF, and brain tissue distribution of PF-06463922 in rats following single oral administration (10 mg/kg)<br><br>Study #152438: Quantitative whole-body autoradiography of male Long Evans rats after a single oral administration of [$^{14}$C]PF-06463922</td><td>Mean fraction unbound of PF-06463922 in plasma proteins at 2 µM (equilibrium dialysis)
<table>
<tr><th>Species</th><th>Mean Fraction Unbound</th></tr>
<tr><td>Mouse</td><td>0.239</td></tr>
<tr><td>Rat</td><td>0.303</td></tr>
<tr><td>Rabbit</td><td>0.358</td></tr>
<tr><td>Human</td><td>0.340</td></tr>
<tr><td>Human (HSA)</td><td>0.474</td></tr>
<tr><td>Human (AAG)</td><td>0.62</td></tr>
</table>
PK parameters of PF-06463922 in plasma, CSF, brain
<table>
<tr><th>Parameter</th><th>Plasma</th><th>CSF</th><th>Brain tissue</th></tr>
<tr><td>$C_{max}$ (ng/mL)</td><td>1560</td><td>198</td><td>1150</td></tr>
<tr><td>$AUC_{24}$ (h*ng/mL)</td><td>12500</td><td>1410</td><td>7970</td></tr>
<tr><td>$T_{max}$ (h)</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>2.69</td><td>2.89</td><td>3.15</td></tr>
</table>
PF-06433922 demonstrated high penetration into brain tissue, with concentrations as high as ~65% those seen in plasma
<ul>
<li>PF-06463922 rapidly and extensively distributed to the tissues by 0.25 hours post dose</li>
<li>$C_{max}$ in tissues was 1-8 hours post dose</li>
<li>By 48 hours, 36 of 52 tissues were below the lower limit of detection. By 672 hours post dose, the lens of the eye, eye, kidneys, renal cortex, nasal turbinates, preputial gland, thyroid, and uveal tract still had measurable concentrations of PF-06463922</li>
<li>Tissues with the highest exposure were uveal tract, liver, intervertebral discs, adrenal gland, and Harderian gland</li>
</ul></td></tr>
<tr><td>Metabolism</td><td></td></tr>
</table>



Reference ID: 4344794

| Type of Study | Major Findings |
|---|---|
| Study #090034: Preliminary assessment of circulating metabolites and chiral inversion of [$^{14}$C]PF-06463922 in human plasma<br><br>Study #094132: Identification of metabolites of PF-06463922 from in-vitro metabolism and in vivo from rat and dog plasma and rat urine and bile | • A benzoic acid metabolite resulting from cleavage of the amide and aromatic ether bonds (M8, PF-06895751) was observed as a major component of human plasma, accounting for 21% of the circulating radioactivity<br>• M8 was detected in both rats and dogs, but at much lower levels than those in humans. Thus, Pfizer assessed M8 in additional in vitro pharmacology and toxicology studies* (see additional information in paragraph below)<br>• Other metabolites identified were pyridine N-glucuronide (M1a, 8%), the pyridine N-oxide (M6, 4.5%) and the pyrazole N-desmethyl metabolite (M2a, 2%); these were present at low levels in all species |
| **Excretion** | |
| Study #8321366: Determination of routes of excretion of [$^{14}$C]PF-06463922 in Wistar Hanover rats after a single oral dose<br><br>Study #8321367: Determination of routes of excretion of [$^{14}$C]PF-06463922 in dogs after a single oral dose | • Following a single oral dose of 10 mg/kg, fecal and urinary excretion accounted for 81% and 14% (males) and 70% and 18% (females) of administered dose in rats within the first 48-72 hours<br><br>• Following a single oral dose of 10 mg/kg, fecal and urinary excretion accounted for 51% and 25% (males) and 71% and 18% (females) of administered dose in Beagle dogs within the first 48 hours |
| **TK data from general toxicology studies** | TK data from long-term studies was incorporated in review of general toxicology studies in section 5.5.1 |
| **TK data from reproductive toxicology studies** | TK data from embryofetal toxicity studies was incorporated in review of reproductive toxicology studies in section 5.5.4 |

*Since the major circulating metabolite of PF-06463922 found in human plasma, the benzoic acid metabolite PF-06895751 (M8), was present at much lower levels in animals than humans, Pfizer conducted several experiments to further assess its safety and activity. In a biochemical kinase panel screen, PF-06895751 was inactive against wild-type ALK at concentrations up to 10 µM. PF-06895751 was also inactive against ROS1 and 40 other kinases at 1 µM. PF-06895751 was further profiled against a broad panel of receptors, enzymes, transporters, and ion channels in a (b) (4) wide ligand profile screen at concentrations up to 10 µM. There was no



Reference ID: 4344794

binding or enzymatic activity at 10 µM for PF-06895751, and primary (on-target) or secondary (off-target) pharmacology related to PF-06895751 is considered unlikely. Further, PF-06895751 was tested for effects on cloned hERG potassium channels expressed in HEK293 cells. PF-06895751 was found to have an effect on hERG inhibition at 300 µM, suggesting a low risk for effects of the metabolite on QTc. In genetic toxicity studies, PF-06895751 was negative for genotoxicity in both an in vitro reverse mutation assay and an in vitro micronuclei induction assay in TK6 cells.

## 5.5. Toxicology

### 5.5.1. General Toxicology

**A 13-week study of PF-06463922 by oral gavage in rats/ Study 16LJ022**

Key Study Findings

- Treatment did not result in any test-item related unscheduled euthanasia
- Target organs of toxicity included skin, pancreas, liver, sciatic nerve, lymph nodes, and kidney

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | Males/females: 1/0.5, 4/2, 7.5 mg/kg per dose, dosed twice daily (2/1, 8/4, 15 mg/kg/day) |
| Route of administration: | Oral gavage |
| Formulation/Vehicle: | HCl acidified ultra-pure water |
| Species/Strain: | Wistar Han rat |
| Number/Sex/Group: | Main: 10/sex/group, recovery: 5/sex/group |
| Age: | 9 weeks |
| Satellite groups/ unique design: | Toxicokinetics: 3/sex/group |
| Deviation from study protocol affecting interpretation of results: | No |

**Observations and Results: changes from control**

| Parameters | Major findings |
|---|---|
| **Mortality** | One control female was euthanized on Day 16 due to gavage error |
| **Clinical Signs** | *Main*<br>MD females: skin scab, thin fur cover, abdominal distension |

| | |
|---|---|
| | HD females: discolored (red, yellow, orange), dry skin with lesions, erected fur, abdominal distension, dehydration<br>HD males: skin scab, thin fur cover<br><br>*Recovery*<br>HD females: minor skin/fur conditions (scabs, dry skin, thin fur cover), abdominal distension |
| **Body Weights** | *Main*<br>HD females: +18% |
| **Ophthalmoscopy** | Unremarkable, pre-dose and Week 13 |
| **Hematology** | *Main*<br>LD: -10%/-15% RBC (M/F), -10% HGB and HCT (M), +24% RETIC (M)<br>MD: +6% MCV and MCH (M)<br>HD: -17% HGB and HCT (F), +10% RETIC (F), +7% MCV (F), +9%/+25% RDW (M/F), +17%/+33% MPV (M/F), +591% neutrophils (F)<br>Dose dependent increase in WBC up to +65%/+148% and fibrinogen up to +25%/+148% (M/F) at HD<br><br>*Recovery*<br>HD: +24% fibrinogen |
| **Clinical Chemistry** | *Main*<br>LD: -68%/-45% creatine kinase (M/F)<br>MD: -52%/-61% creatine kinase (M/F)<br>HD: +49%/274% AST (M/F), +113%/135% ALT, +5% calcium (M/F), +464% ALP (F), 1614% total bilirubin (F), -67%/-36% creatine kinase (M/F)<br><br>Dose dependent increase in cholesterol up to +70%/+200%, triglycerides up to +53%/+58% (M/F), globulin up to +64%, amylase up to +29%/77% (M/F), lipase up to +67% (F), phosphorus up to +28% (F), sodium up to +6% (F), chloride up to 5% (F) at HD<br>Dose dependent decrease in ALB, A/G down to -26%, -52% in both sexes at HD<br><br>*Recovery*<br>MD: +19% cholesterol (M), -50%/-40% creatine kinase (M/F)<br>HD: +41% amylase (F), +25%/17% cholesterol (M/F), +19%/+22% globulin (M/F), -30% A/G (F), -30%/-47% creatine kinase (M/F) |
| **Urinalysis** | *Main*<br>≥MD: ↓pH, incidence of triple phosphate crystals, ketones<br>HD: +94% urine volume (F), -2% specific gravity (F)<br>2 HD females had brown urine and large amounts of bilirubin, consistent with high urinary excretion of serum bilirubin<br><br>*Recovery*<br>Unremarkable |
| **Gross Pathology** | |

| **Sex** | **Male** | | | | **Female** | | | |
|---|---|---|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | **0** | **2** | **8** | **15** | **0** | **1** | **4** | **15** |
| **# Main group, # Recovery** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 4** | **10, 5** | **10, 5** | **10, 5** |
| *Skin* | | | | | | | | |
| Scab, dark | | | | | 1 | | 2 | 8 |
| Scab, pale | | | | | | | | 1 |
| Focus, dark | | | | | | | | 1 |



Reference ID: 4344794

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Discoloration, pale (yellow) | | | | | | | | 1 |
| | *Liver* | | | | | | | | |
| | Discoloration, dark | | | | 5 | | | 1 | 8 |
| | Enlargement | | | | | | | | 3 |
| | Irregular surface | | | | | | | | 2 |
| | *Bile Duct* | | | | | | | | |
| | Dilation | | | | | | | | 2 |
| | Thick | | | | | | | | 2 |
| | *Kidney* | | | | | | | | |
| | Discoloration, dark | | | | | | | | 5, 1R |
| | *Spleen* | | | | | | | | |
| | Enlargement | | | | | | | | 3 |
| | *Thymus* | | | | | | | | |
| | Small | | | | | | | 1 | 8 |
| | *Lymph node, mesenteric* | | | | | | | | |
| | Focus, dark | 3 | 2 | 1 | 4 | | 1 | 1 | 3 |
| | *Lymph node; mandibular, mediastinal, pancreatic, iliac* | | | | | | | | |
| | Focus, dark | | | 4 | 5 | | 1 | 4 | 3 |
| | Enlargement | | | | 1 | | | 1 | 3 |
| | *Adrenal* | | | | | | | | |
| | Small | | | | | | | | 5 |
| | Discoloration, dark | | | | | | | | 1 |

| | |
|---|---|
| **Organ Weights**<br><br>(percent change compared to controls) | *Main*<br>LD<br>Liver: +16% Abs, +15% OW:BW<br>Heart: +15% Abs (F), +14% OW:BW (F)<br>MD<br>Brain: -4% Abs (F), -6% OW:BW (F)<br>Liver: +32% Abs, +28% OW:BW<br>Spleen: +21%/+12% Abs (M/F), +17%/+11% OW:BW (M/F)<br>Heart: +24% Abs (F), +22% OW:BW (F)<br>HD<br>Brain: -5% Abs (F), -17% OW:BW (F)<br>Liver: +47%/+108% Abs (M/F), +39%/+81% OW:BW (M/F)<br>Spleen: +28%/+79% Abs (M/F), +22%/+56% OW:BW (M/F)<br>Heart: +15%/+41% Abs (M/F), +9%/+23% OW:BW (M/F)<br>Thymus: -16%/-51% Abs (M/F), -20%/-56% OW:BW (M/F)<br>Adrenal: -18%/-30% Abs (M/F), -22%/-38% OW:BW (M/F)<br><br>*Recovery*<br>HD (M)<br>Adrenal: -15% Abs, -6% OW:BW<br>HD (F)<br>Brain: -6% Abs, -12% OW:BW<br>Liver: +33% Abs, +26% OW:BW<br>Spleen: +21% Abs, +14% OW:BW<br>Adrenal: -22% Abs, -28% OW:BW |
| **Histopathology Adequate battery:** Yes | • Skin ulceration/inflammation/fibrosis ranging from mild to severe occurred in high dose females |



Reference ID: 4344794

| | |
|---|---|
| | • The pancreas, liver, and kidney were major target organs, primarily in high dose females<br>• See Table 9 for selected histopathology findings |
| **Toxicokinetics** | • Exposure increased in a dose-dependent manner<br>• Exposure was approximately 2-fold higher in males compared to females, leading to the difference in dose administration<br>• There was accumulation in females at all doses, and in males at 15 mg/kg |

| | Dose (mg/kg/day) | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **1 (0.5 BID)** | **2 (1 BID)** | **4 (2 BID)** | **8 (4 BID)** | **15 (7.5 BID)** | |
| **Sex** | **F** | **M** | **F** | **M** | **F** | **M** |
| **Day 1** | | | | | | |
| $C_{max}$ (ng/mL) | 249 | 329 | 1020 | 1610 | 2640 | 3940 |
| $AUC_{24}$ (h*ng/mL) | 3660 | 3750 | 15200 | 18600 | 31700 | 62400 |
| $T_{max}$ (h) | 1 | 1 | 1 | 1 | 1.7 | 1.7 |
| **Day 90** | | | | | | |
| $C_{max}$ (ng/mL) | 388 | 322 | 1490 | 1460 | 3020 | 6600 |
| $AUC_{24}$ (h*ng/mL) | 5770 | 3920 | 25800 | 20600 | 44800 | 13100 |
| $T_{max}$ (h) | 1 | 1 | 1.7 | 1 | 1.7 | 1 |

LD: low dose; MD: mid dose; HD: high dose.
M: male; F: female
-/+: indicates reduction/increase in parameters compared to control.
Abs: absolute organ weight; OW: organ weight; BW: body weight

**Table 9: Selected histopathology findings in rats**

| **Sex** | | **Male** | | | **Female** | | |
|---|---|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | | **2** | **8** | **15** | **1** | **4** | **15** |
| **# Main group, # Recovery** | | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** |
| *Pancreas* | | | | | | | |
| Atrophy; acinar | Minimal | | | 2, 2R | | | 2, 2R |
| | Mild | | | | | | 6, 2R |
| | Moderate | | | 1 | | | |
| *Liver* | | | | | | | |
| Hypertrophy; centrilobular | Minimal | | | | | | 5 |
| Hyperplasia; bile duct | Minimal | | | | | | 2, 2R |
| | Mild | | | | | | 6, 1R |
| | Moderate | | | | | | 1R |
| Single cell necrosis | Minimal | | | | | | 2 |
| Increased cellularity; sinusoid | Minimal | | | | | | 3 |
| Increased hematopoiesis | Minimal | | | | | | 8 |
| *Duct; bile* | | | | | | | |
| Dilation | Mild | | | | | | 3 |
| *Kidney* | | | | | | | |

| | Sex | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| | **Dose (mg/kg/day)** | **2** | **8** | **15** | **1** | **4** | **15** |
| | **# Main group, # Recovery** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** |
| Basophilia; tubular | Minimal | 2 | 4, 2R | 6, 3R | | 4, 2R | 2, 4R |
| | Mild | | | | | | 7, 1R |
| | Moderate | | | | | | 1 |
| Glomerulopathy | Minimal | | | | | 1 | 8, 2R |
| Degeneration/necrosis; mural, artery | Minimal | | | | | | 7 |
| | Mild | | | | | | 1 |
| Cast; hyaline | Minimal | | 1 | | 1 | | 6, 1R |
| Pigment; tubular | Minimal | | | | | | 5, 3R |
| | Mild | | | | | | 1, 1R |
| | Moderate | | | | | | 1 |
| *Heart* | | | | | | | |
| Increased cellularity; Anichkov cells | Minimal | | | | | | 2 |
| *Bone marrow* | | | | | | | |
| Increased cellularity; myeloid | Minimal | | | | | | 1 |
| | Mild | | | | | | 5 |
| | Moderate | | | | | | 4 |
| Increased cellularity; hematopoietic | Minimal | 9 | 6, 1R | 3, 1R | | 4 | 2R |
| | Mild | 1 | 4, 1R | 6, 2R | | 3 | |
| | Moderate | | | 1 | | | |
| *Spleen* | | | | | | | |
| Decreased cellularity; lymphoid, marginal zone | Minimal | 7 | 4, 3R | 2, 3R | 9 | 2, 3R | 3R |
| | Mild | | 5 | 8 | 1 | 8 | 10 |
| Increased hematopoiesis | Minimal | 3 | 10, 1R | 6, 1R | | 6 | 2R |
| | Mild | | | 3 | | 1 | 3 |
| | Moderate | | | 1 | | | 5 |
| | Marked | | | | | | 2 |
| *Lymph node, mesenteric* | | | | | | | |
| Erythrocytosis | Minimal | 3 | 5 | 9 | 2 | 5 | 8 |
| | Mild | | | | 1 | | |
| Increased cellularity; lymphoid | Minimal | | | | 1 | | 4 |
| | Mild | | | | | | 1 |
| *Lymph node; mandibular, mediastinal, pancreatic, iliac* | | | | | | | |
| Increased cellularity; lymphoid | Mild | | | | | | 1 |
| Plasmacytosis | Minimal | | 1 | | | 1 | |
| | Mild | | | | | 1 | |
| | Marked | | | | | | 4 |
| Erythrocytosis | Minimal | | 2 | 3 | 1 | 1 | 1 |

| | Sex | Male | | | Female | | |
|---|---|---|---|---|---|---|---|
| | **Dose (mg/kg/day)** | **2** | **8** | **15** | **1** | **4** | **15** |
| | **# Main group, # Recovery** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** | **10, 5** |
| | Mild | | 1 | 2 | | 3 | 2 |
| Increased hematopoiesis | Minimal | | | | | | 1 |
| *Gland, mammary* | | | | | | | |
| Pigment; increased | Minimal | 1 | 6 | 4 | | | |
| | Mild | | | 1 | | | |
| Atrophy | Minimal | | | 1 | | | |
| *Gland; salivary, mandibular* | | | | | | | |
| Depletion; secretory, granular duct | Minimal | | 2 | 2 | | 2 | 5 |
| *Uterus* | | | | | | | |
| Atrophy | Minimal | | | | | | 6 |
| *Cervix* | | | | | | | |
| Inflammation | Minimal | | | | | | 2 |
| | Mild | | | | | | 1 |

**A 13-week study of PF-06463922 by oral gavage in the Beagle dogs/ Study 16LJ023**

Key Study Findings

- Three deaths occurred at the high dose
- Target organs of toxicity were lungs, skin, lymph nodes and liver

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 1, 3.5, 12.5 mg/kg twice daily (2, 7, 25 mg/kg per day) for 13 weeks |
| Route of administration: | Oral gavage |
| Formulation/Vehicle: | HCl acidified ultra-pure water |
| Species/Strain: | Beagle dog |
| Number/Sex/Group: | 3/sex/group |
| Age: | 10-11 months |
| Satellite groups/ unique design: | None |
| Deviation from study protocol affecting interpretation of results: | No |

**Observations and Results: changes from control**



Reference ID: 4344794

| Parameters | Major findings |
|---|---|
| **Mortality** | 25 mg/kg: 1 male (Day 48), 2 females (Days 46 and 88)<br><br>Cause of death: Pulmonary inflammation (male and 1 female), mandibular bone inflammation (1 female) |
| **Clinical Signs** | *Early sacrifices*<br>Decreased activity, tremors, distended abdomen, high body temperature, limited usage of all paws, breathing difficulties, skin lesions. One female euthanized on Day 88 also showed severe gingival recession starting on Day 60.<br><br>*Scheduled sacrifices*<br>Decreased activity, weakness, recumbency, decreased muscle tone, tremors, warm to touch, abnormal gait, abdominal distension, emesis, liquid feces, increased incidence of skin reddening, swollen skin, dry skin, lesions, thin fur cover |
| **Body Weights** | Unremarkable, predose, weekly, and prior to sacrifice |
| **Ophthalmoscopy** | Unremarkable, predose, weekly, and prior to sacrifice |
| **ECG** | Unremarkable, predose, weekly, and prior to sacrifice |
| **Hematology** | *Early sacrifices*<br>Poikilocytosis, polychromasia, ↑ anisocytosis, ↑ nucleated RBCs<br><br>*Scheduled sacrifices*<br>MD: +23% platelet count (F)<br>HD: -6%/-12% HGB (M/F), +13% RDW, +3% MCV, +44%/+111% platelet count (M/F)<br><br>Dose dependent increase in RETIC up to +677% at HD, WBC up to +176%, neutrophils up to +310%, lymphocytes up to +55%, monocytes up to +290%, leukocytes up to +76%, fibrinogen up to +158% at HD |
| **Clinical Chemistry** | *Early sacrifices*<br>Increased ALP, cholesterol, triglycerides, globulin, amylase, creatine kinase, and chloride; decreased albumin, A/G ratio<br><br>*Scheduled sacrifices*<br>HD: +34%/+87% amylase (M/F)<br><br>Dose dependent increases in ALP up to +154%/+201% (M/F), cholesterol up to +53%, triglycerides up to +104% (M), globulin up to +40% at HD<br>Dose dependent decreases in albumin down -81% and AG down -43% at HD |
| **Urinalysis** | Unremarkable, pre-dosing and prior to sacrifice |
| **Gross Pathology** | *Early sacrifices*<br>Lung: dark, pale, and raised foci, nodules, pale discoloration, failure to collapse, raised foci, adhesions<br>Skin: dark abrasion (hind limb and rear limb footpads, muzzle), chronic active inflammation with edema, increased thickness and dark focus in the dorsal thoracic subcutis with hemorrhage (near ID chip, near dorsal thoracic mass)<br>Mandibular bone: dark area, fracture, mass in 1F |



Reference ID: 4344794

Lymph nodes: enlargement, dark discoloration, abnormal consistency
Adrenal gland: increased thickness and mild cortical hypertrophy

*Scheduled sacrifices*

| Sex | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 0 | 2 | 7 | 25 | 0 | 2 | 7 | 25 |
| # Main group | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 1 |
| *Lungs* | | | | | | | | |
| Focus, dark | | 1 | | 2 | | | | |
| Focus, depressed | 1 | | 1 | 1 | | | | 1 |
| Focus, pale | | | | 1 | | | | |
| Focus, raised | | | 2 | 2 | | | 2 | 1 |
| Discoloration, mottled | | | | | | | | 1 |
| Discoloration, pale | | | | 1 | | | 1 | |
| Nodule | | | 2 | 1 | | | 1 | |
| Abnormal consistency, firm | | | | | | | | 1 |
| *Skin* | | | | | | | | |
| Abrasion, dark | | | | 1 | | | 1 | |
| Focus, raised | | | | | | | 2 | |
| Scab, dark | | | | | | | 1 | |
| *Lymph node, popliteal* | | | | | | | | |
| Enlargement | | 2 | 2 | 2 | | 1 | 3 | 1 |
| Focus, pale | | | | 2 | | | 1 | |
| *Thymus* | | | | | | | | |
| Small | | 1 | 3 | 2 | | 1 | 2 | 1 |
| *Lymph node; mandibular, mediastinal, pancreatic, iliac* | | | | | | | | |
| Enlargement | | | | 2 | | | | |
| Discoloration, dark | | 1 | 2 | 1 | | 2 | 1 | |
| Focus, dark | | | 1 | 1 | | | 1 | 1 |
| *Body cavity* | | | | | | | | |
| Focus, depressed | | | | | | | | 1 |
| Discoloration, dark | | | | | | | | 1 |
| *Prostate* | | | | | | | | |
| Small | | | | 1 | | | | |

**Organ Weights**

LD
Lung: +19% OW:BN
Liver: +19% Abs, +19% OW:BW, +25% OW:BN
Thymus: -36%/-20% Abs, -37%/-24% OW:BW, -41%/-20% OW:BN (M/F)
MD
Liver (F): +39% Abs (F), +38% OW:BW (F), +41% OW:BN
Thymus: +34% Abs, +33% OW:BW, +34% OW:BN
Testis (M): -18% Abs, -25% OW:BW, -23% OW:BN
HD
Lung: +29%/+31% Abs, +36%/+42% OW:BW (M/F)
Liver: +28%/+38% Abs, +33%/+50% OW:BW (M/F)
Spleen: +50% Abs, +50%/+63%, OW:BW, +51%/+43% OW:BN (M/F)
Adrenal gland: +33%/+43% (M/F) Abs, +37%/+54% (M/F) OW:BW, +36% OW:BN
Thymus: -66%/-80% Abs, -65%/-79% OW:BW, -65%/-81% OW:BN (M/F)
Testis (M): -15% Abs, -12% OW:BW, -13% OW:BN
Epididymis (M): -13% (Abs, OW:BW, OW:BN)
Prostate (M): -65% (Abs, OW:BW, OW:BN)



Reference ID: 4344794

| | |
|---|---|
| **Histopathology**<br>**Adequate battery:** Yes | *Scheduled sacrifices*<br>Major target organs included lungs, liver, skin, and lymph nodes<br><br>See Table 10: Selected histopathology in dogs for selected histopathology |
| **Toxicokinetics** | • Exposure increased in a dose-dependent manner<br>• There were no sex-related differences in exposure<br>• Little accumulation occurred |

| | Dose (mg/kg/day) | | |
|---|---|---|---|
| **Parameter** | **2 (1 BID)** | **7 (3.5 BID)** | **25 (12.5 BID)** |
| **Day 1** | | | |
| $C_{max}$ (ng/mL) | 280 | 924 | 2760 |
| $AUC_{24}$ (h*ng/mL) | 2520 | 10000 | 30800 |
| $T_{max}$ (h) | 1 | 1 | 1 |
| **Day 90** | | | |
| $C_{max}$ (ng/mL) | 318 | 1150 | 3590 |
| $AUC_{24}$ (h*ng/mL) | 2820 | 10400 | 31000 |
| $T_{max}$ (h) | 1 | 1 | 1 |

LD: low dose; MD: mid dose; HD: high dose
-/+: indicates reduction or increase in parameters compared to control
M: indicates male; F: indicates female
Abs: absolute organ weight; OW: organ weight; BW: body weight; BN: brain weight

**Table 10: Selected histopathology in dogs**

| **Sex** | | **Male** | | | | **Female** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | | **0** | **2** | **7** | **25** | **0** | **2** | **7** | **25** |
| **# Main group** | | **3** | **3** | **3** | **2** | **3** | **3** | **3** | **1** |
| *Lungs* | | | | | | | | | |
| Inflammation, subacute | Minimal | | | 1 | | | | | |
| | Mild | | | 2 | | | | 3 | 1 |
| | Moderate | | | | 2 | | | | |
| Inflammation, pleural, subacute | Minimal | | | 2 | 1 | | | 1 | |
| *Liver* | | | | | | | | | |
| Hyperplasia, bile duct | Minimal | | 1 | 2 | 2 | | 1 | 2 | |
| | Mild | | | | | | | 1 | |
| | Moderate | | | | | | | | 1 |
| Pigment, Kupffer cell | Minimal | 1 | 1 | 1 | | 1 | | 2 | |
| | Mild | | | | 2 | | | | 1 |
| *Skin* | | | | | | | | | |
| Ulceration | Minimal | | | | 1 | | | | |
| | Mild | | | | | | | 1 | |
| Inflammation | Moderate | | | | 1 | | | 2 | |
| Crust | Minimal | | | | | | | 1 | |
| | Mild | | | | | | | 1 | |
| | Moderate | | | | 1 | | | | |



Reference ID: 4344794

| | Sex | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Dose (mg/kg/day)** | **0** | **2** | **7** | **25** | **0** | **2** | **7** | **25** |
| | **# Main group** | **3** | **3** | **3** | **2** | **3** | **3** | **3** | **1** |
| *Lymph node; mandibular, mediastinal, pancreatic, iliac* | | | | | | | | | |
| Plasmacytosis, medullary | Minimal | | | | 2 | | | | |
| Inflammation | Minimal | | | | | | | 1 | |
| Erythrocytosis, sinus | Mild | | | 2 | | | | | 1 |
| | Moderate | | | 1 | 2 | | 2 | 2 | |
| | Marked | | 1 | | | | | | |
| *Body cavity, oral* | | | | | | | | | |
| Inflammation, chronic active | Marked | | | | | | | | 1 |
| | Mild | | | | 1 | | | | |
| *Jejunum** | | | | | | | | | |
| Atrophy, villous | Minimal | | | | 1 | | | | |
| | Moderate | | | | 1 | | | | |
| Hyperplasia, crypt | Mild | | | | 2 | | | | |
| Degeneration, epithelium | Minimal | | | | 1 | | | | |
| Inflammation, subacute | Minimal | | | | 1 | | | | 1 |
| *Testis* | | | | | | | | | |
| Degeneration/atrophy, tubular | Minimal | | | 2 | 2 | | | | |
| | Moderate | | | 1 | | | | | |
| *Epididymis* | | | | | | | | | |
| Cellular debris | Minimal | | | 1 | 1 | | | | |
| | Mild | | | | 1 | | | | |
| Oligo/aspermia | Mild | | | 1 | | | | | |
| *Prostate* | | | | | | | | | |
| Atrophy, glandular | Minimal | | | | 1 | | | | |
| | Mild | | | | 1 | | | | |

*similar findings in ileum and duodenum

**General toxicology; additional studies**

In a 14-day study in male rats administered 3, 10, and 30 mg/kg PF-06463922 twice daily (6, 20, 60 mg/kg/day), animals treated with 20 and 60 mg/kg/day showed additional changes associated with PF-06463922 treatment that were not described in the 13-week study. Rats treated with ≥ 20 mg/kg/day PF-06463922 showed CNS and cardiovascular changes. PF-06463922 associated CNS effects included teeth chattering, involuntary movements, abnormal gait, uncoordinated air righting reflex, and reduced extensor thrust response. Cardiovascular changes included increases in end diastolic volume, diastolic area, wall thickness, stroke volume, and E and A velocity on Day 2 and Day 10. Echocardiography detected increased left ventricular lumen size, increased wall thickness, and overall hypertrophy. There were no histological findings that correlated with these CNS and cardiovascular events. Male rats treated with 60 mg/kg also showed minimal to moderate seminiferous tubule degeneration. Two of five animals treated with 60 mg/kg were euthanized on Day 13 of the study.

In a 14-day study in Beagle dogs administered 5, 15, and 50 mg/kg/day PF-06463922, cardiovascular changes were observed at doses ≥15 mg/kg/day. These observations included

increases in heart rate, decreases in blood pressure (primarily 12-22 hours post-dose), and increases in PR, QT, and QTc intervals 1-3 hours post-dose as measured by Jacketed External Telemetry. These changes were reported as transient in occurrence and did not correlate with time of maximal drug exposure. In a 1-month repeat-dose study in Beagle dogs administered 2, 7, and 25 mg/kg daily PF-06463922, tissue toxicities were similar to those seen in the 13-week study and were partially to fully reversible at the end of a 1-month recovery period.

### 5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
**Salmonella-E. Coli/mammalian microsome reverse mutation assay / Study 14GR303**

Key Study Findings:
- PF-06463922 was negative for mutagenic activity in the strains tested with and without S9 activation
- Standard positive controls confirm the sensitivity and validity of the assay

GLP compliance: Yes
Test system: Salmonella strains TA1537, TA98, TA100, TA1535; E. coli strain WP2 *uvrA* pKM101; no bacterial toxicity up to 5000 µg/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells
**In vitro micronucleus assay in TK6 cells / Study 14GR304**

Key Study Findings:
- PF-06463922 was positive for inducing micronuclei (MN) in TK6 cells in the 4-hour treatments with and without S9 activation and negative for inducing MN in TK6 cells in the 27-hour treatment without S9 activation
- Standard positive controls induced a significant increase in the frequency of micronucleated TK6 cells, confirming the sensitivity and validity of the assay
- The appearance of centromeres in the micronuclei were also assessed in this study via fluorescent in situ hybridization (FISH) analysis. PF-06463922 induced higher numbers of MN with centromere positive FISH signals in TK6 cells, indicating an aneugenic mechanism (data not shown)



Reference ID: 4344794

**Table 11: In Vitro Micronucleus Findings**

| | 4-Hour -S9 | | 4-Hour +S9 | | 27-Hour -S9 | |
|---|---|---|---|---|---|---|
| Treatment | % Cytotoxicity | Mean % MN | % Cytotoxicity | Mean % MN | % Cytotoxicity | Mean % MN |
| DMSO | 0 | 0.3 | 0 | 0.15 | 0 | 0.2 |
| + Ctrl | 37 | 2.3 | 23 | 2.05 | 98 | 1.45 |
| PF-06463922 | | | | | | |
| low | 20 | 1.25 | 25 | 2.5 | 14 | 0.25 |
| mid | 20 | 1.4 | 43 | 2.5 | 22 | 0.75 |
| high | 24 | 2.35 | 41 | 2.6 | 52 | 0.45 |

4-Hour doses: 293, 345, 406 µg/mL

27-Hour doses: 18.5, 25.6, 57.8 µg/mL

Positive controls: Mitomycin C, cyclophosphamide monohydrate, vinblastine sulfate

GLP compliance: Yes
Test system: human lymphoblast TK6 cells; up to 406 µg/mL (4 hour treatment) +/-S9; up to 57.8 µg/mL (27 hour treatment) -S9
Study is valid: Yes

<u>In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)</u>

**In vivo micronucleus assay in rats / Study 14LJ084**

Key Study Findings:

- PF-06463922 was positive for inducing micronuclei in rat bone marrow
- The positive control induced a significant increase in the frequency of micronucleated polychromatic erythrocytes (MNPCE) in rat bone marrow, confirming the sensitivity and validity of the study

GLP compliance: Yes
Test system: Wistar Han rat, bone marrow micronuclei; 10, 30 and 100 mg/kg/day for 2 days
Positive control: 40 mg/kg cyclophosphamide
Study is valid: Yes

Results

**Table 12: In Vivo Wistar Han rat Micronucleus Findings**

| Test Article | Dose[b] (mg/kg/day) | Number/Sex/ Group | PCE/Total Erythrocytes Mean ± SD | | MNPCE Scored (per 24000 PCE) | |
|---|---|---|---|---|---|---|
| | | | Male | Female | Male | Female |
| Vehicle Control (acidified deionized water, pH 3.00 ± 0.25) | 0 | 6 | 0.518 ± 0.00 | 0.525 ± 0.00 | 1 | 6 |
| PF-06463922 | 10 | 6 | 0.525 ± 0.01 | 0.529 ± 0.01 | 19* | 17* |
| | 30 | 6 | 0.527 ± 0.01 | 0.524 ± 0.01 | 18* | 18* |
| | 100 | 6 | 0.528 ± 0.01 | 0.531 ± 0.01 | 32* | 41* |
| Positive Control (Cyclophosphamide) | 40 | 6 | 0.551 ± 0.01 | 0.554 ± 0.01 | 439* | 509* |

*(Applicant Figure reproduced from Study 14LJ084)*

- All three test article doses are statistically significant for micronuclei when compared to the concurrent control. After discussion with Dr. Ramadevi Gudi, the

pharmacology/toxicology team determined that although increases at the 10 and 30 mg/kg dose groups are within or slightly outside the historical control data, the inconsistencies with the studies used in the pooling of the historical controls limits the reliance on that data. In addition, there is a clear increase in the frequency of the MN (5 to 10-fold increase) in the test article dose levels compared to the concurrent controls. No studies were conducted to verify that in vivo micronuclei formation was due to aneugenicity.

### 5.5.3. Carcinogenicity

Not submitted or required for the proposed indication.

### 5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Neither submitted nor required

Embryo-Fetal Development

**A preliminary embryo-fetal development study of PF-06463922 by oral gavage in rats / Study 15GR479**

Key Study Findings

- Low embryo-fetal viability, low mean fetal body weights, and incidence of external and visceral malformations occurred at all doses
- There were no fetuses available for morphological evaluation at doses ≥4 mg/kg/day

| | |
|---|---|
| Conducting laboratory and location: | (b) (4) |
| GLP compliance: | Yes |

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0.5, 2, 7.5, and 15 mg/kg given twice daily (1, 4, 15, 30 mg/kg/day) on gestation days (GDs) 6-17 |
| Route of administration: | Oral gavage |
| Formulation/Vehicle: | Acidified deionized water (0.001N HCl) |
| Species/Strain: | Wistar Han rats |
| Number/Sex/Group: | 6 females/group |
| Satellite groups: | None |
| Study design: | Female rats were bred naturally; mating day was designated GD 0. Presumed pregnant females were assigned to groups and |



Reference ID: 4344794

| | |
|---|---|
| | administered treatment twice daily on GDs 6-17. Rats were euthanized on GD 21. |
| Deviation from study protocol affecting interpretation of results: | No |

**Observations and Results**

| Parameters | Major findings |
|---|---|
| Mortality | At 30 mg/kg/day, three animals were euthanized due to clinical signs, weight loss, and decreased food consumption. |
| Clinical Signs | *Early euthanasia*<br>Abnormal gait, increased vocalization, dehydration, liquid vaginal discharge, ungroomed fur, wet and yellow staining on abdominal fur<br><br>*Scheduled euthanasia*<br>15 mg/kg: Hyperreactivity, dehydration<br>30 mg/kg: Hyperreactivity, dehydration, abnormal gait, decreased activity, hunched posture, erect fur, yellow staining on abdominal fur, ungroomed fur, wet abdominal fur, partly closed eyes, liquid vaginal discharge, yellow tongue, splayed hindlimbs, firm and swollen right hindpaw |
| Body Weights | Decreased maternal weight gain (↓60% vs. control) occurred during GDs 6-9 in the 30 mg/kg group. Mean maternal body weights were decreased at 4, 15, and 30 mg/kg beginning on GD 15 (-24% to -5% compared to control) |
| Necropsy findings Cesarean Section Data | |

| | 0 | 1 mg/kg | 4 mg/kg | 15 mg/kg | 30 mg/kg |
|---|---|---|---|---|---|
| **Number pregnancies** | 6 | 5 | 6 | 6 | 6 |
| **Number pregnancies examined** | 6 | 5 | 6 | 6 | 3 |
| **Viable fetuses** | 63 | 36 | 0 | 0 | 0 |
| **Mean gravid uterine weight (g)** | 71.45 | 48.78 | 1.85 | 1.47 | 1.33 |
| **Mean early resorptions** | 0.2 | 2.4 | 9 | 9.8 | 9.7 |
| **Mean late resorptions** | 0 | 0.6 | - | - | - |
| **Post- implantation loss** | 1.28% | 30.63% | 100% | 100% | 100% |
| **Mean live fetuses/litter** | 10.5 | 7.2 | 0 | 0 | 0 |
| **Mean fetal body weight (relative to controls)** | - | -17% | - | - | - |
| | | | | | |

| | |
|---|---|
| Necropsy findings<br>Offspring | <u>1 mg/kg</u><br>1 fetus with multiple malformations:<br>External: medially rotated hindlimbs, a supernumerary digit on the left forepaw, gastroschisis<br>Visceral: protrusion of multiple organs through abdominal opening (a portion of liver, stomach, small intestine, spleen, pancreas)<br><br>2 additional fetuses: small right kidney, interrupted aortic arch |
| Toxicokinetics | • The AUC exposures in rats at doses of 1, 4, 15, and 30 mg/kg were approximately 1.2x, 5x, 19x, and 60x those achieved in patients given the 100 mg PF-06463922 dose<br><br><u>Maternal exposure at GD 17</u> |

| | Dose (mg/kg/day) | | | |
|---|---|---|---|---|
| **Parameter** | **1 (0.5 BID)** | **4 (2 BID)** | **15 (7.5 BID)** | **30 (15 BID)** |
| $C_{max}$ (ng/mL) | 272 | 1060 | 3820 | 20300 |
| $AUC_{24}$ (h*ng/mL) | 6810 | 27200 | 107000 | 339000 |
| $T_{max}$ (h) | 1 | 1 | 4 | 7 |

**A preliminary embryo-fetal development study of PF-06463922 by oral gavage in rabbits / Study 15GR478**

Key Study Findings

- PF-06463922 related abortions were noted at doses of 15 and 30 mg/kg, and there were no viable fetuses at either dose
- Primary effects of PF-06463922 were low embryo-fetal viability, incidence of external and visceral abnormalities, and increased incidence of resorption at 4 mg/kg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

<u>Methods</u>

Dose and frequency of dosing: 0.5, 2, 7.5, and 15 mg/kg given twice daily (1, 4, 15, 30 mg/kg/day) on gestation days (GDs) 7-19

Route of administration: Oral gavage

Formulation/Vehicle: Acidified deionized water (0.001N HCl)

Species/Strain: New Zealand white rabbits

Number/Sex/Group: 8 females/group

Satellite groups: None

Study design: Female rabbits were naturally bread to untreated males and mating day was designated

GD 0. Presumed pregnant females were assigned to groups and administered treatment twice daily on GDs 7-19. Rabbits were euthanized on GD 29.

Deviation from study protocol affecting interpretation of results: No

**Observations and Results**

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>1 mg/kg: One rabbit was euthanized on GD 10 due to limited usage of the left and right hindlimbs. The etiology of the hindlimb paresis was unknown, and considered to be unrelated to the test article<br>15 mg/kg: 4 rabbits aborted between GD 19-21 and were euthanized<br>30 mg/kg: 4 rabbits aborted between GD 19-22 and were euthanized</td></tr>
<tr><td>Clinical Signs</td><td>Early euthanasia<br>Weight loss and lower food consumption was noted in 3 females Days 19-22 (prior to aborting), ungroomed fur, fur loss, thin fur cover, soft feces, liquid feces, presence of red liquid material and red aborted tissue material<br><br>Scheduled euthanasia<br>Liquid feces, soft feces, ungroomed fur</td></tr>
<tr><td>Body Weights</td><td>Mean maternal body weight was increased at GD 8-19 for 1, 4, 15 mg/kg animals and overall for the interval of GD 7-20 at 30 mg/kg (about 10%↑ vs. controls for all groups)</td></tr>
<tr><td>Necropsy findings<br>Cesarean Section Data</td><td>
<table>
<tr><th></th><th>0</th><th>1 mg/kg</th><th>4 mg/kg</th><th>15 mg/kg</th><th>30 mg/kg</th></tr>
<tr><td>Number pregnancies</td><td>8</td><td>8</td><td>8</td><td>8</td><td>8</td></tr>
<tr><td>Number pregnancies examined</td><td>8</td><td>7</td><td>8</td><td>4</td><td>4</td></tr>
<tr><td>Viable fetuses</td><td>82</td><td>73</td><td>63</td><td>0</td><td>0</td></tr>
<tr><td>Mean gravid uterine weight (g)</td><td>567</td><td>612</td><td>459</td><td>22</td><td>22</td></tr>
<tr><td>Mean early resorptions</td><td>0.3</td><td>0.7</td><td>1</td><td>8</td><td>9.3</td></tr>
<tr><td>Mean late resorptions</td><td>0.4</td><td>0.3</td><td>0.8</td><td>-</td><td>-</td></tr>
<tr><td>Post- implantation loss</td><td>6.17%</td><td>10.12</td><td>18.56%</td><td>100%</td><td>100%</td></tr>
<tr><td>Mean live fetuses/litter</td><td>10.3</td><td>10.4</td><td>7.9</td><td>0</td><td>0</td></tr>
<tr><td>Mean fetal body weight (relative to controls)</td><td>-</td><td>106%</td><td>103%</td><td>-</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Necropsy findings<br>Offspring</td><td>There were 2, 1, and 3 fetuses with malformations in the control, 1, and 4 mg/kg/day dose groups, respectively. The single fetus in the 1 mg/kg/day group was noted to have an absent innominate artery and a malpositioned origin of the right subclavian artery, but these are common</td></tr>
</table>

<table>
<tr><td></td><td>vessel variations found in rabbits. Therefore, the higher incidence of malformation at 4 mg/kg/day was considered test-article related.<br><br><u>4 mg/kg</u><br>Single fetus: domed head, malrotated forelimbs, forepaw hyperextension, high arched palate<br>2 additional fetuses: malpositioned and misshapen kidneys and a short ureter, one of which also noted with a retroesophageal subclavian artery</td></tr>
<tr><td>Toxicokinetics</td><td>• The AUC exposures in rabbits at doses of 1, 4, 15, and 30 mg/kg/day were approximately 0.1x, 0.6x, 3x, and 7x those achieved in patients given the 100 mg lorlatinib dose<br><br><u>Maternal exposure at GD 19</u>
<table>
<tr><td></td><td colspan="4">Dose (mg/kg/day)</td></tr>
<tr><td>Parameter</td><td>1<br>(0.5 BID)</td><td>4<br>(2 BID)</td><td>15<br>(7.5 BID)</td><td>30<br>(15 BID)</td></tr>
<tr><td>$C_{max}$ (ng/mL)</td><td>37.8</td><td>235</td><td>909</td><td>2860</td></tr>
<tr><td>$AUC_{24}$ (h*ng/mL)</td><td>546</td><td>3160</td><td>17000</td><td>40200</td></tr>
<tr><td>$T_{max}$ (h)</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
</table></td></tr>
</table>

**An investigative study of the effects of PF-06463922 on zebrafish development/ Study 16GR239**

Pfizer performed an investigative evaluation of the effects of PF-06463922 on zebrafish embryos. Briefly, wild-type pond zebrafish were obtained, and 12 mating groups were established using 2 females and 1 male per group. Eggs from each mating group were pooled. Eggs were plated 5 per well in a 24 well plate with embryo medium and incubated with PF-06463922 (0.25 to 1000 µM), prepared medium control, or solvent control until 120 hours post fertilization. Zebrafish were then anesthetized with tricaine solution and a dissecting microscope was used to determine phenotypic differences as compared to control. A scoring system of 1-5 was used for major organ systems, with 1 being severely affected, and 5 being normal. Differences in liver, yolk ball, body shape, circulation, edema, motility, and heart rate were captured as affected (1) or not affected (0). After morphological assessment, zebrafish were homogenized for plasma concentration and tissue bioanalysis via LC-MS/MS.

The developmental lowest observed effect concentration (LOEC) of zebrafish exposed to PF-06463922 was 0.25 µM. From 0.25-3.91 µM, the only PF-06463922-related effect observed was fewer iridophores in the eye (100% of zebrafish scored). At concentrations ≥7.82 µM, PF-06463922 affected arches/jaws, body shape, circulation, face, fins, heart, liver, motility, neural tube, notochord, somites, tail, and yolk. PF-06463922 also caused edema at concentrations ≥7.82 µM. The LOEC for death was 7.82 µM (3% of the exposed embryos died). 100% death



Reference ID: 4344794

occurred at concentrations of ≥31.3 µM. The mean whole body concentrations of PF-06463922 at 3.91 µM, 7.82 µM, and 15.63 µM were 9.2, 18.5, and 104 ng/mL, respectively.

Prenatal and Postnatal Development

Neither submitted nor required

### 5.5.5. Other Toxicology Studies

None.

X X

Elizabeth Spehalski, Primary Reviewer Whitney Helms, Team Leader



Reference ID: 4344794

# 6 Clinical Pharmacology

## 6.1. Executive Summary

Lorlatinib (also known as PF-06463922) is a small molecule inhibitor of the Anaplastic Lymphoma Kinase (ALK) and c-ROS oncogene 1 (ROS1) kinase activities. Pfizer seeks approval of lorlatinib for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). The proposed lorlatinib dosing regimen is 100 mg orally once daily (QD) with or without food.

The recommended dosing regimen was selected based on safety and tolerability results of the phase 1 dose escalation portion of Study B7461001, which determined that 100 mg QD was well tolerated. The primary evidence of efficacy supporting the 100 mg QD dose is based on the overall response rate (ORR) and intracranial ORR (IC-ORR) in Study B7461001, which is 48% and 55%, respectively. An exposure-response (E-R) relationship was not observed between lorlatinib steady state exposure metrics and ORR and IC-ORR. However, the E-R analysis is mainly based on exposure at the proposed approved dosage and limited range of exposure. E-R relationships for Grade 3-4 hypercholesterolemia and for any Grade 3-4 adverse reaction were observed at exposures achieved at the recommended dosage, with higher probability of the occurrence of adverse reactions with increasing lorlatinib exposure.

**Recommendations**

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 210868. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

| Review Issue | Recommendations and Comments |
|---|---|
| **Pivotal and Supportive evidence of effectiveness** | The primary evidence of effectiveness comes from dose expansion cohorts of Study B7461001. |
| **General dosing instructions** | The proposed lorlatinib dosing regimen of 100 mg QD with or without food is effective and has a manageable safety profile.<br>• Statistically significant exposure-response relationships for Grade 3-4 hypercholesterolemia and for any Grade 3-4 adverse reactions were observed at exposures achieved at the recommended dosage, with higher probability of the occurrence of adverse reactions with increasing lorlatinib exposure. These findings support the selection of the proposed dosing regimen along with the dose modification and toxicity management strategy outlined in the label.<br>• In the Phase 2 portion of B7461001, 7.6% of patients permanently discontinued treatment due to an AEs and 23.3% of patients required dose reductions for an AEs. |



Reference ID: 4344794

| Review Issue | Recommendations and Comments |
|---|---|
| | • The most frequent adverse reactions that led to dose reductions or interruptions were edema (9%), cognitive effects (5%), hypertriglyceridemia (5%), hypercholesterolemia (4.1%), peripheral neuropathy (4.1%), increased lipase (3.1%), dyspnea (2.7%), mood effects (2.7%), pneumonia (2.4%), hallucinations (2%), and fatigue (2.0%). |
| **Dosing in patient subgroups (intrinsic and extrinsic factors)** | • No dose adjustment is needed for patients with mild hepatic impairment. The PK of lorlatinib in patients with moderate and severe hepatic impairment is unknown. See Post-Marketing Requirements and Commitments for the PMR regarding hepatic impairment.<br>• No dose adjustment is needed for patients with mild and moderate renal impairment. The PK of lorlatinib in patients with severe renal impairment is unknown. See Post-Marketing Requirements and Commitments for the PMR regarding severe renal impairment. |
| **Drug-drug interactions** | • Concomitant use of LORBRENA decreases the concentration of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of LORBRENA with CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures.<br>• Itraconazole, a strong CYP3A inhibitor, increases exposure of lorlatinib after a single dose. Avoidance of strong CYP3A inhibitors or a dose reduction to 75 mg lorlatinib is recommended based on clinical DDI data and supportive PBPK simulations.<br>• Rifampicin, a strong CYP3A inducer, decreases the exposure of lorlatinib after a single dose. In addition, 83% of healthy subjects who received multiple daily doses of rifampicin concomitantly with a single dose of lorlatinib had severe hepatotoxicity with Grade 3-4 AST/ALT elevations. A possible mechanism for hepatotoxicity is through activation of the Pregnane X Receptor (PXR) by LORBRENA and rifampin, which are both PXR agonists. The risk of hepatotoxicity with concomitant use of lorlatinib and moderate CYP3A inducers is unknown.<br>• Lorlatinib is contraindicated with strong CYP3A inducers. Avoidance of the concomitant use of moderate CYP3A inducers is recommended. See Post-Marketing Requirements and Commitments for the PMR to investigate the mechanism of the observed severe hepatotoxicity. |
| **Labeling** | Generally acceptable. The review team has specific content and formatting change recommendations. |



Reference ID: 4344794

| Review Issue | Recommendations and Comments |
|---|---|
| **Bridge between the to-be-marketed and clinical trial formulations** | The anhydrous free-base tablet formulation was used in the clinical pharmacology studies, whereas the (b) (4) tablet formation was used in Trial B7461001. In Study B7461005, a PK bridge was estimated between the (b) (4) and anhydrous free-base formulations and demonstrated bioequivalence. In Study B7461016, the anhydrous free-base tablet formulation was bioequivalent to the to-be-marketed commercially scaled formulation, which is also an anhydrous free-base tablet. |

**Post-Marketing Requirements and Commitments**

| PMR or PMC | Key Issue(s) to be Addressed | Rationale | Key Considerations for Design Features |
|---|---|---|---|
| PMR | Lorlatinib dose in patients with moderate and severe hepatic impairment | Hepatic metabolism plays a major role in the elimination of lorlatinib. The recommended dose of lorlatinib in patients with moderate to severe hepatic impairment has not been established. The clinical study will determine whether dose adjustment is needed in these specific populations. | Complete ongoing PK Study B7461009 to determine whether dose adjustment is needed in patients with moderate and severe hepatic impairment. |
| PMR | Lorlatinib dose in patients with severe renal impairment | Severe renal impairment can affect the renal clearance of lorlatinib; it may also affect the expression of hepatic drug metabolism enzymes and transporters. The recommended dose of lorlatinib has not been established for patients with severe renal impairment. The clinical study will determine whether dose adjustment is needed in this specific population. | Complete ongoing PK Study B7461010 to determine whether dose adjustment is needed in patients with severe renal impairment. |



Reference ID: 4344794

| PMR or PMC | Key Issue(s) to be Addressed | Rationale | Key Considerations for Design Features |
|---|---|---|---|
| PMR | Mechanism of hepatotoxicity observed in B7461011 with rifampicin induction | Severe hepatotoxicity was observed in subjects following multiple daily doses of rifampicin and a single co-administered dose of lorlatinib. A plausible mechanism for this hepatotoxicity may be through the synergistic activation of the PXR by lorlatinib and rifampin, which are both PXR agonists. PXR agonists are generally CYP3A inducers. Since the mechanism of the hepatotoxicity is unknown, there is a potential safety risk for severe hepatotoxicity when lorlatinib is co-administered with CYP3A inducers and PXR agonists. A preclinical study should be designed to assess this mechanism and provide labeling information regarding hepatotoxicity. | Evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR and non-PXR agonists) and non-CYP3A inducers (PXR agonists and non-PXR agonists) using a pharmacologically-relevant animal model capable of demonstrating the clinically observed hepatoxicity signal. |

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Steady-state lorlatinib maximum plasma concentration ($C_{max}$) and area under the curve (AUC) increased proportionally over the dose range of 10 mg to 200 mg orally once daily (0.1 to 2 times the recommended dose). At the recommended dosage, the mean [coefficient of variation (CV) %] $C_{max}$ was 577 ng/mL (42%) and the $AUC_{0\text{-}24h}$ was 5650 ng·h/mL (39%) in patients with cancer, and there was no accumulation.

***Absorption***

The median lorlatinib $T_{max}$ was 1.2 hours (0.5 to 4 hours) following a single oral 100 mg dose and 2 hours (0.5 to 23 hours) following 100 mg orally once daily at steady state.

The mean absolute bioavailability is 81% (90% confidence interval [CI] 75.7%, 86.2%) after oral administration compared to intravenous administration.



Reference ID: 4344794

***Distribution***

In vitro, protein binding of lorlatinib to human plasma proteins, including serum albumin and α1-acid glycoprotein, was 66% at a concentration of 2.4 µM and the blood-to-plasma ratio was 0.99. The mean (CV%) steady state volume of distribution ($V_{ss}$) was 305 L (28%) following a single intravenous 50 mg dose (0.5 times the recommended dose).

***Elimination***

The mean plasma half-life ($t_{1/2}$) of lorlatinib was 24 hours (40%) after a single oral 100 mg dose of lorlatinib. The mean oral clearance (CL/F) was 11 L/h (35%) following a single oral 100 mg dose and increased to 18 L/h (39%) at steady state, suggesting autoinduction.

Metabolism: In vitro, lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

In plasma, a benzoic acid metabolite (M8) of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib accounted for 21% of the circulating radioactivity in a human [$^{14}$C] mass balance study. The oxidative cleavage metabolite, M8, is pharmacologically inactive. Therefore, data related to M8 are not further presented in this review.

Excretion: Following a single oral 100 mg dose of radiolabeled lorlatinib, 48% of the radioactivity was recovered in urine (< 1% as unchanged) and 41% in feces (about 9% as unchanged).

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

Pfizer proposed a dosing regimen of 100 mg administered orally, daily, with or without food. The MTD was not reached in the dose escalation portion in Study B7461001 which dosage of 10 mg to 200 mg lorlatinib QD were evaluated. Grade 1/2 CNS toxicity occurred in 1 of 3 patients enrolled in the 200 mg QD cohort during the first cycle of treatment. Additionally, in the 150 and 200 mg QD cohorts, the majority of patients experienced adverse reactions resulting in temporary discontinuation and/or dose reduction. Patients did not tolerate the 75 mg or 100 mg BID dosing regimens. Lorlatinib was considered tolerable at the next highest dose, 100 mg QD, which was selected as the recommended phase 2 dose (RP2D) and was evaluated in the dose expansion portion in Study B7461001.



Reference ID: 4344794

**Therapeutic Individualization**

Specific Populations:

No clinically meaningful differences in lorlatinib pharmacokinetics were observed based on age (19 to 85 years), sex, race/ethnicity, body weight, mild to moderate renal impairment (CLcr 30 to 89 mL/min), mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin > 1.5 × ULN and any AST), or metabolizer phenotypes for CYP3A5 and CYP2C19. The effect of moderate to severe hepatic impairment or severe renal impairment on lorlatinib pharmacokinetics is unknown.

Drug-Drug Interactions:

*CYP3A Inducers:* Twelve healthy subjects received rifampicin, a strong CYP3A inducer that also activates PXR, 600 mg once daily for 8 days (Days 1 to 8) and a single oral 100 mg dose or LORBRENA on Day 8. The co-administration of rifampin with LORBRENA reduced the mean lorlatinib $AUC_{inf}$ by 85% and $C_{max}$ by 76%. Grade 2-4 increases in ALT/AST occurred within 3 days of lorlatinib dosing. Grade 4 ALT/AST elevations occurred in 50% of subjects, Grade 3 ALT/AST elevations in 33%, and Grade 2 ALT/AST elevations occurred in 8% of subjects. ALT and AST returned to within normal limits within 7 to 34 days (median 15 days). The effect of the concomitant use of moderate CYP3A inducers on lorlatinib pharmacokinetics or the risk of hepatotoxicity with the concomitant use of moderate CYP3A inducers is unknown. LORBRENA is contraindicated with strong CYP3A inducers. Discontinue strong CYP3A inducers for (b) (4) (b) (4) 3 plasma half-lives of the strong CYP3A inducers prior to initiating treatment with lorlatinib. Avoid concomitant use of LORBRENA with moderate CYP3A inducers. If concomitant use of moderate CYP3A inducers cannot be avoided, monitor ALT, AST and bilirubin as recommended.

*CYP3A Inhibitors:* Itraconazole, a strong CYP3A inhibitor, resulted in a 42% increase in $AUC_{inf}$ and a 24% increase in $C_{max}$ of a single oral 100 mg dose of lorlatinib. Concomitant use with a strong CYP3A inhibitor increased lorlatinib plasma concentrations, which may increase the incidence and severity of adverse reactions of lorlatinib. Avoid the concomitant use of LORBRENA with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce LORBRENA dose as recommended.

*CYP3A Substrates:* LORBRENA 150 mg orally once daily for 15 days decreased $AUC_{inf}$ by 64% and $C_{max}$ by 50% of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate). Concomitant use of LORBRENA decreases the concentration of CYP3A substrates, which may reduce the efficacy of these substrates. Avoid concomitant use of LORBRENA with CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures.



Reference ID: 4344794

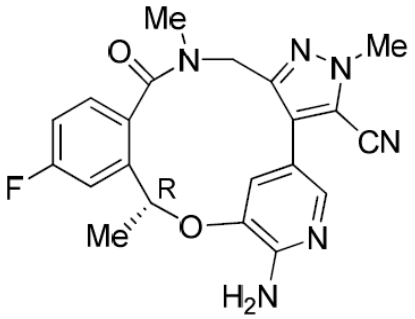
**Outstanding Issues**

The mechanism of the hepatotoxicity observed in the rifampicin drug interaction study (B7461011) will be evaluated within a PMR stated as follows: Evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR and non-PXR agonists) and non-CYP3A inducers (PXR agonist and non-PXR agonists) using a pharmacologically-relevant animal model capable of demonstrating the clinically observed hepatotoxicity signal. The study should be designed to (b) (4) provide labeling information or instructions for hepatotoxicity.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of lorlatinib ADME and clinical PK information are presented in the table below.

| **Physiochemical properties** | |
|---|---|
| **Chemical structure and molecular weight** |  <br>Chemical Structure of lorlatinib (Source: NDA210868, Figure 3.2.S.1-1)<br>Molecular weight: 406.41 g/mol<br>Log P: 2.45 at pH 9<br>LogD: 2.23 at pH 5, 2.47 at pH 7, and 2.45 at pH 9 |
| **Aqueous solubility** | Lorlatinib is a weak base with a pKa of 4.92 and exhibits pH dependent solubility characteristics.<br>**Aqueous solubility** / **Solubility (mg/mL)**<br>Water (pH 8.02) / 0.17<br>0.1N HCl (pH 2.55) / 32.38<br>0.05M Acetate buffer (pH 4.58) / 0.37<br>0.05M Phosphate buffer (pH 6.86) / 0.1<br>(Source: NDA210868, Table 3.2.S.1.3-1) |
| **Pharmacology** | |
| **Mechanism of Action** | Lorlatinib is a small molecule inhibitor of the (ALK) (IC50 values ranging from 0.65 to 65 nM for wild-type and mutated ALK) and c-ROS oncogene 1 (IC50 values ranging from 0.23 to 1.3 nM) kinase activities. |
| **Active Moieties** | Lorlatinib and its benzoic acid metabolite (PF-06895751 or M8), resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib, were observed to be the major species in plasma, accounting for 44% and 21%, respectively. PF-06895751 is pharmacologically inactive. |



Reference ID: 4344794

| | |
|---|---|
| **QT/QTc Prolongation** | In 272 patients who received lorlatinib at the recommended dose and had a baseline PR assessment in activity-estimating portion of Study B7461001, of whom 7 had a baseline PR > 200 ms, the maximum mean change from baseline for PR interval was 14.2 ms (two-sided 90% upper CI 16.2 ms). Among the 265 patients with 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 1.1% of patients.<br><br>In 275 patients who received lorlatinib at the recommended dose in the activity-estimating portion of Study B7461001, no large mean increases from baseline in the QTc interval (i.e., > 20 ms) were detected. |
| **General Information** | |
| **Bioanalysis** | Lorlatinib and its metabolite, M8, were measured using validated LC-MS/MS methods. A summary of the method validation reports is included as an appendix (19.4 OCP Appendices). |
| **Healthy Volunteers vs. Patients** | PK characteristics were similar between healthy subjects and the target populations based on population PK analyses. |
| **Drug exposure at steady state following the therapeutic dosing regimen** | Based on the results of the dose escalation trial B7461001 (b) (4)), the observed geometric mean (CV%) $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ of lorlatinib in patients treated at the 100 mg QD dosing regimen is 5121 ng·h/mL (30%) and 550.2 ng/mL (32%). |
| **Minimal effective dose or exposure** | Not determined. Lorlatinib 100 mg was the only dose regimen tested in patients with NSCLC. |
| **Maximal tolerated dose or exposure** | In Study B7461001, patients with NSCLC were treated with lorlatinib up to doses of 200 mg QD. The MTD was not reached or determined. |
| **Dose Proportionality** | Lorlatinib showed dose-proportional increase in both $C_{max}$ and AUC across the dose range of 10 to 200 mg following a single dose and multiple doses. See 19.4 OCP Appendices for detail. |
| **Accumulation** | The mean accumulation ratio ($R_{ac}$) following lorlatinib 100 mg QD was 1.07 (29%). |
| **Variability** | Following 100 mg QD dose, the inter-subject variability (CV%) of steady state $AUC_{tau}$ and $C_{max}$ was 30% and 32%, respectively. |
| **Absorption** | |
| **Bioavailability** | In Study B7461007, the absolute bioavailability of lorlatinib was 80.78% (90% CI: 75.73-86.16%) in healthy volunteers. |
| **$T_{max}$** | In Study B7461001, the median lorlatinib $T_{max}$ was 1.2 hours (0.5 to 4 hours) following a single oral 100 mg dose and 2 hours (0.5 to 23 hours) following 100 mg orally once daily at steady state in patients with NSCLC. |
| **Relative Bioavailability (oral solution)** | **$AUC_{0\text{-}inf}$ (GMR, 90% CI)**: 1.08 (1.04-1.12)<br>**$C_{max}$ (GMR, 90% CI)**: 1.30 (1.21-1.39)<br>**$T_{max}$ (hours) (range)**: Solution 1.0 (0.5-1.5); Tablet 1.5 (0.5-2.0)<br><br>In Study B7461008, the exposure of lorlatinib was not altered following a single dose of 100 mg oral solution and a single dose of 100 mg immediate-release tablet (Anhydrous free-base) in healthy volunteers under fasting conditions. |



Reference ID: 4344794

| | | | |
|---|---|---|---|
| **Food effect (Fed/fasted)** | **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
| | 1.05 (1.01-1.08) | 0.91 (0.85-0.97) | Fed<br>2.0 (1.0-6.0)<br>Fasted<br>1.5 (0.5-2.0) |
| | In Study B7461008, no clinically relevant food effect was observed on the exposure of lorlatinib following the concomitant administration of single 100 mg immediate-release tablet (anhydrous free-base) with a high-fat (approximately 50% of total caloric content of the meal) and high calorie (approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calorie totaling approximately 1000 calories) meal in healthy volunteers. | | |
| **PPI effect (Rabeprazole)** | **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
| | 1.01 (0.98-1.04) | 0.71 (0.66-0.76) | PPI<br>2.0 (1.5-6.0)<br>Fasted<br>1.5 (0.5-2.0) |
| | In Study B7461008, no clinically relevant PPI effect was observed on the exposure of lorlatinib following the concomitant administration of single 100 mg immediate-release tablet (anhydrous free-base) with repeated doses of rabeprazole in healthy volunteers under fasting condition. | | |
| **Relative Bioavailability (Different formulations)** | In Study B7461005, the relative bioavailability of the old tablet formulation (b) (4) ) was compared to the two extemporaneous tablet formulations (anhydrous free base and (b) (4) (b) (4) *vs. anhydrous free base formulations* | | |
| | **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
| | 0.95 (0.90-1.00) | 0.85 (0.78-0.93) | Anhydrous free base<br>1.5 (1.0-3.0)<br>(b) (4)<br>1.5 (1.0-3.0) |
| | The exposure of lorlatinib was not altered following a single dose of 100 mg anhydrous free base tablet and a single dose of 100 mg (b) (4) tablet in healthy volunteers under fasting condition. | | |
| | (b) (4) *vs. anhydrous free base formulations* | | |
| | **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
| | 0.99 (0.94-1.04) | 1.01 (0.92-1.09) | Anhydrous free base<br>1.5 (1.0-2.0)<br>(b) (4)<br>1.5 (1.0-3.0) |
| | The exposure of lorlatinib was not altered following a single dose of 100 mg (b) (4) tablet and a single dose of 100 mg (b) (4) tablet in healthy volunteers under fasting condition. | | |

| | |
|---|---|
| **Relative Bioavailability (commercial formulation)** | In Study B7461016, the relative bioavailability of the anhydrous free base tablet from clinical batches was compared to the commercial scaled anhydrous free base tablets (25, (b) (4) 100 mg).<br><br>*100 mg commercial (4×25 mg) vs. 100 mg clinical (4×25 mg) anhydrous free base formulations* |

| **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
|---|---|---|
| 1.01 (0.98-1.05) | 1.07 (0.96-1.18) | Commercial<br>1.0 (1.0-4.0)<br>Clinical<br>1.5 (1.0-2.0) |

The exposure of lorlatinib was not altered following a single dose of 4×25 mg commercial anhydrous free base tablets and a single dose of 4×25 mg clinical anhydrous free base tablets in healthy volunteers under fasting condition.

*100 mg commercial (b) (4) vs. 100 mg clinical (4×25 mg) anhydrous free base formulations*

| **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
|---|---|---|
| 1.01 (0.98-1.05) | 1.01 (0.91-1.12) | Commercial<br>1.0 (1.0-4.0)<br>Clinical<br>1.5 (1.0-2.0) |

The exposure of lorlatinib was not altered following a single dose of (b) (4) mg commercial anhydrous free base tablets and a single dose of 4×25 mg clinical anhydrous free base tablets in healthy volunteers under fasting condition.

*100 mg commercial (1×100 mg) vs. 100 mg clinical (4×25 mg) anhydrous free base formulations*

| **$AUC_{0\text{-}inf}$ (GMR, 90% CI)** | **$C_{max}$ (GMR, 90% CI)** | **$T_{max}$ (hours) (range)** |
|---|---|---|
| 1.05 (1.01-1.09) | 1.07 (0.97-1.18) | Commercial<br>1.0 (1.0-4.0)<br>Clinical<br>1.5 (1.0-2.0) |

The exposure of lorlatinib was not altered following a single dose of 1×100 mg commercial anhydrous free base tablets and a single dose of 4×25 mg clinical anhydrous free base tablets in healthy volunteers under fasting condition.

| | |
|---|---|
| **Distribution** | |
| **Volume of Distribution** | Based on non-compartmental analysis in Study B7461007, the geometric mean volume of distribution ($V_d$) was 305 L (28%) following a single intravenous 50 mg dose. |
| **Plasma Protein Binding** | In vitro, protein binding of lorlatinib to human plasma proteins, including serum albumin and α1-acid glycoprotein, was 66% at a concentration of 2.4 µM. |
| **Blood to Plasma Ratio** | The mean blood-to-plasma ratio was 0.99 for lorlatinib. |
| **Elimination** | |
| **Half-life** | In Study B7461007, the mean plasma half-life ($t_{1/2}$) was 27 hours (19%) following a single intravenous 50 mg dose. In Study B7461001, the mean apparent plasma half-life ($t_{1/2}$) of lorlatinib was 24 hours (40%) after a single oral 100 mg dose of lorlatinib. |
| **Clearance** | In Study B7461001, the mean oral clearance (CL/F) was 11 L/h (35%) following a single oral 100 mg dose and increased to 18 L/h (39%) at steady state, suggesting autoinduction. |
| ***Metabolism*** | |

| | |
|---|---|
| **Primary metabolic pathway(s)** | In vitro, lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3 to 3 lorlatinib metabolites, M6, M1a, and M2a. CYP3A4 (100%) is responsible for M6 formation. CYP3A4 (34-60%), CYP3A5 (40%), CYP2C8 (0-24%), CYP2C19 (0-35%), and (0-8%) are responsible for M2a formation. UGT1A4 (90%) and UGT1A3 (10%) are responsible for M1a formation. In plasma, M6, M1a, and M2a represent 4.5%, 8.0%, and 2.3%, respectively, and are not consider the major lorlatinib metabolite. M8, resulting from cleavage of the amide and aromatic ether bonds of lorlatinib, is the major lorlatinib metabolite representing 21% in plasma, but is inactive. The pathway leading to the M8 formation is unknown. |
| **Inhibitor/Inducer** | In vitro, lorlatinib activates PXR ($EC_{50}$ value of 2.85 µM and $E_{max}$ value of 13.8) and CAR ($EC_{50}$ and $E_{max}$ values were not estimated due to atypical dose-response curves).<br>Lorlatinib induces CYP3A4 mRNA (>40-fold), which is comparable to rifampin (45-fold). Lorlatinib induces CYP3A4 activity, but is not comparable to rifampin. In human hepatocytes, lorlatinib appears to have time-dependent inhibition characteristics ($K_I$ value of 7.92 µM and $k_{inact}$ value of 0.081 $min^{-1}$) at higher lorlatinib concentrations. Lorlatinib also induces CYP2B6 mRNA and activity.<br><br>Lorlatinib and M8 do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Lorlatinib inhibits CYP3A, but does not induce CYP1A2, CYP2B6, and CYP3A. M8 does not inhibit CYP3A, and does not induce CYP1A2, CYP2B6, and CYP3A.<br><br>Lorlatinib and M8 do not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.<br><br>Lorlatinib inhibits P-glycoprotein (P-gp), organic cation transporter (OCT)1, organic anion transporter (OAT)3, multidrug and toxin extrusion (MATE)1, and intestinal breast cancer resistance protein (BCRP). Lorlatinib does not inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OCT2, MATE2K, and systemic BCRP. M8 does not inhibit for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K. |
| ***Excretion*** | |
| **Primary excretion pathways (% dose) ±SD** | In a human mass balance Study B7461004 with mean total radioactivity recovery of 89%, radioactivity recoveries in feces and urine were 41% (9% unchanged lorlatinib) and 48% (<1% unchanged lorlatinib), respectively. |

### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes. Pfizer stated that in Study B7461001, the MTD was not reached in the dose escalation portion. Patients were treated at a dosage of up to 200 mg QD lorlatinib. However, 1 of 3 patients experienced Grade 1 or 2 CNS toxicity during the first cycle of treatment. However, in the 150 and 200 mg QD cohorts, the majority of patients experienced adverse reactions resulting in temporary discontinuations and/or dose reductions. Patients also did not tolerate the 75 mg or 100 mg BID dosing regimens. As a result, lorlatinib was considered tolerable at the next highest dose, 100 mg QD, which was the recommended phase 2 dose (RP2D) evaluated in the dose expansion portions in Study B7461001.

The efficacy results from Study (B7461001), along with the clinical pharmacology program collectively provide adequate evidence for the effectiveness of lorlatinib in patients with patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer



Reference ID: 4344794

(NSCLC) who have progressed on alectinib as first-line therapy or on crizotinib and at least one other ALK kinase inhibitor (see Section 8.1.2 for more details).

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

A significant E-R relationship for efficacy was not identified based on data from Study B761001. Significantly positive E-R relationships between lorlatinib exposure and grade ≥ 3 hypercholesterolemia and grade ≥ 3 TEAE were identified. Given the significant efficacy results and acceptable safety profile observed in subgroup of patients enrolled Study B761001 in which only a single dosing regimen of 100 mg QD was evaluated, an alternative lower dose for the general population, based on the E-R relationships for efficacy and safety, cannot be justified. Therefore, the proposed dosing regimen of 100 mg QD is acceptable for the general population.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

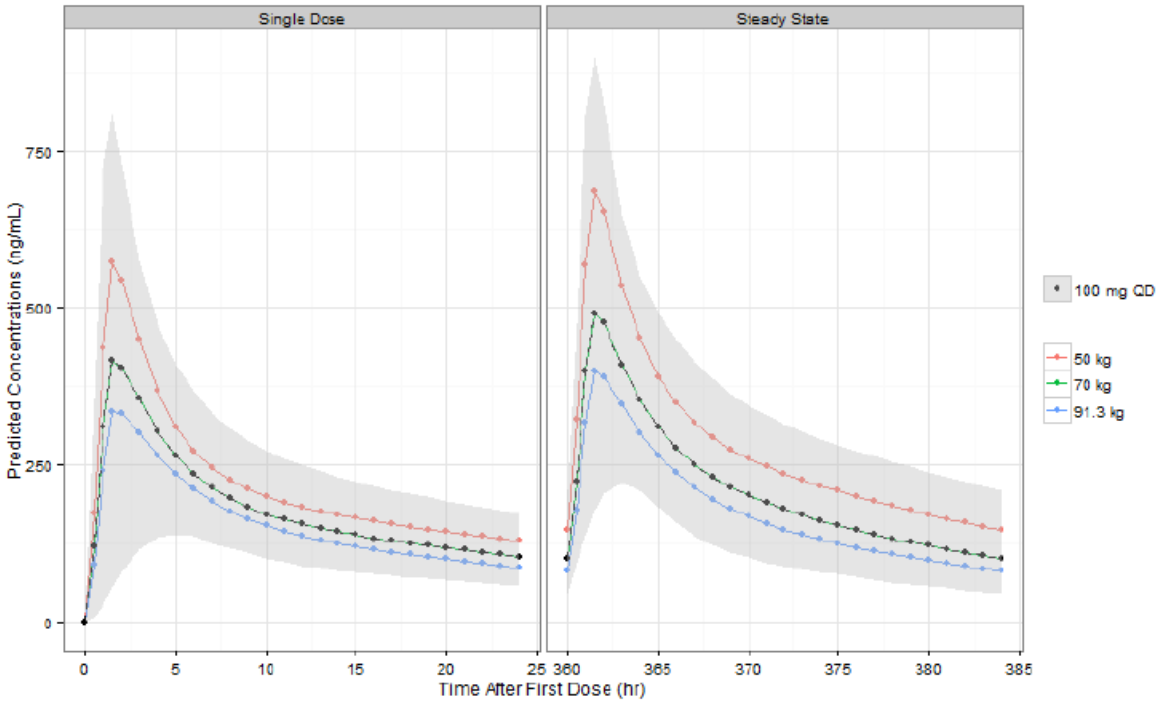
Population PK analysis suggests that intrinsic patient factors, including age (19 to 85 years), sex, race/ethnicity, mild to moderate renal impairment (CLcr 30 to 89 mL/min), mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin > 1.5 × ULN and any AST), have no clinically meaningful effect on lorlatinib pharmacokinetics. Therefore, no dose adjustment is needed in these specific populations.

Baseline body weight was identified as covariate for clearance (CL) and volume of distribution (V2). Modeling results showed that compared to a subject of 70 kg (50th percentile of the analysis population), the CL of a subject of 50 kg (10th percentile of the analysis population) was reduced by 22.3% and the CL of a subject of 91.3 kg (90th percentile of the analysis population) was increased by 22%. This effect was determined not to be clinically important. Figure 5 shows the median predicted lorlatinib concentration time profiles for a low and high BWT individual (10th and 90th percentile of the analysis population, respectively) are contained within the 95% prediction interval (PI) of the typical individual with a body weight of 70kg, after single dose and at steady state. Therefore, dose adjustment based on body weight is not warranted.



Reference ID: 4344794

**Figure 5 Simulated Body Weight Effect on Lorlatinib Pharmacokinetics**




ePharmacology artifact ID RA13520697.
The shaded gray ribbon represents the 95% prediction interval for a typical 70 kg White male with no PPI use, a baseline albumin of 4 mg/dL, and dosed at 100 mg. 50 and 91.3 kg are the $10^{th}$ and $90^{th}$ percentile baseline body weights, of pooled healthy volunteers and subjects. All covariates other than weight are set at the typical

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Figure 13*

Baseline standardized creatinine clearance (normalized by body weight) was selected as a statistically significant covariate on CL in the final popPK model. However, the effect was not considered clinically meaningful. Table 13 shows the individual steady state CL estimates from the popPK model summarized by renal impairment groups. The range of individual estimates of lorlatinib clearance for patients with mild and moderate renal impairment overlaps with the range for the patients with normal renal function, though there is a trend of decreasing median and median individual lorlatinib CL estimates with worsening renal impairment. Therefore, dose adjustment for patients with mild or moderate renal impairment is not warranted.



Reference ID: 4344794

**Table 13 Individual Lorlatinib Steady State CL Estimates Summarized by Renal Impairment Groups**

| Baseline Renal Impairment | N | Baseline CrCL (mL/min) Median (Range) | Lorlatinib Steady State Clearance (L/hr) Median (Range) | Lorlatinib Steady State Clearance (L/hr) Mean ± SD |
|---|---|---|---|---|
| Normal | 133 | 115.24 (90.23-195.18) | 15.17 (10.15-23.09) | 15.21 ± 2.52 |
| Mild | 104 | 74.23 (60.53-89.98) | 12.70 (9.33-18.25) | 12.90 ± 1.80 |
| Moderate | 41 | 53.59 (31.58-59.93) | 11.61 (8.60-15.77) | 11.50 ± 1.66 |

*Pharmacogenomics*

ALK Kinase Domain mutations

*Exploratory analysis of ALK kinase domain mutations in Study B7461001*: Tumor tissue (archival and/or de novo biopsy) and peripheral blood samples were collected at screening/baseline and at the end of treatment (EOT) for analysis of ALK kinase domain mutations potentially associated with resistance to ALK inhibitors in tumor and plasma circulating nucleic acid (CNA). Blood samples for CNA analysis were also collected at Cycle 3 Day 1 in Phase 2 (according to Pfizer, only a limited number of EOT samples were collected at the time of the data cut off and the analysis for both tumor tissue and CNA will be updated at a later date). Per protocol, archival tumor samples were to be collected from all patients. De novo biopsies were optional at screening in Phase 1 and at the EOT in Phase 1 and Phase 2 portions and were mandatory at screening (unless when posed a safety risk) in the Phase 2 portion of Study B761001. Tumor samples were analyzed by NGS. Plasma CNA samples were analyzed by digital polymerase chain reaction (PCR) BEAMing technology in Phase 1 (predefined set of 11 to 17 mutations) and by NGS or by PCR in Phase 2.

Out of the 215 patients included in the FDA efficacy dataset, 203 (94.4%) had tumor samples (Phase 1 (N=14) and Phase 2 (N=189)) and 204 (94.8%) had plasma samples (Phase 1 (N=13) and Phase 2 (N=191)) portions of Study B761001 available for analysis. Of these, 33/203 (16.2%) tumor samples and 6/204 (<1%) plasma samples were not analyzable and circulating tumor DNA was not detected in 39/204 (19.1%) plasma samples.

Tumor: Out of 170 analyzed tumor samples (approximately 90% de novo biopsies), 23 unique ALK mutations were detected either alone or in combination in samples from 40 patients (Phase 1 (N=1) and Phase 2 (N=39)) portions of Study B761001. The most frequent mutations included G1202R, G1269A, L1196M, F1174C, F1174L and E1129V. Twenty-five patients (62.5%) harboring at least 1 ALK mutation experienced a BOR of PR (N=24) or CR (N=1) with DOR ranging from 1.38+ to 14.4+ months; 8 of these patients had tumor samples positive for



Reference ID: 4344794

G1202R. Out of 30 evaluable patients with CNS metastases at baseline, 15 patients experienced an intracranial BOR of PR (N=3) or CR (N=12) with DOR ranging from 1.41+ to 14.52 months. ALK mutations appeared to be more frequent among patients who received > 1 prior ALK TKI. Listing of ALK mutations detected in tumor tissue is provided in Table 14.

**Table 14 ICR-assessed best overall response in previously treated ALK-positive NSCLC patients with ALK kinase domain mutations detected in tumor tissue (N=40)**

| *ALK Mutations | ICR-BOR | | DOR (months) | |
|---|---|---|---|---|
| | Overall | Intracranial | Overall | Intracranial |
| *EXP-2: Prior crizotinib only* | | | | |
| G1269A; G1128A | PR | CR | 6.90+ | 6.90+ |
| F1174L; F1174V | PR | SD | 2.83+ | NA |
| C1156Y | PR | CR | 2.79+ | 2.79+ |
| D1160H | PD | PD | NA | NA |
| G1269A | PR | SD | 4.14+ | NA |
| L1196M | PR | CR | 6.96+ | 6.93+ |
| L1196M | PR | PR | 5.55+ | 5.55+ |
| *EXP-3: Prior crizotinib and 1-2 lines of chemotherapy or prior ALK inhibitor (not crizotinib) ± prior chemotherapy* | | | | |
| I1171S | PR | NE | 4.17 | NA |
| L1198F | NE | NE | NA | NA |
| E1129V | PR | CR | 1.38+ | 1.41+ |
| G1202R | CR | NE | 6.96+ | NA |
| G1202R | PD | PD | NA | NA |
| G1269A | PR | NE | 6.93+ | NA |
| I1171N | PR | SD | 4.17 | NA |
| L1196M | PD | PD | NA | NA |
| *EXP-4: Two prior ALK inhibitors ± chemotherapy* | | | | |
| G1202R; F1174C | PR | CR | 9.78+ | 11.10+ |
| C1156Y; G1202del; V1180L | PD | PD | NA | NA |
| G1202R; F1174L | PR | CR | 6.08 | 6.04 |
| I1171T; E1161D | PR | PR | 2.3 | 2.56 |
| G1202R | PR | CR | 2.76 | 2.76 |
| G1202R | PR | PR | 14.4+ | 14.52 |
| G1202R | PR | SD | 6.93 | NA |
| R1113Q | SD | SD | NA | NA |
| T1151K | SD | SD | NA | NA |
| I1171T | SD | SD | NA | NA |
| I1171N | PR | NE | 1.44+ | NA |
| *EXP-5: Three prior ALK inhibitors ± chemotherapy* | | | | |
| G1269A; F1174C; D1203N; P1213H | SD | SD | NA | NA |
| G1202R; F1174L; L1122V | SD | SD | NA | NA |
| F1174L; D1203N; R1192P | PR | NE | 4.14+ | NA |
| G1202R; E1129V | PR | CR | 7.16+ | 7.16+ |
| G1202R; F1174C | SD | NE | NA | NA |
| G1202R | SD | CR | NA | 8.31 |
| G1202R | PD | NE | NA | NA |

| | | | | |
|---|---|---|---|---|
| G1202R | PR | NE | 4.20+ | NA |
| G1202R | PR | SD | 5.55+ | NA |
| E1129V | PR | CR | 14.4+ | 12.38+ |
| E1129V | SD | SD | NA | NA |
| G1269A | PR | CR | 7.16+ | 7.16+ |
| L1196M | PR | CR | 7.09+ | 7.09+ |
| *Phase 1* | | | | |
| F1174C | PD | NE | NA | NA |

Source: Study B7461001 Interim Clinical Study Report and efficacy datasets; BOR: best overall response; DOR: duration of response. *Not all detected ALK mutations may be associated with primary or acquired resistance to ALK inhibitors; + denotes ongoing patients; ICR: independent central review; NA: not applicable; NE: not evaluable; PD: progressive disease; PR: partial response; CR: complete response; SD: stable disease

Plasma CNA: Of 159 plasma samples that were analyzed, 26 unique ALK mutations were detected either alone or in combination with other mutations in 49 samples (Phase 1 (4) and Phase 2 (45) of Study B761001); Twenty-nine patients harboring at least 1 ALK mutation experienced a BOR of PR with DOR ranging from 1.45+ to 14.49+ months. Out of 33 evaluable patients with CNS metastases at baseline, 18 patients experienced an intracranial BOR of PR (N=8) or CR (N=10) with DOR ranging from 2.56 to 14.52 months. The most frequent ALK mutations included G1202R, G1269A, L1196M, F1174C, F1174L (as in the tumor analysis), C1156Y and I1171N. There was a significant discordance between the blood-based and the tumor-based assay results obtained with samples from the same patients. Also, six ALK mutations, N1335K, E1210Q, P1329S, F1245C, E1210K and T1151M were detected in CNA but not in tumor samples, while 3 ALK mutations E1161K, T1151K and G1202del were detected in tumor but not in CNA samples.

*Reviewer comment: In agreement with non-clinical data, responses (PR or CR) were observed among patients with different ALK kinase domain mutations as detected in tumors and/or CNA samples, including G1202R which is associated with resistance to first- and second-generation ALK inhibitors. The potential coverage of this and other recalcitrant ALK resistance mutations by lorlatinib may be an important consideration in the context of sequential ALK inhibitors.*

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Food-Drug Interactions

The effect of food on lorlatinib PK was evaluated in a single 100 mg dose, randomized, 4 period, 4 treatment, 4 sequence, crossover study (B7461008) with a washout period of at least 10 days in 24 healthy subjects who received the 100 mg anhydrous free-base formulation. The fasting condition was defined as a 10 hour overnight fast. A breakfast meal with high-fat (approximately 50% of total caloric content of the meal) and high calorie (approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calorie totaling approximately 1000 calories) content was consistent with the recommendations in the FDA Guidance for Industry



Reference ID: 4344794

for Food-Effect Bioavailability and Fed Bioequivalence Studies. PK samples were collected from pre-dose to 96 hours post-dose. Administration of a single 100 mg dose of lorlatinib with a high-fat, high-calorie meal in healthy subjects resulted in no change in AUC and $C_{max}$ and increased $t_{max}$ by a median of 0.5 hours as compared to the fasted condition (Table 15). A preliminary food effect study in 6 NSCLC patients administered the 100 mg (b) (4) tablet formulation (B7461001) showed similar results; a high-fat meal resulted in no change in AUC and $C_{max}$. These results support the labeling recommendation of administering lorlatinib with or without food.

**Table 15 PK Parameters of a single dose of lorlatinib after a high-fat meal as compared with fasted state**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | High-Fat Meal | Fasted State | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 8779 (24) | 8712 (24) | 1.05 (1.01 – 1.08) |
| $AUC_{0\text{-}96h}$ (ng·hr/mL) | 8262 (22) | 8191 (21) | 1.05 (1.01 – 1.08) |
| $C_{max}$ (ng/mL) | 488.5 (26) | 547.8 (20) | 0.91 (0.85 – 0.97) |

Source: B7461008 Final Study Report; Table 12, 13; Page 48

Proton-pump inhibitor (PPI) Drug Interactions

The effect of PPI on lorlatinib PK was evaluated in a single 100 mg dose, randomized, 4 period, 4 treatment, 4 sequence, crossover study (B7461008) with a washout period of at least 10 days in 24 healthy subjects who received the 100 mg anhydrous free-base formulation. The fasting condition was defined as a 10 hour overnight fast. In the period of concomitant medications, 20 mg QD dosing of Pariet (rabeprazole) as 2× 10 mg tablets in the evening from Day 1 through Day 5 and a 100 mg single dose of lorlatinib administered in the fasted state as 4 × 25 mg tablets on the morning of Day 6. PK samples were adequately collected from pre-dose to 96 hours post-dose. Administration of a single 100 mg dose of lorlatinib with rabeprazole in healthy subjects resulted in no change in AUC, 29% decrease in $C_{max}$ and increased $t_{max}$ by a median of 0.5 hours as compared to fasted condition (Table 16). These results suggest that lorlatinib can be taken concomitantly with PPIs without adjusting the lorlatinib dose.

**Table 16 PK Parameters of a single dose of lorlatinib after concomitant with rabeprazole as compared with fasted state**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | Rabeprazole (PPI) | Fasted State | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 8629 (24) | 8712 (24) | 1.01 (0.97 – 1.04) |
| $AUC_{0\text{-}96h}$ (ng·hr/mL) | 8011 (21) | 8191 (21) | 1.00 (0.96 – 1.03) |
| $C_{max}$ (ng/mL) | 383 (28) | 547.8 (20) | 0.71 (0.66 – 0.77) |

Source: B7461008 Final Study Report; Table 12, 13; Page 48



Reference ID: 4344794

Relative Bioavailability (Solution)

The relative bioavailability of the lorlatinib oral solution and anhydrous free-base tablets was evaluated in a single 100 mg dose, randomized, 4 period, 4 treatment, 4 sequence, crossover study (B7461008) with a washout period of at least 10 days in 24 healthy subjects. The fasting condition was defined as a 10 hour overnight fast. PK samples were adequately collected from pre-dose to 96 hours post-dose. Administration of a single 100 mg dose of oral solution resulted in no change in AUC, 1.29-fold slight increase in $C_{max}$ and decreased $t_{max}$ by a median of 0.5 hours as compared to tablet formulation (Table 17). These results show that there is no clinically relevant difference between the bioavailability of the lorlatinib oral solution and tablet formulations.

**Table 17 PK Parameters of a single dose of lorlatinib oral solution vs. anhydrous free-base tablets under fasting condition**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | Oral solution | Anhydrous free-base tablet | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 9359 (24) | 8712 (24) | 1.08 (1.04 – 1.12) |
| $AUC_{0\text{-}96h}$ (ng·hr/mL) | 8789 (21) | 8191 (21) | 1.08 (1.04 – 1.11) |
| $C_{max}$ (ng/mL) | 704.7 (22) | 547.8 (20) | 1.29 (1.21 – 1.39) |

Source: B7461008 Final Study Report; Table 12, 13; Page 48

Relative Bioavailability (Different formulations)

The relative bioavailability of 2 extemporaneous tablet formulations (anhydrous free base and (b) (4)) of lorlatinib relative to the reference (b) (4) immediate release tablet formulation was evaluated in a randomized, 3 period, 6 sequence, crossover study (B7461005) with a washout period of at least 7 days in 18 healthy subjects. The treatment was administered after an overnight fast of at least 10 hours. No food was allowed for at least 4 hours post-dose. PK samples were adequately collected from pre-dose to 120 hours post-dose. Administration of a single 100 mg dose of lorlatinib anhydrous free base tablet resulted in no change in AUC and slight decrease in $C_{max}$ (15%) as compared to lorlatinib (b) (4) tablet (Table 18). These results show that there is no clinically relevant difference between lorlatinib anhydrous free base tablet and lorlatinib (b) (4) tablet formulations.



Reference ID: 4344794

**Table 18 PK Parameters of a single dose of lorlatinib anhydrous free base tablet vs. lorlatinib (b) (4) tablet**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | Anhydrous free base | (b) (4) | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 7629 (20) | 7937 (22) | 0.95 (0.90 – 1.00) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 7433 (19) | 7752 (22) | 0.95 (0.90 – 1.00) |
| $C_{max}$ (ng/mL) | 491.7 (33) | 566.5 (30 | 0.85 (0.87 – 0.93) |

Source: B7461005 Final Study Report; Table 12, 13; Page 41

Administration of a single 100 mg dose of lorlatinib (b) (4) tablet resulted in no change in AUC and $C_{max}$ as compared to lorlatinib (b) (4) tablet (Table 19). These results show that there is no clinically relevant difference between lorlatinib (b) (4) tablet and lorlatinib (b) (4) tablet formulations.

**Table 19 PK Parameters of a single dose of lorlatinib (b) (4) tablet vs. lorlatinib (b) (4) tablet**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | (b) (4) | (b) (4) | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 8027 (18) | 7937 (22) | 0.99 (0.94 – 1.04) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 7831 (17) | 7752 (22) | 0.99 (0.94 – 1.04) |
| $C_{max}$ (ng/mL) | 578.7 (23) | 566.5 (30) | 1.01 (0.93 – 1.09) |

Source: B7461005 Final Study Report; Table 12, 13; Page 41

Relative Bioavailability (Commercial formulation)

The relative bioavailability of the commercial tablet formulation of lorlatinib relative to the reference anhydrous free base immediate release tablet formulation was evaluated in a randomized, 4-period, 4 treatment, 4 sequence, crossover study (B7461016) with a washout period of at least 10 days in 16 healthy subjects. The treatment was administered after an overnight fast of at least 10 hours. PK samples were collected from pre-dose to 120 hours post-dose. Administration of a single 100 mg dose of the commercial lorlatinib tablet resulted in no change in AUC and $C_{max}$ as compared to lorlatinib clinical anhydrous free base tablet (Table 20 and Table 21). These results show that there is no clinically relevant difference between commercial and clinical tablets of lorlatinib.



Reference ID: 4344794

**Table 20 PK Parameters of a single dose of lorlatinib commercial tablet vs. lorlatinib clinical anhydrous free base tablet**

| Exposure Parameters | Geometric Mean (%CV) | | | |
|---|---|---|---|---|
| | Clinical 4 × 25 mg Tablets | Commercial 4 × 25 mg Tablets | Commercial (b) (4) Tablets | Commercial 1 × 100 mg Tablets |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 7683 (18) | 7769 (21) | 7770 (18) | 8054 (19) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 7482 (18) | 7526 (21) | 7539 (18) | 7785 (19) |
| $C_{max}$ (ng/mL) | 532.0 (25) | 567.3 (28) | 539.8 (27) | 567.3 (34) |

Source: B7461016 Final Study Report; Table 11; Page 46

**Table 21 Geometric mean ratios of a single dose of lorlatinib commercial tablet vs. lorlatinib clinical anhydrous free base tablet**

| Exposure Parameters | Geometric Mean Ratio (90% CI) | | |
|---|---|---|---|
| | Commercial 4 × 25 mg Tablets | Commercial (b) (4) mg Tablets | Commercial 1 × 100 mg Tablets |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 1.01 (0.98 – 1.05) | 1.01 (0.98 – 1.05) | 1.05 (1.01 – 1.09) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 1.01 (0.97 – 1.04) | 1.01 (0.97 – 1.04) | 1.04 (1.01 – 1.08) |
| $C_{max}$ (ng/mL) | 1.07 (0.96 – 1.18) | 1.01 (0.92 – 1.12) | 1.07 (0.97 – 1.18) |

Source: B7461016 Final Study Report; Table 12; Page 46

Drug Interactions as perpetrator (CYP3A probe)

The effect of lorlatinib to mediated inhibition or induction of CYP3A on the PK of the CYP3A probe substrate, midazolam, was evaluated in Study B7461001. There were 2 lorlatinib dose cohorts (25 and 150 mg QD) with 3 NSCLC patients in each cohort. Patients were treated with a single 2 mg oral dose of midazolam on Day -7 and again concurrently with lorlatinib QD (Cycle 1 Day 1 to 15) on Cycle 1 Day 15. PK samples were adequately collected from pre-dose to 96 hours post-dose. Administration of repeated 150 mg QD doses of lorlatinib appeared to show decrease in AUC (64%) and $C_{max}$ (50%) of midazolam (Table 22 and Table 23). The cohort with a single 2 mg dose of midazolam and 25 mg lorlatinib QD showed similar results; decrease in AUC (63%) and $C_{max}$ (40%). These results show that concomitant use of lorlatinib may decrease the concentration of CYP3A substrates, which may reduce the efficacy of these drugs. The results support the labeling recommendation to avoid concomitant use of lorlatinib with CYP3A substrates.



Reference ID: 4344794

**Table 22 PK Parameters [Geometric Mean (%CV)] of a single dose of midazolam before and after repeated doses of lorlatinib**

| Exposure Parameters | Day -7 Lead In (Alone) | | Cycle 1 Day 15 (with Lorlatinib) | |
|---|---|---|---|---|
| | 25 mg QD Lorlatinib | 150 mg QD Lorlatinib | 25 mg QD Lorlatinib | 150 mg QD Lorlatinib |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 54.53 (43) | (42.2, 46.8)[a] | 21.32 (18) | 16.09 (29) |
| $AUC_{0\text{-}24h}$ (ng·hr/mL) | 51.3 (47) | 36.49 (20) | 20.43 (18) | 14.44 (25) |
| $C_{max}$ (ng/mL) | 16.06 (42) | 11.56 (48) | 9.697 (40) | 5.734 (43) |
| CL/F (L/hr) | 36.68 (43) | (42.7, 47.4)[a] | 93.86 (18) | 124.2 (29) |
| $t_{1/2}$ (hr) | 4.62 (42) | (2.35, 7.89)[a] | 3.343 (61) | 5.257 (96) |

[a] n = 2; poor PK characterization of terminal phase in one subject with $AUC_{extrap}$ % > 20%.
Source: B7461001 Final Study Report; Table 14.4.4.3.1.1; Pages 3517-3520

**Table 23 Geometric mean ratios of a single dose of midazolam before and after repeated doses of lorlatinib**

| Exposure Parameters | Geometric Mean Ratio (90% CI) | |
|---|---|---|
| | 25 mg QD Lorlatinib | 150 mg QD Lorlatinib |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 0.37 (0.27 – 0.49) | NA |
| $AUC_{0\text{-}24h}$ (ng·hr/mL) | 0.39 (0.27 – 0.58) | NA |
| $C_{max}$ (ng/mL) | 0.60 (0.35 – 1.04) | NA |

NA (not available) due to number of subjects < 3 for comparison.

Drug Interactions with lorlatinib as a substrate (CYP3A inhibition)

The effect of itraconazole, a strong CYP3A inhibitor, on lorlatinib PK was evaluated a 2-period, fixed-sequence, crossover study in 16 healthy subjects. The study consisted of 6 treatments: single doses of lorlatinib 50 mg (n = 2), 75 mg (n = 2) or 100 mg (n = 12) in Period 1 and lorlatinib 50 mg, 75 mg or 100 mg in combination with multiple dose itraconazole (200 mg QD Days 1 to 11) in Day 5 of Period 2 after a washout period of at least 10 days between lorlatinib doses in Periods 1 and 2. PK samples were collected from pre-dose to 168 hours post-dose. The treatment was administered after an overnight fast of at least 10 hours. Administration of repeated 200 mg QD doses of itraconazole resulted in significant increases in the AUC (1.42-fold) and $C_{max}$ (1.24-fold) of lorlatinib (Table 24). Similar increases in exposure were also seen in the cohorts with 50 and 75 mg lorlatinib.



Reference ID: 4344794

**Table 24 PK Parameters of a single dose of lorlatinib with or without concomitant itraconazole**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | 100 mg lorlatinib dose | 100 mg lorlatinib dose + 200 mg itraconazole QD | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 7338 (37) | 10400 (31) | 1.42 (1.29 – 1.56) |
| $AUC_{0\text{-}168h}$ (ng·hr/mL) | 7119 (36) | 10180 (30) | 1.43 (1.30 – 1.57) |
| $C_{max}$ (ng/mL) | 413.6 (24) | 514.4 (24) | 1.24 (1.10 – 1.40) |
| CL/F (L/hr) | 13.6 (37) | 9.6 (31) | |
| $t_{1/2}$ (hr) | 23.1 (4.9) | 29.8 (6.3) | |

Source: B7461012 Final Study Report; Table 15; Page 65

However, given that lorlatinib has, time-dependent PK, possibly due to an auto-induction effect on CYP3A, the effect of itraconazole on the steady state PK of lorlatinib is unknown. Itraconazole is metabolized by CYP3A, and therefore autoinduction of CYP3A by lorlatinib at steady state may affect itraconazole exposure and therefore its inhibitory effect on CYP3A. Thus, the reviewer developed a PBPK model to evaluate the effect of concomitant itraconazole and lorlatinib, both dosed to steady state, on the PK of lorlatinib at steady state. The PBPK simulations predicted a 30% increase in steady state lorlatinib exposure after multiple doses of 100 mg QD lorlatinib and 200 mg QD itraconazole. However, the steady state exposure of lorlatinib with concurrent use of 75 mg QD lorlatinib and 200 mg QD itraconazole is predicted to be equivalent to that of 100 mg QD lorlatinib alone (refer to Table 102 in the 19.4 OCP Appendices). Both the clinical PK data and the PBPK simulations therefore support the labeling recommendation that the concomitant use of strong CYP3A inhibitors and lorlatinib should be avoided. If the concomitant use of a strong CYP3A inhibitor cannot be avoided, the starting dose of lorlatinib should be reduced from 100 mg orally once daily to 75 mg orally once daily. Refer to the PBPK review in the 19.4 OCP Appendices for details.

Drug Interactions as victim (CYP3A induction)

The effect of rifampicin, a strong CYP3A inducer, on lorlatinib PK was evaluated with a 2-period, fixed-sequence, crossover study in 12 healthy subjects. PK samples were collected from pre-dose to 120 hours post-dose. The treatment was administered after an overnight fast of at least 10 hours. A single 100 mg dose of lorlatinib was administered on Day 1 and PK was collected over the next 6 days. Subsequently, subjects were scheduled to receive 600 mg of rifampin daily from Day 6 to 17 with a single 100 mg dose of lorlatinib administered concomitantly with rifampicin on Day 13. Overall, the PK results showed that lorlatinib exposure ($AUC_{0\text{-}inf}$) was reduced by over 85% and $C_{max}$ was reduced by 76% in presence of rifampicin (Table 25). However, following the single concomitant administration of lorlatinib and rifampicin on Day 13, the study treatment was terminated on Day 14 due to severe hepatotoxicity (≥ Grade 2) in 10 of 12 subjects, and no further rifampicin was administered. Subjects were followed until hepatotoxicity resolved.

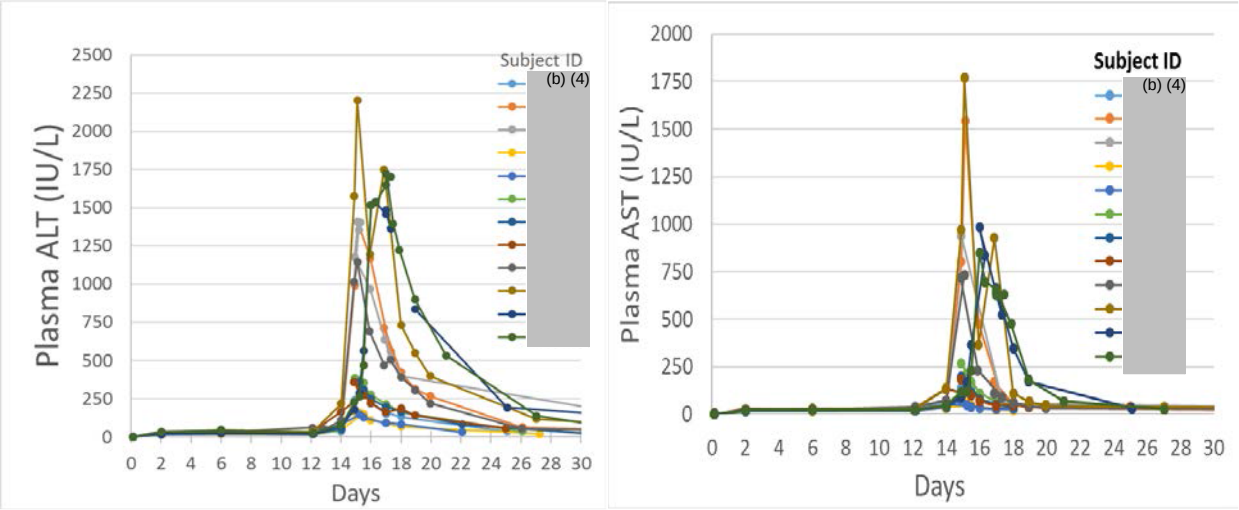
**Table 25 PK Parameters of lorlatinib with or without concomitant rifampicin**

| Exposure Parameters | Geometric Mean (%CV) | | |
|---|---|---|---|
| | 100 mg lorlatinib dose | 100 mg lorlatinib dose + 600 mg rifampicin QD | Geometric Mean Ratio (90% CI) |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 8766 (19) | 1299 (30) | 0.15 (0.13 – 0.17) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 8597 (19) | 1200 (32) | 0.14 (0.12 – 0.16) |
| $C_{max}$ (ng/mL) | 621.4 (26) | 148.4 (31) | 0.24 (0.22 – 0.26) |
| CL/F (L/hr) | 11.39 (20) | 76.91 (30) | |
| $t_{1/2}$ (hr) | 21.22 (19) | 10.16 (24) | |

Source: B7461011 Final Study Report; Tables 14 and 15; Page 53

As shown in Figure 6, when the first dose of lorlatinib was administered (Day 1) and when rifampicin was given on subsequent days up to Day 12, no elevation of ALT was observed. However, after receiving a single concomitant dose of lorlatinib with rifampicin on Day 13, significant ALT elevation occurred starting on Day 14 in all 12 healthy subjects. Similar increases in AST (Figure 6) and Gamma GT (not shown) were also observed.

**Figure 6 Time course of the increase in plasma ALT and AST liver over the treatment period of all 12 healthy subjects.**




Source: B7461011 Final Study Report; Figure 16.2.8.1.4; Pages 155 and 156

Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single concomitant dose of lorlatinib with rifampicin. Grade 4 ALT or AST elevations occurred in 50% of subjects, Grade 3 ALT or AST elevation occurred in 33% and Grade 2 ALT or AST elevations occurred in 8%. ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); the median time to recovery was 18 days in subjects with Grade 3-4 ALT or AST elevations and 7 days in subjects with Grade 2 ALT or AST elevations. Six subjects had elevations reaching 20 times the upper limit normal ULN and 5 of these subjects were

hospitalized as a result; elevated liver test returned to normal levels at a median of 15 days (7 to 34 days) after the single dose of lorlatinib.

In Study B7461011, three patients received concomitant treatment with a moderate CYP3A inducer, modafinil, during the lorlatinib treatment period. Modafinil is a low PXR activator, as compared to rifampicin. The routine hepatic safety laboratory measurements that occurred during the period of concomitant lorlatinib and modafinil treatment did not show significant AST or ALT elevation (<50 IU/L) from baseline.

Currently, the mechanism of this hepatotoxicity is unknown. In Study B7461011, the change in exposure of the main lorlatinib metabolite, M8 (PF-6895751), was minimal with an approximate 26% decrease in $AUC_{inf}$ 1 and a 1.3-fold increase in $C_{max}$ in the presence of rifampicin compared to lorlatinib dosed alone (Table 26). Hence the liver enzyme increases observed in the study were not due to substantially increased levels of lorlatinib or M8.

**Table 26 PK Parameters of M8 (main lorlatinib metabolite) with or without concomitant rifampicin**

| Exposure Parameters | Geometric Mean (%CV) | |
|---|---|---|
| | 100 mg lorlatinib dose | 100 mg lorlatinib dose + 600 mg rifampicin QD |
| $AUC_{0\text{-}inf}$ (ng·hr/mL) | 4453 (38) | 3291 (60) |
| $AUC_{0\text{-}120h}$ (ng·hr/mL) | 4105 (33) | 3169 (60) |
| $C_{max}$ (ng/mL) | 59.02 (29) | 76.45 (38) |
| $t_{1/2}$ (hr) | 29.14 | 18.43 |

Source: B7461011 Final Study Report; Table 16; Page 57

Likewise rifampicin steady state plasma exposure (AUC and $C_{max}$) in the presence of lorlatinib in Day 9 (Table 27) of the study were within the range of exposures reported in the literature for 600 mg QD rifampicin administered as a single agent [Burger et al. 2006, Ruslami et al. 2007, Rifampicin (Rifadin®) Package Insert]. Similarly, plasma levels of the desacetyl metabolite of rifampin in Day 9 were comparable to values reported in the literature. This indicates the absence of a substantive direct effect of lorlatinib on the plasma PK of rifampin and its metabolite.



Reference ID: 4344794

**Table 27 PK Parameters of rifampicin and deacetyl rifampicin on day 9 of the concomitant rifampicin and lorlatinib**

| Exposure Parameters | Geometric Mean (%CV) on Day 9 | |
|---|---|---|
| | Rifampicin | Deacetyl Rifampicin |
| $AUC_{0-24}$ (ng·hr/mL) | 50970 (51) | 4750 (72) |
| $AUC_{0-120h}$ (ng·hr/mL) | 52490 (53) | 4275 (85) |
| $C_{max}$ (ng/mL) | 11460 (34) | 796.8 (49) |
| $t_{1/2}$ (hr) | 2.72 | 3.45 |

Source: B7461011 Final Study Report; Table 17 and 18; Pages 59 and 60

To further investigate the observed hepatotoxicity in Study B7461011, data on the metabolic profiling of pooled B7461011 samples, in vivo evaluation of lorlatinib and rifampicin in rats, and an in vitro evaluation of lorlatinib and rifampicin in human hepatocytes were evaluated. The metabolic profiling conducted with the clinical pooled samples (plasma collected over 24 hours) collected in Study B7461011 did not identify any new or previously unidentified metabolite of lorlatinib that was specifically generated by rifampicin induction (Table 28), suggesting that the observed increases in ALT or AST in Study B7461011 cannot be ascribed to a previously unidentified lorlatinib metabolite.

**Table 28 Qualitative assessment of the level of lorlatinib (PF-06463922) and its metabolites on Day 1 (Period 1) and Day 9 (Period 2)**

| Drug substance | m/z | Group 1 (Moderate AST elevations) | | Group 2 (High AST elevations) | |
|---|---|---|---|---|---|
| | | Period 1 | Period 2 | Period 1 | Period 2 |
| PF-06463922 | 407 | ++++ | +++ | ++++ | +++ |
| M1a | 583 | ++ | ++ | ++ | + |
| M2a | 393 | ++ | ++ | ++ | + |
| M2b | 393 | + | + | + | ND |
| M3a | 569 | ND | ND | + | + |
| M6 | 423 | ++ | ++ | ++ | ++ |
| M8 | 167 | ++ | ++ | ++ | ++ |

m/z = Mass-to-charge ratio; ND = Not detected; + = trace abundance; ++ = low abundance; +++ = moderate abundance; ++++ = high abundance.

Note: Group 1 represents individuals where ALT or AST level was 600 IU/L or less. Group 2 represents individuals where ALT or AST level was over 600 IU/L.
Source: Preclinical Study Report 113346; Table 8-1; Page 8

Likewise, the in vitro metabolism studies of [$^{14}$C]lorlatinib in un-induced and rifampin-induced human hepatocytes indicated that the metabolism of lorlatinib was increased with rifampicin induction. However, no metabolite specific to rifampicin induction was observed (Table 29).



Reference ID: 4344794

**Table 29 Levels of lorlatinib (PF-06463922) and its metabolites with or out without rifampicin induction in human hepatocytes**

| Drug substance | m/z | [$^{14}$C](carbonyl)-PF-06463922 | | [$^{14}$C](pyrazole)-PF-06463922 | |
|---|---|---|---|---|---|
| | | Un-induced | Rifampin-induced | Un-induced | Rifampin-induced |
| PF-06463922 | 407 | 49.4 | 25.1 | 52.4 | 24.6 |
| M1a | 583 | 24.2 | 24.9 | 32.6 | 36.2 |
| M2a | 393 | 4.2 | 2.4 | 2.7 | 2.3 |
| M2b | 393 | 0.3 | 0.9 | 0.1 | 0.4 |
| M4a | 599 | 3.1 | 9.3 | 1.8 | 6.1 |
| M12c | 599 | ND | 9.5 | 2.5 | 7.5 |
| M12b | 599 | ND | ND | 2.3 | 3.4 |
| M6 | 423 | 0.7 | 0.7 | 0.8 | 2.7 |
| U[a] | | 9.0 | 13.9 | 4.7 | 16.9 |

m/z = mass to charge ratio; ND = Not detected.
a. Total unidentified radiochemical peaks.

Source: Preclinical Study Report 015951; Table 8.1; Page 10

In a 2-week investigative rat study, at pharmacologic doses of lorlatinib (6 mg/kg, a dose that produces similar plasma exposures as in humans at steady state 100 mg QD), concomitant administration of lorlatinib and rifampicin did not result in hepatotoxicity. However, this preclinical model to assess the DDI may be confounded since rifampicin is a weak PXR activator in rats as compared to humans. Overall, the data suggest that the hepatotoxicity appear not to be due to a direct PK interaction.

However, a PD interaction of lorlatinib and rifampicin leading to the hepatotoxicity cannot be ruled out. PXR activation may be a possible mechanism associated to hepatotoxicity, which is based on the following observations.

1. First, lorlatinib and rifampicin are a strong PXR agonists in humans. Lorlatinib tested over a concentration range of 0.01-100 µM activated hPXR in a dose-dependent fashion with $EC_{50}$ and $E_{max}$ concentrations (2.85 µM and 14-fold, respectively) comparable to those for rifampicin. PXR is a nuclear receptor that regulates transporters and enzymes. It is also responsible for the regulation of cholesterol and bile acids homeostasis as well as lipogenesis in the liver. Chronic activation of PXR alters cholesterol and lipids, which can lead to hepatic steatosis and elevated AST and ALT levels.
2. Severe hepatotoxicity has also been seen clinically in drug interaction studies with rifampicin and ritonavir. Although the mechanism of this toxicity is unknown, ritonavir is also known to be a strong PXR agonist and induces CYP3A mRNA but inhibits CYP3A activity.
3. Hepatotoxicity and alterations of lipid metabolism were observed in rats and dogs given supratherapeutic doses of lorlatinib (studies submitted in current NDA).



Reference ID: 4344794

4. Alterations in lipid metabolism (cholesterol and/or triglycerides) were seen in rats and dogs, which were also observed in humans in Study B7461011, and these changes are consistent with PXR activation by lorlatinib.
5. Clinical PK data in the rifampicin DDI trial suggest that the hepatotoxicity is not due to a direct PK interaction between rifampicin and lorlatinib.

The available data support increased PXR activation by as a possible mechanism for the hepatotoxicity. A PMR will investigate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR and non-PXR agonists) and non-CYP3A inducers (PXR agonists and non-PXR agonist) using a relevant animal model. Results from the PMR may be used to provide labelling information or instructions regarding hepatoxicity.

Overall, due to the potential risk of severe hepatotoxicity, concomitant use of strong CYP3A inducers (including rifampicin) are contraindicated. There may be circumstances in which patients may need to receive concomitant moderate CYP3A inducers. This poses a safety risk for severe hepatotoxicity since moderate CYP3A inducers may also be PXR agonists, Therefore, FDA recommends that the concomitant use of moderate CYP3A inducers should be avoided. If these drugs must be used together, additional safety monitoring should be implemented.

To reduce the risk of hepatotoxicity for patients who were previously treated with strong CYP3A inducers, discontinue the strong CYP3A inducer for 3 plasma elimination half-lives of the strong CYP3A inducers prior to initiating lorlatinib.

In vitro studies (Metabolism)
CYP enzymes: In vitro studies indicate that lorlatinib is a time-dependent inhibitor ($K_I$ value of 7.92 µM and $k_{inact}$ value of 0.081 $min^{-1}$) as well as an inducer of CYP3A ($EC_{50}$ value of 0.288 µM and $E_{max}$ value of 5.99) in human hepatocytes (Table 30) and that it activates PXR ($EC_{50}$ value of 2.85 µM and $E_{max}$ value of 13.8). Lorlatinib induces CYP2B6 (Table 30) and activates the human constitutive androstane receptor (CAR). However, the induction of CYP2B6 is much lower than phenobarbital (positive control), suggesting that the induction may not be clinically relevant. Lorlatinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, but may potentially inhibit CYP3A4 (Table 31). Lorlatinib major circulating metabolite, M8, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, and CYP2D6 (Table 32). M8 does not induce CYP1A2, CYP2B6, and CYP3A (data not shown; in Preclinical Study Report 104203).



Reference ID: 4344794

**Table 30 Lorlatinib induction of mRNA and activity level (fold change) of CYP enzymes from 1 human hepatocyte lot (Lot HC7-4)**

| | CYP1A2 | | CYP2B6 | | CYP3A4 | |
|---|---|---|---|---|---|---|
| Lorlatinib (µM) | mRNA | Activity | mRNA | Activity | mRNA | Activity |
| 0.1% DMSO | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 0.03 | 0.986 | 1.02 | 0.774 | 1.09 | 2.23 | 1.41 |
| 0.1 | 0.881 | 0.954 | 1.05 | 1.45 | 8.31 | 2.36 |
| 0.3 | 0.598 | 0.765 | 1.60 | 1.9 | 26.3 | 4.88 |
| 0.5 | 0.661 | 0.983 | 3.17 | 2.55 | 34.9 | 6.28 |
| 1 | 0.669 | 0.920 | 4.82 | 3.62 | 33.9 | 6.04 |
| 3 | 0.648 | 0.934 | 4.94 | 5.07 | 33.5 | 3.77 |
| 10 | 0.970 | 1.05 | 7.16 | 6.84 | 49.7 | 2.05 |
| 30 | 1.33 | 1.23 | 10.5 | 7.26 | 65.1 | 1.86 |
| 50 | 1.61 | 1.17 | 16.5 | 7.21 | 128 | 1.86 |
| 75 | 1.62 | 0.698 | 27.1 | 4.03 | 271 | 1.48 |
| 125 | 1.96 | 0.182 | 43.7 | 0.705 | 536 | 1.01 |
| Positive inducer[a] | 33.0 | 16.2 | 12.5 | 11.0 | 45.9 | 7.68 |

[a] omeprazole 30 µM for CYP1A2, phenobarbital 750 µM for CYP2B6, rifampicin 10 µM for CYP3A4

Source: Preclinical Study Report 125344; Tables 7.3, 7.4, and 7.5; Pages 17-19

**Table 31 Calculated R1 values for lorlatinib inhibition of CYP activities in Human Liver Microsomes**

| Model | CYP | $K_i$[b] (µM) | [I] (µM) | 1+ [I]/$K_i$ | Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|
| | | | Systemic[c] | | |
| Basic ($R_1$) | CYP1A2 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2B6 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C8 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C9 | 22 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C19 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2D6 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Testosterone | 11.5 | 1.42 | >1.1[d] | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Midazolam | 5.0 | 1.42 | >1.1[d] | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Nifidipine | 11.0 | 1.42 | >1.1[d] | 1+ [I]/$K_i$ >1.1 |
| | | | Intestinal[e] | | |
| Basic ($R_1$) | CYP3A4/5 Testosterone | 11.5 | 984 | >11[d] | 1+ [I]/$K_i$ >11 |
| | CYP3A4/5 Midazolam | 5.0 | 984 | >11[d] | 1+ [I]/$K_i$ >11 |
| | CYP3A4/5 Nifidipine | 11.0 | 984 | >11[d] | 1+ [I]/$K_i$ >11 |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-H; Page 50

**Table 32 Calculated R1 values for M8 or PF-06895751 inhibition of CYP activities in Human Liver Microsomes**

| Model | CYP | $K_i$[b] (μM) | [I][c] (μM) | 1+ [I]/$K_i$ | Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|
| Basic ($R_1$) | CYP1A2 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2B6 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C8 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C9 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2C19 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP2D6 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Testosterone | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Midazolam | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | CYP3A4/5 Nifedipine | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-J; Page 52

UGT enzymes: Lorlatinib and M8 do not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 (Table 33 and Table 34).

**Table 33 Calculated R1 values for lorlatinib inhibition of UGT activities in Human Liver Microsomes**

| Model | UGT | $K_i$[b] (μM) | [I][c] (μM) | 1+ [I]/$K_i$ | Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|
| Basic ($R_1$) Without 2% BSA | 1A1 | 23 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A4 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A6 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A9 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B7 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B15 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| Basic ($R_1$) With 2% BSA | 1A1 | 18.5 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A4 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A6 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A9 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B7 | 32 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B15 | >50 | 1.42 | <1.1 | 1+ [I]/$K_i$ >1.1 |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-L; Page 54

**Table 34 Calculated R1 values for M8 or PF-06895751 inhibition of UGT activities in Human Liver Microsomes**

| Model | UGT | $K_i$[b] (μM) | [I][c] (μM) | 1+ [I]/$K_i$ | Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|
| Basic ($R_1$) Without 2% BSA | 1A1 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A4 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A6 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A9 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B7 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B15 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| Basic ($R_1$) With 2% BSA | 1A1 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A4 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A6 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 1A9 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B7 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |
| | 2B15 | >50 | 1.05 | <1.1 | 1+ [I]/$K_i$ >1.1 |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-N; Page 56

Transporters: Lorlatinib inhibits P-glycoprotein (P-gp), organic cation transporter (OCT)1, organic anion transporter (OAT)3, multidrug and toxin extrusion (MATE)1, and intestinal breast cancer resistance protein (BCRP) (Table 35). Lorlatinib does not inhibit organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OCT2, MATE2K, and systemic BCRP. M8 does not inhibit for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K (Table 36).

**Table 35 Calculated R1 and R2 values for lorlatinib inhibition of transporter activities**

| | Transporter | $[I]_1$[b] (μM) | $[I]_{1,u}$[c] (μM) | $[I]_2$[d] (μM) | IC50 (μM) | [I]/IC50 | [I]/IC50 Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|---|---|
| Systemic | P-gp | 1.42 | -- | -- | 2.99 | >0.1[e] | $[I]_1/IC_{50} \geq 0.1$ |
| | BCRP | 1.42 | -- | -- | >94.9 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| | OATP1B1 | 1.42 | -- | -- | 32.6 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| | OATP1B3 | 1.42 | -- | -- | >100 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| | OCT1[f] | 1.42 | -- | -- | 4.21 | >0.1[e,g] | $[I]_1/IC_{50} \geq 0.1$ |
| | OCT2 | -- | 0.483 | -- | >50 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| | OAT1 | -- | 0.483 | -- | >50 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| | OAT3 | -- | 0.483 | -- | 2.72 | >0.1[e] | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| | MATE1[h] | | 0.483 | -- | 3.71 | >0.1[e] | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| | MATE2K[h] | | 0.483 | -- | >50 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| Intestinal | P-gp | -- | -- | 984 | 2.99 | >10[e] | $[I]_2/IC_{50} \geq 10$ |
| | BCRP | -- | -- | 984 | >94.9 | >10[e] | $[I]_2/IC_{50} \geq 10$ |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-D; Page 46

**Table 36 Calculated R1 and R2 values for M8 or PF-06895751 inhibition of transporter activities**

| Transporter | $[I]_1$[b] (μM) | $[I]_{1,u}$[c] (μM) | IC50 (μM) | [I]/IC50 | [I]/IC50 Threshold Cutoff For Potential DDI |
|---|---|---|---|---|---|
| P-gp | 1.05 | -- | >268 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| BCRP | 1.05 | -- | >268 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| OATP1B1 | 1.05 | -- | >268 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| OATP1B3 | 1.05 | -- | >268 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| OCT1[d] | 1.05 | -- | >50 | <0.1 | $[I]_1/IC_{50} \geq 0.1$ |
| OCT2 | -- | 0.217 | >100 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| OAT1 | -- | 0.217 | >100 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| OAT3 | -- | 0.217 | >100 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| MATE1[e] | -- | 0.217 | >50 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |
| MATE2K[e] | -- | 0.217 | >50 | <0.1 | $[I]_{1,u}/IC_{50} \geq 0.1$ |

Source: 2.6.5 Pharmacokinetics Tabulated Summary; Table 2.6.5.15-E; Page 47

X X

Adeniyi Oluseyi, Ph.D.
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Reference ID: 4344794

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# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

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Table 11 below lists the clinical trials included in the NDA submission. The evidence to support the clinical efficacy of lorlatinib in patients with metastatic ALK-positive NSCLC who progressed on one or more prior ALK inhibitors was obtained in Study B7461001. The primary efficacy population includes patients in both the dose escalation and dose expansion phases of Study B7461001 who received lorlatinib 100 mg daily and who received prior treatment with one or more ALK inhibitor with or without prior chemotherapy.

The primary safety data used to characterize the safety profile of lorlatinib in patients with metastatic ALK-positive NSCLC are also from Study B7461001. The primary safety population includes all patients enrolled on Study B7461001 who received at least one dose of lorlatinib at any dose level and schedule.

**Table 37 Listing of clinical trials relevant to this NDA**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | No. of Centers and Countries |
|---|---|---|---|---|---|---|
| ***Pivotal Study to Support Efficacy and Safety*** | | | | | | |
| B7461001 | Open-label, multicenter, dose finding (phase I) and activity estimating study in adult patients with ALK or ROS1-positive NSCLC | Dose finding: various<br><br>Cohort expansion by biomarker status (ALK or ROS1) and line of therapy: 100 mg orally daily | Dose finding: RP2D<br><br>Dose expansion: Primary: ORR and CNS ORR by IRC<br>Key secondary: PFS, OS, DOR, PRO of global QOL | Dose finding ALK-positive patients: 27.8 months (95% CI 20, 32)<br><br>Dose expansion cohorts EXP2:5: 6.9 months (95% CI 6.9, 7.2) | Dose finding: 54<br><br>Dose expansion: 275<br><br>Japanese LIC: 3 | 47 centers in 14 countries worldwide |

RP2D-recommended phase II dose, ORR-overall response rate, CNS-central nervous system, IRC-independent review committee, PFS-progression-free survival, OS-overall survival, DOR-duration of response, PRO-patient reported outcomes, QOL-quality of life



Reference ID: 4344794

## 7.2. Review Strategy

The FDA statistical and clinical NDA review team consisted of one primary clinical reviewer, Dr. Nicole Drezner, and one primary statistical reviewer, Dr. Jonathon Vallejo.

The NDA submission contained data from one non-randomized, multi-cohort, dose-finding and activity-estimating trial, Study B7461001, entitled, "Phase 1/2 Study of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients with Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations" to support the indication. The review of efficacy is based on Study B7461001, including the Clinical Study Report (CSR), case report forms (CRFs), statistical analysis plan (SAP), datasets, and Statistical Analysis System (SAS) program.

The clinical review of safety evaluated the primary safety population of all enrolled patients in Study B7461001, defined as all patients who received at least one dose of study drug and consisting of 332 patients. The population of 295 patients across the dose-finding and dose expansion portions of the study who received at least one dose of study drug at the RP2D of 100 mg was also evaluated in the safety analyses. The review of safety considered the CSR, SAS datasets, CRFs, and case narratives.

**Data Sources**

The electronic submission was received on December 5, 2017, and is located in the following network path: Application 210868 - Sequence 0001 - 0001 (1) 12/05/2017 ORIG-1 /Multiple Categories/Subcategories. The submission included clinical study protocols, the SAP, CSRs, SAS transport datasets in legacy format, and SAS codes for the NDA submission.

Using the primary data from Study B7461001, the clinical reviewer confirmed Pfizer's safety analyses by conducting analyses of primary data using MedDRA Adverse Event Diagnosis Service (MAED) and JMP programs. Methods used to perform analyses for specific issues (i.e. detailed assessment of a particular safety issue) are explained in the pertinent section of the review.

**Data and Analysis Quality**

The statistical reviewer was able to replicate Pfizer's primary analysis and other submitted efficacy results based on the submitted data. The report and analysis plan were provided in the NDA submission. The reviewer was able to reproduce Pfizer's analysis datasets from the raw datasets and to evaluate documentation of data quality control/assurance procedures.



Reference ID: 4344794

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Study B761001

**Trial Design**

Study B761001 was a global, two-part, multi-cohort, open-label, non-randomized, multicenter trial of lorlatinib in 334 patients with advanced ALK-positive or advanced ROS1-positive NSCLC. In Study B761001, patients with asymptomatic brain metastases were allowed in all cohorts. Part 1 was designed as a dose-finding study in patients with advanced ALK- or ROS1-positive NSCLC who were either treatment-naïve or had progressed after any prior ALK TKI, with or without prior chemotherapy; patients received lorlatinib once or twice daily with a total cumulative daily dose range of 10 mg – 200 mg; planned enrollment for Part 1 was 12-36 patients. Part 2 was designed as a dose expansion study with 30-80 patients planned for enrollment into one of six cohorts selected by line of therapy, type of prior therapy, and ALK/ROS1 status. A Japanese patient only lead-in cohort (LIC) was also enrolled concurrently with Part 2 enrollment.

Additionally, in the dose-finding portion of Study B7461001 (Part 1), a midazolam DDI study was performed to evaluate the potential of lorlatinib to inhibit or induce CYP3A using midazolam as a CYP3A probe substrate, with the midazolam interaction planned to be evaluated at 3-4 dose levels starting at the second lorlatinib dose level (25 mg). At least 3 evaluable patients per cohort were assessed for the effect of repeat lorlatinib administration on the pharmacokinetics of midazolam; these patients received a single 2 mg oral dose of midazolam on Day -7 and a second single 2 mg oral dose of midazolam concurrently with lorlatinib on Cycle 1 Day 15.

The effect of food on the pharmacokinetics of lorlatinib was evaluated in a food effect sub-study in approximately 6 patients enrolled in the dose finding portion of the study. The first half of the patients to participate in this sub-study were tested under fed followed by fasted conditions, and the next half were tested under fasted followed by fed conditions. Lorlatinib was administered in the morning under either fed or fasted conditions on Day -7 and on Cycle 1 Day 1, respectively. After Cycle 1 Day 1 in the food effect cohort only, lorlatinib was administered with food regardless of the condition under which the patient was last dosed. No trial drug was administered during the interval between Day -7 and Day 1 of the first cycle.

To evaluate the potential interaction of lorlatinib on drugs that are metabolized via pathways that include CYP2B6, CYP2C9, P-gp, and select UGT isoforms, a drug-drug interaction study was conducted in approximately 30 ALK-positive NSCLC patients (6 evaluable patients for each drug probe). Additionally, an evaluation of the effects of lorlatinib on the PR interval was conducted via continuous Holter telemetry comparing the patient's pre-drug



Reference ID: 4344794

baseline values with observations of PR interval changes associated with exposure of lorlatinib following a single dose and again at steady state.

Patients participating in the DDI and Holter monitoring study were instructed that when possible, breakfast, lunch and dinner should be consumed at approximately at the same times on days of Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14). On Day -2 and Cycle 1 Day 15, the probe substrate should be administered in the fasted state, when possible, (no food at least 2 hours before through 2 hours after probe substrate dosing). On days of continuous Holter monitoring (Day -1, Cycle 1 Day 1 and Cycle 1 Day 14), patients should be advised to not undergo any exercise. On Holter monitoring days, substances that could alter ECG readings (such as caffeine-containing products, alcohol and tobacco containing products) should be avoided. The study schema for the DDI and Holter Monitoring Study is reproduced in Figure 6, below.

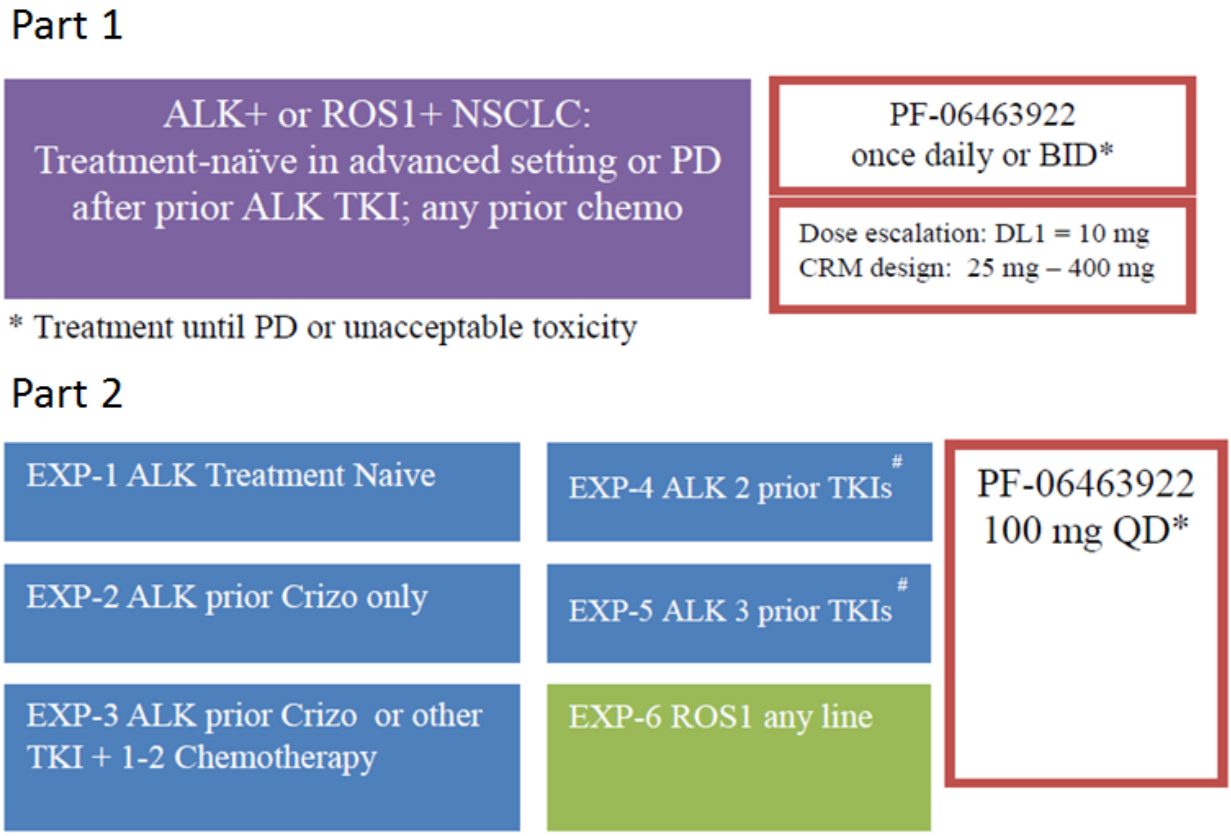
*Reviewer's comment: The DDI and Holter monitoring part of the trial are ongoing at the time of this review and will be analyzed in a separate clinical study report (CSR).*

The study schemas presented in Figure 7 below, abstracted from the protocol, summarize the design and cohort enrollment criteria for Parts 1, 2, and the Japan LIC.



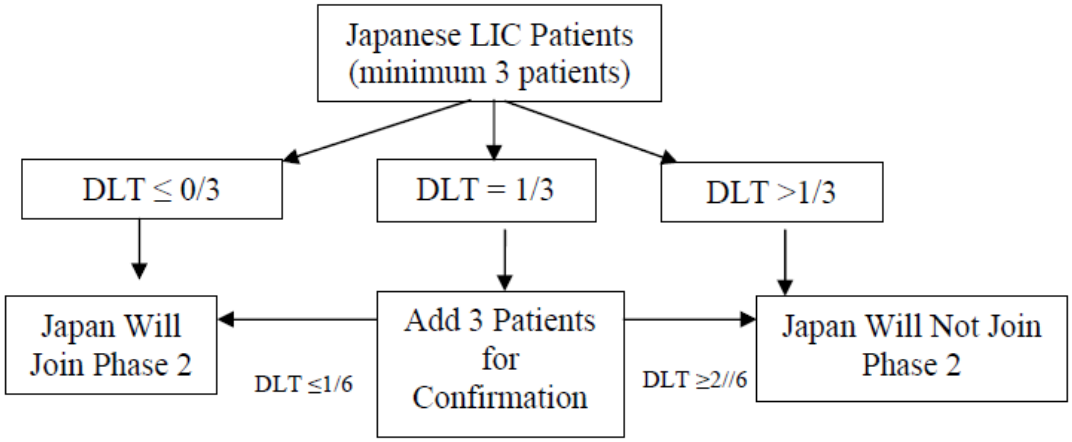
Reference ID: 4344794

**Figure 7: Study Schemas of B761001**

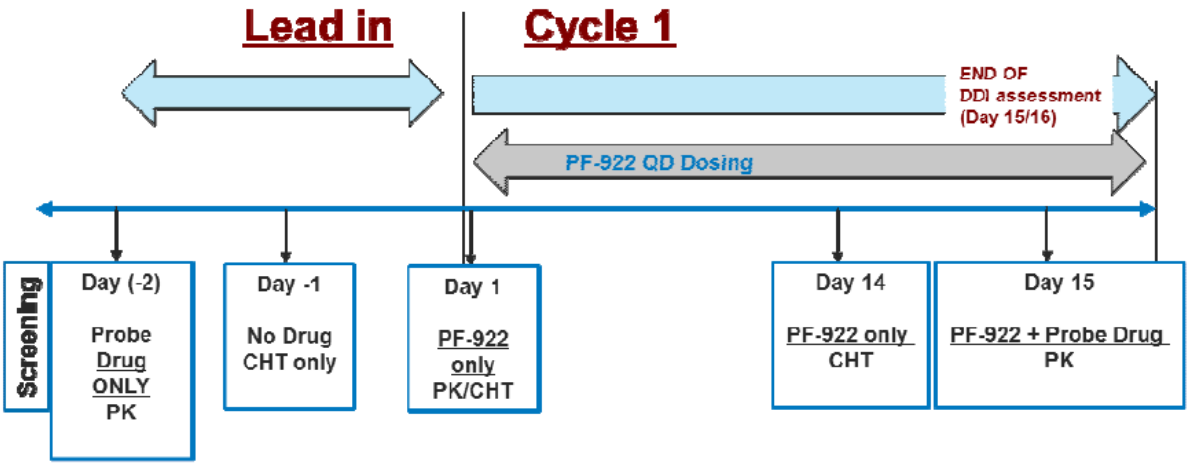



# = Prior 2 or 3 TKIs refers to line of therapy. For example, if the same TKI were given twice, that would be considered as 2 prior lines of treatment. Any number of lines of prior chemotherapy were allowed.
PD: Progressive disease

*Reviewer comment: Patients in EXP-3 who had received prior treatment with an ALK TKI other than crizotinib may have received any number of prior chemotherapy regimens in any disease setting, including no prior chemotherapy.*




DDI and Holter Monitoring Study




The primary objective of Part 1 was to estimate the maximum tolerated dose (MTD) for lorlatinib in patients with advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic CNS metastases.

The primary objective of the Japanese patient only lead-in cohort (LIC) was to evaluate the safety and tolerability of lorlatinib in Japanese patients before starting enrollment of Japanese patients in Part 2. Japan participated in Part 2 after completion of LIC.

The primary objective of Part 2 was to evaluate overall and intracranial anti-tumor activity of

lorlatinib in patients with advanced ALK-positive NSCLC and advanced ROS1-positive NSCLC.

Key inclusion criteria

- Histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, American Joint Committee on Cancer [AJCC] v7.0) that carries an ALK rearrangement, as determined by the FDA-approved fluorescence in situ hybridization (FISH) assay (Abbott Molecular Inc.) or by immunohistochemistry (IHC) (Ventana, Inc.), or a ROS1 rearrangement as determined by FISH or real time polymerase chain reaction (RT-PCR) or next generation sequencing (NGS) via a local diagnostic test. A central laboratory confirmation by a Sponsor-selected, validated test will retrospectively determine final ROS1 status. All patients (ALK- and ROS1-positive) must have archival tissue sample available and collected prior to enrollment.
- Disease status requirements:
    - Part 1: ALK-positive NSCLC patients who are either treatment naïve in the advanced setting or have had disease progression after at least one prior ALK TKI. ROS1-positive NSCLC patients must either be treatment naïve in the advanced setting or have had disease progression after at least one prior ROS1 TKI.
    - Part 2: ALK-positive NSCLC must either be or have had:
        - Treatment-naïve (i.e. no prior chemotherapy in the metastatic setting and no prior ALK TKI allowed) [EXP-1]
        - Disease progression after crizotinib only. No prior chemotherapy is allowed in the metastatic setting [EXP-2]
        - Disease progression after crizotinib and 1 or 2 prior chemotherapy regimens in the metastatic setting [EXP-3]
        - Disease progression after 1 prior ALK TKI other than crizotinib. Patients may have had any number of prior chemotherapy regimens in any disease setting [EXP-3]
        - Disease progression after 2 prior ALK TKIs. Patients may have had any number of prior chemotherapy regimens in any disease setting [EXP-4]
        - Disease progression after 3 prior ALK TKIs. Patients may have had any number of prior chemotherapy regimens in any disease setting [EXP-5]
    - Part 2: ROS1-positive NSCLC patients may be:
        - Treatment naïve (i.e. no prior chemotherapy in the metastatic disease setting and no prior ROS1 TKI) or have received any number of prior therapies [EXP-6]
    - DDI and Holter Monitoring Study patients may be:
        - ALK- or ROS1-positive NSCLC patients who meet the above disease status requirements for EXP-2 through EXP-6
- Tumor requirements:
    - Part 1: At least one measurable extracranial target lesion according to RECIST v1.1. Patients with asymptomatic CNS metastases (including patients asymptomatic due to stable or decreasing doses of steroids within 2 weeks prior



Reference ID: 4344794

to study entry) are eligible. Brain metastases may be newly diagnosed or present as progressive disease after surgery, whole brain radiotherapy, or stereotactic radiotherapy. Patients with asymptomatic radiologically suspected leptomeningeal disease (LM) or carcinomatous meningitis (CM) and negative cerebrospinal fluid (CSF) are eligible for Part 1.
    - Part 2: At least one measurable extracranial target lesion according to RECIST v1.1. Patients with asymptomatic CNS metastases (including patients asymptomatic due to stable or decreasing doses of steroids within 2 weeks prior to study entry) are eligible. Brain metastases may be newly diagnosed or present as progressive disease after surgery, whole brain radiotherapy, or stereotactic radiotherapy. Patients with LM or CM will be eligible if the LM/CM is visualized on MRI or if documented baseline CSF-positive cytology is available.
    - DDI and Holter Monitoring Study: At least one measurable intracranial or extracranial lesion according to RECIST v1.1. Patients with asymptomatic CNS metastases (including patients asymptomatic due to stable or decreasing doses of steroids within 2 weeks prior to study entry) are eligible. Brain metastases may be newly diagnosed or present as progressive disease after surgery, whole brain radiotherapy, or stereotactic radiotherapy. Patients with LM or CM will be eligible if the LM/CM is visualized on MRI or if documented baseline CSF-positive cytology is available.
- Age ≥ 18 years (or ≥ 20 years if required by local regulation)
- ECOG performance status (PS):
    - Part 1: 0 to 1
    - Part 2: 0, 1, or 2
- Adequate bone marrow function:
    - Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
    - Platelets ≥ 100 x $10^9$/L
    - Hemoglobin ≥ 9 g/Dl
- Adequate pancreatic function:
    - Total serum amylase ≤ 1.5 x upper limit of normal (ULN)
    - Serum lipase ≤ 1.5 x ULN
- Adequate renal function:
    - Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution
- Adequate liver function:
    - Total serum bilirubin ≤ 1.5 x ULN
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; ≤ 5 x ULN if liver metastases are present
- Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤ 1 except for adverse events (AEs) that in the investigator's judgment do not constitute a safety risk for the patient

<u>Key exclusion criteria</u>



Reference ID: 4344794

- Spinal cord compression unless good pain control has been attained and there is stabilization or recovery of neurological function in the 4 weeks prior to study entry
- Major surgery within 4 weeks of study entry. Minor surgical procedures (e.g. port insertion) are not excluded, but sufficient time (e.g. up to 2 weeks) should have passed for wound healing
- Radiation therapy (except palliative therapy to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤ 10 fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have been completed at least 2 weeks prior to study entry. Whole brain radiation must have been completed at least 4 weeks prior to study entry.
- Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study entry
- Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
- Previous high dose chemotherapy requiring stem cell rescue
- Prior irradiation to > 25% of the bone marrow
- Active and clinically significant bacterial, fungal, or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness
- Clinically significant cardiovascular disease (active or <3 months prior to enrollment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), second-degree or third-degree AV block (unless paced), or any AV block with PR interval > 220 msec.
- Ongoing dysrhythmias of NCI CTCAE Grade ≥ 2, uncontrolled atrial fibrillation of any grade, bradycardia defined as < 50 bpm, machine-read ECG with QTc > 470 msec or congenital long QT syndrome
- Predisposing characteristics for acute pancreatitis (e.g. uncontrolled hyperglycemia, current gallstone disease, alcoholism)
- History of extensive, disseminated, bilateral, or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis and pulmonary fibrosis. Patients with a history of radiation pneumonitis are not excluded.
- Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior
- Active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease, or previous gastric resection or lap band
- Patients with abnormal left ventricular ejection fraction (LVEF)
- Current use or anticipated need for food and drugs that are known strong or moderate CYP3A4 inhibitors
- Current use or anticipated need for drugs that are known strong CYP3A4 inducers
- Current use of drugs that are CYP3A4 substrates with narrow therapeutic indices
- Concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices



Reference ID: 4344794

- Concurrent use of drugs that are sensitive CYP2B6 substrates
- Current use or anticipated need for drugs that are known strong CYP2C19 inhibitors
- Current use or anticipated need for drugs that are known strong CYP2C8 inhibitors
- Current use or anticipated need for drugs that are known P-gp substrates with a narrow therapeutic index.

In the dose-finding portion of Study B7461001, lorlatinib was supplied for oral administration as 5 mg, 25 mg, and 100 mg (b) (4) tablets in High Density Polyethylene (HDPE) bottles with desiccant. In the dose expansion portion of the study, lorlatinib was supplied for oral administration as 25 mg free base tablets in HDPE bottles with desiccant. In all study parts, lorlatinib was administered once daily (QD) (or twice daily [BID] for some dose cohorts in the dose finding phase) continuously in 21-day cycles. Patients self-administered lorlatinib in the outpatient setting; on the days of PK sample collections, lorlatinib was administered in the clinic. Patients were instructed to take lorlatinib with at least 8 oz (240 mL) of water, with or without food, except for the patients in the food effect cohort in the dose finding portion of the study; for the fasting portions of the food effect cohort, lorlatinib was administered following an overnight fast of at least 10 hours, and for the fed portions of the food effect cohort, lorlatinib was administered following a test breakfast meal. Patients were instructed to take lorlatinib at approximately the same time each day, however, a variance of 12 hours was allowed for any given dose. For patients receiving BID dosing, lorlatinib was to be taken approximately 12 hours apart, with an allowable 3-hour variance in administration. Patients were instructed to record all doses (and missed and vomited doses) in a dosing diary supplied by the site; at Day 1 of each cycle visit and at the end of treatment, all unused or partially used bottles must have been returned to the investigators.

The dose levels evaluated in the dose finding portion of Study B7461001 are provided in Figure 8 below, abstracted from the study protocol.



Reference ID: 4344794

**Figure 8 Lorlatinib dose levels (Applicant figure)**

| DOSE LEVEL (DL)mg mg/day | Phase 1* | MDZ DDI# Evaluation |
|---|---|---|
| 5 | DL -1 | -1 |
| 10 | Starting Dose | n/a |
| 25 | DL 2** | 1 |
| 50 | DL 3 | n/a |
| 75 | DL 4 | 2 |
| 100 | DL 5 | |
| 150 | DL 6 | 3 |
| 200 | DL 7 | |
| 250 | DL 8 | 4 |
| 300 | DL 9 | |
| 400 | DL 10 | |

* Dose levels may be skipped in the CRM algorithm depending on the observed toxicities.
**CRM design design commences after the evaluation of toxicities observed in DL2.
# Potential dose levels (one dose at each level) for MDZ DDI substudy.
n/a: not applicable

| Current Dose Level | Dose Level -1 | Dose Level -2 |
|---|---|---|
| 75 mg BID | 50 mg BID | 25 mg BID* |
| 50 mg BID | 35 mg BID | 25 mg BID* |
| 35 mg BID | 25 mg BID | 10 mg BID* |
| 25 mg BID | 10 mg BID | 5 mg BID |

*Further dose reduction to the next lower dose schedule in this table in patients who are otherwise benefiting from PF-06463922 treatment may be permitted after discussion with the Sponsor's medical monitor.

The starting dose of 10 mg for Part 1 of Study B7461001 was selected based on the 1-month repeat toxicology studies in rats and dogs in which the human equivalent starting dose was calculated to be 8.6 mg based on the severely toxic dose in 10% of the rats (STD10) of 8 mg/kg/day, and 150 mg based on the highest non-severely toxic dose (HNSTD) of 25 mg/kg/day in the dog (assuming a body surface are of 1.8 $m^2$ in humans). Because the rat was determined to be the more sensitive species and provided a lower starting dose, the dose of lorlatinib was rounded to 10 mg and used as the starting dose for the first-in-patient study. At the starting dose of 10 mg once daily, the projected unbound exposure ($AUC_{24}$, 249 ng/ml) is approximately 23-fold lower than the unbound exposure observed ($AUC_{24}$, 5760 ng/ml) at the rat STD10 dose.

After the 25 mg dose level was evaluated and cleared the dose-limiting toxicity (DLT) observation period, higher doses of lorlatinib were assigned to each cohort of patients using a Continuous Reassessment Method (CRM) model; the goal of Part 1 was to determine the dose of lorlatinib closest to but no higher than a 33% probability of a DLT. Each dose cohort initially included at least 3 patients evaluable for toxicity within the first cycle; patients who discontinued treatment before completing Cycle 1 or received less than 16 of 21 planned doses for reasons other than treatment-related toxicity could be replaced for DLT evaluation but

would remain in the overall safety and efficacy analyses. Intra-patient dose escalation was permitted if all the following conditions were met:

- Cycle 1 was completed without any DLTs
- Maximum drug-related toxicity during prior cycles was Grade ≤ 2 and did not require dose modification
- Observation of Grade ≥ 3 laboratory abnormalities not requiring dose modifications was permitted
- Three patients at the next highest dose level completed Cycle 1 without a DLT

The severity of adverse events (AEs) was graded according to NCI CTCAE version 4.03; a DLT was considered to be any of the following events occurring in the first cycle of treatment (21 days) attributable to lorlatinib:

- Hematologic:
    - Grade 4 neutropenia lasting > 7 days
    - Febrile neutropenia (defined as ANC < 1000/mm$^3$ with a single temperature of ≥38.3$^o$C (≥ 101$^o$F) or a sustained temperature of ≥ 38$^o$C (≥100.4$^o$F) for > 1 hour)
    - Grade ≥ 3 neutropenic infection
    - Grade ≥ 3 thrombocytopenia with bleeding
    - Grade 4 thrombocytopenia
- Non-hematologic:
    - Grade ≥ 3 pancreatitis
    - Grade ≥ 3 toxicities (excluding Grade ≥ 3 laboratory abnormalities not requiring dose modifications persisting after optimal treatment with standard medical therapy (e.g. anti-emetics, anti-diarrheals)
    - Symptomatic Grade ≥ 3 QTc prolongation or asymptomatic Grade ≥ 3 QTc prolongation that has been confirmed by repeat testing and re-evaluated by a qualified person, and persists after correction of reversible causes such as electrolyte abnormalities and hypoxia
    - ≥ 20% decrease in LVEF compared to baseline echocardiogram or Multi-Gated Acquisition Scan (MUGA) using the same method
- Other:
    - Failure to deliver at least 16 out of the 21 prescribed daily doses (approximately 75% planned dose for Cycle 1) due to toxicities attributable to study drug
    - Failure to restart dosing after 21 days (1 cycle) due to toxicities attributable to study drug

Dose modification guidelines for the study are summarized in the following tables. If recovery from lorlatinib-related toxicity did not occur within 42 days from the last dose, patients were discontinued from lorlatinib treatment. Dose reduction of lorlatinib was allowed depending on the type and severity of toxicity encountered; patients requiring more than three dose reductions of lorlatinib were discontinued from treatment. Patients in Part 1 of the study experiencing a DLT could resume dosing at the next lower dose level (if applicable) once recovery was achieved.



Reference ID: 4344794

**Table 38 Lorlatinib dose modification guidelines (Applicant tables)**

**Non-Hematologic Toxicities**

| Toxicity | Grade 1** | Grade 2** | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Pancreatitis | If both amylase and lipase are Grade ≤2 in the absence of radiological findings of pancreatitis: continue at the same dose level without dosing interruption. Repeat lipase and amylase.<br>If radiologically confirmed pancreatitis: withhold dose. Repeat radiology and lipase and amylase weekly. If appropriate, resume treatment at one dose level lower if radiology has returned to baseline and lipase and amylase are Grade ≤2. | | Discontinue | Discontinue |
| Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect) | Asymptomatic, radiographic findings only: No need for dose adjustment. Initiate appropriate monitoring.<br>Symptomatic: Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment. | Withhold current dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume treatment at one dose level lower. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment. | Discontinue | Discontinue |
| Prolonged QTc interval | Assess electrolytes and concomitant medications.<br>Correct any electrolyte abnormalities, or hypoxia.<br>Continue at the same dose level. | Assess electrolytes and concomitant medications.<br>Correct any electrolyte abnormalities, or hypoxia.<br>Continue at the same dose level. | Withhold dose.<br>Assess electrolytes and concomitant medications.<br>Correct any electrolyte abnormalities, or hypoxia.<br>Upon recovery to Grade ≤1 resume treatment at one dose level lower. | Discontinue |

| Toxicity | Grade 1** | Grade 2** | Grade 3 | Grade 4 |
|---|---|---|---|---|
| LVEF Dysfunction | Not Applicable | Not Applicable | Discontinue | Discontinue |
| Other<br>(see separate tables below for Lipid and CNS toxicities and subsection on PR Interval Prolongation below) | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤1(or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose.* | Withhold dose until toxicity is Grade ≤1(or has returned to baseline), then reduce the dose by 1 level.* Or discontinue at the discretion of the investigator. |

* Patients who develop asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue PF-06463922 without dose modification at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require PF-06463922 dose modification.

** In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

**Hematologic Toxicities**

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Lymphopenia | Continue at the same dose level. | Continue at the same dose level. | If no evidence of infection or other clinically significant toxicity, continue at the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then rechallenge at the same dose or reduce the dose by 1 dose level. | If no evidence of infection or other clinically significant toxicity, continue at same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level. |
| Other | Continue at the same dose level. | Continue at the same dose level. | Withhold dose until toxicity is Grade ≤1 (or has returned to baseline), then rechallenge at the same dose or reduce the dose by 1 dose level. | Withhold dose until toxicity is Grade ≤1 (or has returned to baseline) then rechallenge at the same dose or reduce the dose by 1 dose level. |

**Lipid Elevation Toxicities**

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Total Cholesterol | Continue at the same dose. Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment. | Introduce the use of a statin or other lipid lowering agent as appropriate, and continue at the same dose. | Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent, or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose. | Introduce the use of a statin or other lipid lowering agent as appropriate, or, increase the dose of ongoing statin/ lipid lowering agent, or change to a new agent. Withhold dose until toxicity is Grade ≤ 2 and then reduce the dose by 1 dose level or rechallenge at the same dose. |
| Triglycerides | Continue at the same dose. Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment. | Introduce the use of a statin or other lipid lowering agent as appropriate, and continue at the same dose. | Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Either continue study drug at the same dose without interruption or withhold dose until toxicity is Grade ≤ 2 and then continue at the same dose. | Introduce the use of a statin or other lipid lowering agent as appropriate, or increase the dose of ongoing statin/lipid lowering agent or change to a new agent. Withhold dose until toxicity is Grade ≤ 2 and then reduce the dose by 1 dose level or rechallenge at the same dose. |

**CNS Effect Toxicities**

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| CNS effects* | Continue at the same dose or withhold dose until recovery to baseline and then continue at the same dose. | Continue at same dose or withhold dose until recovery to Grade ≤1. Consider dose reduction or rechallenge at the same dose. | Withhold dose until toxicity is Grade ≤1. Reduce dose to the next lower dose. | Discontinue |

* Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision.

**PR Interval Prolongation**

| Event | Asymptomatic | Symptomatic |
|---|---|---|
| First-degree heart block (PR-interval >200 msec) | **No dose hold or reduction needed.** Assess concomitant medications. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if symptoms develop that may be related to heart block. | **Withhold dose**. Assess concomitant medications. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at same dose or consider dose reduction when symptoms resolve. |
| Second-degree heart block | **Withhold dose.** Assess concomitant medications. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at same dose or consider dose reduction if subsequent ECG does not show 2nd degree block. | **Withhold dose.** Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree block resolves. If patients revert to 1st degree block with no symptoms, resume at reduced dose. |
| Complete Heart Block | **Withhold dose**. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered.<br><br>If pacemaker placed, may resume at full dose.<br><br>If no pacemaker placed, restart at reduced dose only when symptoms resolve AND PR < 200 msec. | |

**Table 39 Lorlatinib dose level reductions (Applicant tables)**

Part 1

| Current Dose Level | Dose Level -1 | Dose Level -2 |
|---|---|---|
| 200 mg QD | 150 mg QD | 100 mg QD |
| 150 mg QD | 100 mg QD | 50 mg QD |
| 100 mg QD | 50 mg QD | 25 mg QD |
| 75 mg QD | 50 mg QD | 25 mg QD |
| 50 mg QD | 25 mg QD | N/A |

| Current Dose Level | Dose Level -1 | Dose Level -2 |
|---|---|---|
| 75 mg BID | 50 mg BID | 25 mg BID* |
| 50 mg BID | 35 mg BID | 25 mg BID* |
| 35 mg BID | 25 mg BID | 10 mg BID* |
| 25 mg BID | 10 mg BID | 5 mg BID |

*Further dose reduction to the next lower dose schedule in this table in patients who are otherwise benefiting from PF-06463922 treatment may be permitted after discussion with the Sponsor's medical monitor.

Part 2

| Current Dose Level | Dose Level -1 | Dose Level -2 | Dose Level -3 |
|---|---|---|---|
| 100 mg QD | 75 mg QD | 50 mg QD | 25 mg QD |

Palliative radiation was allowed during the study for the treatment of painful bony lesions, provided that the lesions were known at the time of study entry and the investigator clearly indicated that the need for palliative radiotherapy was not indicative of disease progression. If palliative radiation was indicated for bony metastases, lorlatinib treatment was stopped one day before the start of radiation and resumed after recovery from acute radiation toxicities to baseline.

The following tables, abstracted from the protocol, outline the timing of procedures and evaluations for Study B7461001.

**Table 40 Study calendars for Study B7461001 (Applicant table)**

Part 1

| | | | CYCLE 1 (21 days) | | | CYCLE 2 (21 days) | CYCLES 3- 25 (Up to Month 18) (21 days) | CYCLES > 25 (Months > 18) (21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protocol Activity** | **Screening[1] (≤28 days)** | **Lead-in PK (Day -7)** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 1** | **Day 1 of Every Other Cycle** | **End of Treatment[27]** | **Follow- Up[26]** |
| **Visit Window (days)** | **N/A** | **+1** | **±1** | **±1** | **±1** | **±2** | **±2** | **± 2** | **±2** | **±7** |
| Informed consent[2] | X | | | | | | | | | |
| Tumor history | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Physical examination including weight | X | (X) | (X) | | | X | X | X | | |
| Baseline signs and symptoms[3] | | X | X | | | | | | | |
| Height | X | | | | | | | | | |
| Weight | X | | X | | | X | X | X | | |
| Vital signs[4] | | X | X | X | X | X | X | X | X | |
| Performance status[5] | X | | X | | | X | X | X | X | |
| **Laboratory** | | | | | | | | | | |
| Hematology[6] | X | | (X) | | X | X | X | X | X | |
| Blood Chemistry[7] | X | | (X) | | X | X | X | X | X | |
| Coagulation[8] | X | | (X) | | | | | | X | |
| Lipids[9] | X | | (X) | | X | X | X | X | X | |
| Urinalysis[10] | X | | (X) | | | | | | X | |
| Pregnancy test[11] | X | X | (X) | | | X | X | X | X | |
| (12-lead) ECG[12] | X | X | X | X | X | X | X | | X | |
| LVEF Assessments (Echocardiogram or MUGA)[28] | X | | | | | X | X | Every 4 Cycles | X | |
| **Registration and Treatment** | | | | | | | | | | |
| Registration[13] | | X | | | | | | | | |

| | | | CYCLE 1 (21 days) | | | CYCLE 2 (21 days) | CYCLES 3- 25 (Up to Month 18) (21 days) | CYCLES > 25 (Months > 18) (21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protocol Activity** | **Screening[1] (≤28 days)** | **Lead-in PK (Day -7)** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 1** | **Day 1 of Every Other Cycle** | **End of Treatment[27]** | **Follow- Up[26]** |
| **Visit Window (days)** | **N/A** | **+1** | **±1** | **±1** | **±1** | **±2** | **±2** | **± 2** | **±2** | **±7** |
| PF-06463922 Treatment[14,15] | | X | Once a day or twice a day, continuously | | | | | | | |
| Midazolam Treatment for patients participating in the midazolam sub-study[16] | | X (MDZ only) | | | X | | | | | |
| **Tumor Assessments** | | | | | | | | | | |
| CT and MRI Scan or Equivalent[17] | X | | | | | | X and then every 6 weeks ±1 week | Every 12 weeks ±1 week | (X) | |
| Cerebrospinal Fluid[18] | X | | | | | | X | X | | |
| **Other Clinical Assessments** | | | | | | | | | | |
| Adverse Events[19] | | X | X | X | X | X | X | X | X | X |
| Concomitant Medications and non-drug supportive interventions[20] | X | | X | | | X | X | X | | X |
| EORTC QLQ-C30, QLQ-LC13[25] | | X | | | | X | X | X | X | |
| Neurological exam[29] | X | Only as clinically indicated | | | | | | | | |
| Survival Follow-up | | | | | | | | | | X |
| **Other Samples** | | | | | | | | | | |
| Archival Tumor Tissue Specimen[21] | X | | | | | | | | | |
| De Novo Tumor Specimens[22] | 'X' | | | | | | | | 'X' | |
| Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[23] | X | | | | | | | | X | |
| Banked Biospecimen[24] | X | | | | | | | | | |

For footnotes, see CSR

Part 2

| | | | CYCLE 1 (21 days) | | | CYCLE 2 (21 days) | CYCLES 3 – 38 (Up to Month 30) (21 days) | CYCLES >38 (Months >30) (21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protocol Activity** | **Screen[1] (≤28 days)** | **Lead-in PK (Day -7)** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 1** | **Day 1 of Every Other Cycle** | **End of Treatment[27]** | **Follow- Up[26]** |
| **Visit or Assessment Window (days) Unless Otherwise Noted** | **N/A** | **+1** | **±1** | **±1** | **±1** | **±2** | **±2** | **± 2 days** | **±2** | **±7** |
| Informed consent[2] | X | | | | | | | | | |
| Tumor history | X | | | | | | | | | |
| Medical history | X | | | | | | | | | |
| Physical examination | X | (X) | (X) | | | X | X | X | | |
| Baseline signs and symptoms[3] | | X | X | | | | | | | |
| Height | X | | | | | | | | | |
| Weight | X | | X | | | X | X | X | | |
| Vital signs[4] | | | X | X | X | X | X | X | X | |
| Performance status[5] | X | | X | | | X | X | X | X | |
| Contraceptive check (as appropriate) | | (X) | X | | | X | X | X | | |
| **Laboratory** | | | | | | | | | | |
| Hematology[6] | X | | (X) | | X | X | X | X | X | |
| Blood Chemistry[7] | X | | (X) | | X | X | X | X | X | |
| Lipids[8] | X | | (X) | | X | X | X | X | X | |
| Hypogonadism (male patients)[9] | X | | | | X | X | C5D1 and Q 4 cycles thereafter | Every 4 Cycles | X | |
| Coagulation[10] | X | | (X) | | | | | | X | |
| Urinalysis[11] | X | | (X) | | | | | | X | |
| Pregnancy test[12] | X | X | (X) | | | X | X | X | X | |
| (12 lead) ECG[13] | X | X | X | X | X | X | X (upto Cycle 5) | | X | |

| | | | CYCLE 1 (21 days) | | | CYCLE 2 (21 days) | CYCLES 3 – 38 (Up to Month 30) (21 days) | CYCLES >38 (Months >30) (21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protocol Activity** | **Screen[1] (≤28 days)** | **Lead-in PK (Day -7)** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 1** | **Day 1 of Every Other Cycle** | **End of Treatment[27]** | **Follow- Up[26]** |
| **Visit or Assessment Window (days) Unless Otherwise Noted** | N/A | +1 | ±1 | ±1 | ±1 | ±2 | ±2 | ± 2 days | ±2 | ±7 |
| LVEF Assessments (Echocardiogram or MUGA)[28] | X | | | | | X | X | Every 4 Cycles | X | |
| **Registration and Treatment** | | | | | | | | | | |
| Registration[14] | | X | (X) | | | | | | | |
| PF-06463922 Treatment[15,16] | | X | Once a day continuously | | | | | | | |
| **Tumor Assessments** | | | | | | | | | | |
| CT and MRI Scan or Equivalent[17] | X | | | | | | X and then every 6 weeks ±1 week | Every 12 weeks ± 1 | (X) | (X) |
| Cerebrospinal fluid if leptomenigeal/carcinomatous meningitis [LM/CM]disease is present[18] | X | | | | | | | | | |
| **Other Clinical Assessments** | | | | | | | | | | |
| Adverse Events[19] | | X | X | X | X | X | X | X | X | X |
| Concomitant medications and non drug supportive interventions[20] | X | | X | | | X | X | X | | X |
| EORTC QLQ-C30, QLQ-LC13[25] | | X | X | | | X | X | X | X | |
| Cognitive Assessment[29] | X | X | X | | | X | X up to Cycle 6 and then D1 of every other cycle | X | X | |
| Mood Assessment[30] | | X | X | | | X | X up to Cycle 6 and then D1 of every other cycle | X | X | |

| | | | CYCLE 1 (21 days) | | | CYCLE 2 (21 days) | CYCLES 3 – 38 (Up to Month 30) (21 days) | CYCLES >38 (Months >30) (21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protocol Activity** | **Screen[1] (≤28 days)** | **Lead-in PK (Day -7)** | **Day 1** | **Day 8** | **Day 15** | **Day 1** | **Day 1** | **Day 1 of Every Other Cycle** | **End of Treatment[27]** | **Follow- Up[26]** |
| **Visit or Assessment Window (days) Unless Otherwise Noted** | N/A | +1 | ±1 | ±1 | ±1 | ±2 | ±2 | ± 2 days | ±2 | ±7 |
| Suicidal Ideation and Behavior[31] | | X | X | | | X | X up to Cycle 6 and then D1 of every other cycle | X | X | |
| Survival Follow-up | | | | | | | | | | X |
| **Other Samples** | | | | | | | | | | |
| Archival Tumor Tissue Specimen[21] | X | | | | | | | | | |
| De Novo Tumor Specimens[22] | X | | | | | | | | 'X' | |
| Blood Specimens for Circulating Nucleic Acid (CNA) Profiling[23] | X | | | | | | X | | X | |
| Banked Biospecimen[24] | X | | | | | | | | | |

For footnotes, see CSR

Treatment with lorlatinib was to continue until the development of objective disease progression according to RECIST v1.1, unless in the investigator's opinion the patient was still deriving clinical benefit, or unacceptable toxicity. Protocol-specified reasons for early treatment discontinuation included: patient request, global deterioration of health status, pregnancy, significant protocol violation, lost to follow-up, patient refusal, or study termination by the Sponsor.

The study period was from the date of informed consent until the date of the safety follow-up visit. After completion of the study period, patients were to be followed for survival every 2 months from the date of the last dose of lorlatinib.

An independent review committee (IRC) was established to evaluate radiologic scans for tumor response assessments. Several contract research organizations (CROs) were used in the conduct of Study B7461001, including for the IRC.

**Study Endpoints**

In Study B761001, overall response rate (ORR) was assessed according to RECIST v1.1 and intracranial response rate (IC-ORR) was assessed according to modified RECIST for intracranial response assessment. According to the modified RECIST criteria for the assessment of intracranial response described in the protocol for Study B7461001, in the presence of CNS metastases ≥ 5 mm in diameter assessed by gadolinium contrasted MRI with slices of 1 mm, up to 5 CNS lesions were permitted to be identified as target lesions in addition to 5 extracranial lesions identified as target lesions per the standard RECIST v1.1 criteria. Confirmation of response was required at least 4 weeks after the initial response was observed.

The primary endpoint of Part 1 was Cycle 1 dose-limiting toxicities (DLTs). ORR as assessed by investigator was a secondary endpoint. Secondary endpoints included ORR and IC-ORR as assessed by independent central radiology (ICR) assessment and investigator, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

The primary endpoint of the Japanese LIC was Cycle 1 DLTs. ORR was also collected.

The primary endpoints of Part 2 were ORR and IC-ORR as assessed by independent central radiology (ICR) assessment. Secondary endpoints included ORR and IC-ORR as assessed by investigator, PFS, OS, and DOR.

In Part 1 and Part 2, patient reported outcomes (PROs) were also collected via the EORTC QLQ-C30 and QLQ-LC13.

**Statistical Analysis Plan**

The ITT analysis set as defined in the protocol included all enrolled patients with documented ALK or ROS1 rearrangement who received at least one dose of lorlatinib (including Day-7 Lead-in dose).

The primary analysis of ORR was the point estimate of ORR accompanied by the corresponding exact 95% confidence interval (CI). Time-to-event endpoints (PFS and OS) were described using Kaplan-Meier methods. All analyses were performed on the ITT population. These analyses were to be performed on the efficacy endpoints in both Part 1 and Part 2.

The statistical analysis plan (SAP) specified that the primary ORR analysis was to be performed separately for each cohort EXP-1 through EXP-6. In addition, the SAP stated that the primary analysis would be performed on the following pooled subgroups: EXP-2:EXP-5 (inclusive of all patients in cohorts EXP-2, EXP-3, EXP-4, and EXP-5), EXP-2:EXP-3, and EXP-4:EXP-5. Finally, the primary analysis was to be performed on the following subgroups of EXP-3:

- EXP-3A: Patients with prior crizotinib therapy and prior regimens of chemotherapy.
- EXP-3B: Patients with 1 prior non-crizotinib ALK TKI therapy with or without prior regimens of chemotherapy.

The primary analysis of ORR per ICR assessment was to be performed when, for each subgroup, all the treated patients have reached at least three tumor assessments on treatment or had otherwise progressed, died, withdrawn from treatment or withdrawn consent.

Part 1 employed a continual reassessment model (CRM) to estimate the MTD. A total of 54 patients were enrolled, 15 of whom were ALK+ and treated at 100 mg of lorlatinib. No formal statistical hypothesis was tested.

The Japanese LIC enrolled 3 patients, 2 of whom had ALK-positive tumors.

In Part 2, the sample size was based on the 95% CI which would result for different levels of response in the pooled subgroups and cohorts. The following number of patients were enrolled in the selected cohorts:

- EXP-2: 27 patients
- EXP-3A: 28[1] patients
- EXP-3B: 32 patients
- EXP-4: 65 patients
- EXP-5: 46 patients.

No formal statistical hypotheses were tested.

*Reviewer's Comment: Pfizer reported the pooled subgroup EXP-2:EXP-3A rather than EXP-2:EXP-3. As described below, FDA requested Pfizer to report efficacy data for all patients across the study who were purported to have ALK-positive NSCLC and received 100 mg of lorlatinib. Pfizer did not report this, but rather reported efficacy by part for patients in this group. This review defines the primary efficacy population as any patient in Study B761001 who was purported to have ALK-positive NSCLC and received 100 mg of lorlatinib.*

[1] This includes one patient who was not confirmed as ALK+ prior to enrollment.



Reference ID: 4344794

**Primary Efficacy Population**

In this review, the primary efficacy population is comprised of all patients who received 100 mg of lorlatinib in Part 1, Part 2, or the Japanese lead-in cohort who were purported to have ALK-positive NSCLC at the start of the study.

**Protocol Amendments**

The protocol for Study B7461001 was amended seven times after its initial submission on June 28, 2013. In Amendment 1, dated September 17, 2013, an assessment of left ventricular ejection fraction (LVEF) was added to ensure safety monitoring of any LVEF dysfunction. An exclusion criterion for patients with abnormal LVEF, and a dose-limiting toxicity (DLT) definition modification for dose modifications in case of toxicity were added to the protocol. Disease control rate (DCR) at 6 and 12 weeks was added as a secondary endpoint. Amendment 2 was submitted on March 28, 2014, and made minor clarifications and corrections were made. In Amendment 3, submitted on October 29, 2014, clarification was made that additional doses in the dose finding portion of the study may be explored outside of the continual reassessment method (CRM) model recommendations to optimize the RP2D determination. The sample sizes for expansion cohorts EXP-1 and EXP-4 were increased to study a total of 40 patients using a two-stage design, with the trial being terminated after the first 20 patients enrolled in cohorts EXP-1 and EXP-4 if ≤ 7 patients responded. For expansion cohorts EXP-2 and EXP-3, the planned sample size was increased to 60 patients per cohort after initial testing in 30 patients per cohort. This amendment also added a Japanese-patient only lead-in cohort to investigate the safety and PK of lorlatinib in Japanese patients. In Amendment 4, dated July 22, 2015, identification of and justification for the RP2D was presented. The overall sample size of the dose expansion portion of the study was increased from 200 to 240 patients with the addition of cohorts EXP-4, to include approximately 40 patients with advanced ALK-positive NSCLC relapsing after 2 prior lines of ALK inhibitor therapies, and EXP-5, to include approximately 40 patients with advanced ALK-positive NSCLC relapsing after 3 prior lines of ALK-inhibitor therapies. The sample sizes for cohorts EXP-2 and EXP-3 were reduced from 60 to 40 patients. Required assessments in the dose expansion portion of the study including assessments of cognition, mood, and SIB were added; a rater to administer these assessments at each site was also required. The sample size for the Japanese LIC was reduced from 30 patients to 3 Japanese patients. In Amendment 5, dated March 11, 2016, the exclusion criteria were updated to exclude patients with a PR interval > 200 msec or with 2$^{nd}$ or 3$^{rd}$ degree atrioventricular (AV) block within 3 months prior to study entry; dose modification guidelines for patients with PR interval prolongation were also added. Amendment 6, dated July 15, 2016, added a Drug-Drug interaction (DDI) and Holter monitoring in parallel with the ongoing dose expansion portion of the study. Finally, Amendment 7, dated March 23, 2018, added additional monitoring (transthoracic echocardiograms) for patients enrolled in France and Germany, per the request of Health Authorities in those countries.

Statistical changes to the protocol are summarized in Table 41.



Reference ID: 4344794

**Table 41: Summary of Protocol Amendments**

| Amendment | Date | Protocol changes |
|---|---|---|
| Original | 06/28/2013 | |
| 1 | 09/17/2013 | • Added "Disease Control Rate (DCR) at 6 and 12 weeks" to the list of secondary endpoints to be analyzed.<br>• For clarification of the Phase 2 sample size determination, added "If the total number of responding patients is equal to or greater than 20 for each subpopulation, then the null hypothesis will be rejected." |
| 2 | 03/28/2014 | • Updated Part 2 Study Endpoints to clarify efficacy analyses to be performed in Phase 1 and Phase 2 to allow an in-depth characterization of the efficacy profile in the different subpopulations. |
| 3 | 10/29/2014 | • Increased Phase 1 and Phase 2 sample size.<br>• Additional patients (approximately 15) beyond 36 may be enrolled to better characterize RP2D, which could include safety, PK, alternative dosing schedules (if applicable), food effect, etc.<br>• In Phase 2, sample size changed from approximately 160 to 200 patients. Cohorts EXP-2 increased from 40 to 60 patients. Cohort containing patients who had received 1-2 prior ALK therapies (later defined as EXP-3 and EXP-4) increased from 40 to 60 patients.<br>• Added a Japanese patient-only Lead-In Cohort (LIC) to investigate the safety and PK of PF-06463922 in Japanese patients. |
| 4 | 07/22/2015 | • Update to the type and allocation of patients in the subgroup categories (EXP) in Phase 2. EXP-1:EXP-6 defined.<br>• Increase in Phase 2 sample size from 200 to 240 patients.<br>• Change in sample size of patients receiving Lead-In Dose in Phase 2 from 30 patients to approximately 10 Non-Japanese patients and 3 Japanese patients. |
| 5 | 03/11/2016 | • No major changes. |



Reference ID: 4344794

| | | |
|---|---|---|
| 6 | 07/15/2016 | • Removal of some required assessments in Phase 1, Phase 2, and Japanese Patient Only Lead-In Cohort (LIC), and reduction of frequency in some assessments in Phase 1, Phase 2, and Japanese LIC.<br>• Decreased sample size in EXP-1 from 40 to 30. Increased sample size in EXP-4 from 40 to 70.<br>• Increase in overall sample size in Phase 2 from 240 to 260 and overall sample size in the study. |

On August 30, 2017, a Type B Pre-NDA meeting was held for lorlatinib. The following discussion occurred during the meeting, describing the populations to be reported:

> *FDA and Pfizer agreed to provide analyses of ORR and DOR in the following populations: all patients with documented ALK mutation enrolled in the phase 2 portion of study, all patients with documented ALK mutation receiving 100 mg lorlatinib across the entire study, all patients enrolled in the Phase 2 portion of the study purported to be ALK positive and received prior treatment, and all patients receiving 100 mg lorlatinib across the entire study purported to be ALK positive and received prior treatment. The analysis to be presented in product labeling will be determined during review of the application. The dataset will contain the appropriate flags to allow identification of subgroups as described above.*

### 8.1.2. Study Results

**Compliance with Good Clinical Practices**

Pfizer stated in the clinical study report (CSR) for Study B7461001 that the study was conducted in compliance with good clinical practice (GCP) guidelines, and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

**Financial Disclosure**

Pfizer submitted a list of investigators (NDA Module 1.3.4) and FDA forms 3454 and 3455. Pfizer appeared to adequately disclose the financial interests/arrangements of the clinical investigators. The financial disclosure data does not raise concerns about the integrity of the data.

Pfizer provided certification, using FDA form 3454, that none of the financial interests or arrangements described in 21 CFR Part 54 existed for 405 of the 418 clinical investigators in the covered studies listed in Table 13 below. Pfizer identified 10 clinical investigators who were full-time or part-time employees of the Sponsor of the covered study. Due diligence activities were required for 0 of the 418 clinical investigators.



Reference ID: 4344794

Thirteen (3.1%) of the 418 clinical investigators listed in the study report had financial information to disclose.

**Table 42 List of Studies (Reviewer Table)**

| Protocol number | Protocol name | Disclosure start date | Disclosure cut-off date |
|---|---|---|---|
| B7461001 | Phase 1/2 study of PF-06463922 (an ALK/ROS1 tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer harboring specific molecular alterations | 1/8/2014 | 3/15/2017 |
| B7461004 | A phase 1 open-label, radiolabeled, single-dose study to investigate the absorption, metabolism, and excretion of [14C]PF-06463922 in healthy male volunteers | 9/30/2015 | 11/5/2015 |
| B7461011 | A phase one, open label, two-period, two-treatment, fixed sequence, cross-over study to estimate the effect of multiple dose rifampin on the single dose pharmacokinetics of PF-06463922 in healthy volunteers | 7/6/2016 | 10/7/2016 |
| B7461012 | 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 healthy volunteers in the fasted condition | 8/16/2016 | 5/4/2017 |

**Patient Disposition**

Of the 334 patients enrolled on Study B7461001, two patients were not treated: one patient in the dose escalation portion of the study (patient (b) (6), 75 mg daily cohort), and one patient in the dose expansion portion of the study (patient (b) (6) cohort EXP-4) who died before the start of treatment. Pfizer excluded patient (b) (6) who was enrolled in cohort EXP-3, from the ITT population as the patient did not have confirmation of ALK-positivity at the start of study. The median duration of follow-up for the ALK-positive patients enrolled in the



Reference ID: 4344794

dose escalation portion of Study B7461001 was 28.7 months (95% CI 20, 32) and was 6.9 months (95% CI 6.9, 7.2) for the patients enrolled in cohorts EXP-2 through EXP-5 in the dose expansion portion of the study. Tables 14 and 15 summarize patient disposition for the full analysis set (ISS population) as of the data extraction date of March 15, 2017.

*Reviewer's comment: ALK-positivity for patient (b) (6) was confirmed by Pfizer after the start of the study, so this patient is included in FDA's analyses of the ITT population.*

**Table 43 Patient disposition (dose escalation portion) - full analysis population from Study B7461001 (Reviewer table)**

| Number of patients (%) | Total | 100 mg QD |
|---|---|---|
| Assigned to study treatment | 55 | 17 |
| Treated[a] | 54 (100) | 17 (100) |
| Treatment ongoing at data cut-off | 19 (35) | 7 (41) |
| Discontinued treatment | 35 (65) | 10 (60) |
| Reason for discontinuation: | | |
| Adverse event | 5 (9.3) | 0 |
| Global deterioration of health status | 4 (7.4) | 1 (5.9) |
| Objective progression or relapse | 20 (37) | 8 (47) |
| Patient died | 2 (3.7) | 1 (5.9) |
| Patient refused participation | 2 (3.7) | 0 |
| Other[b] | 2 (3.7) | 0 |

[a] Includes patient (b) (6) who was neither ALK-positive nor ROS1-positive
[b] Reason provided for patient (b) (6) was "patient held study drug for longer than 42 days," and for patient (b) (6) was to "go back to his country."

*Reviewer's comment: Of the 17 patients in the dose escalation portion of the study treated at the RP2D, 15 had ALK-positive NSCLC and are included in the primary efficacy population.*



Reference ID: 4344794

**Table 44 Patient disposition (dose expansion phase and Japanese lead-in cohort) - full analysis population from Study B7461001 (Reviewer table)**

| Number of patients (%) | EXP-1 | EXP-2 | EXP-3 | EXP-4 | EXP-5 | EXP-6 | Japanese LIC | Total |
|---|---|---|---|---|---|---|---|---|
| Assigned to study treatment | 30 | 27 | 60 | 66 | 46 | 47 | 3 | 279 |
| Treated | 30 | 27 | 60 | 65 | 46 | 47 | 3 | 278 |
| Ongoing treatment at data cut-off | 25 (83) | 21 (78) | 39 (65) | 31 (48) | 20 (44) | 21 (45) | 2 (67) | 159 (57) |
| Discontinued treatment | 5 (17) | 6 (22) | 21 (35) | 34 (52) | 26 (57) | 26 (55) | 1 (33) | 119 (43) |
| Reason for discontinuation: | | | | | | | | |
| AEs | 1 (3.3) | 2 (7) | 4 (7) | 3 (4.6) | 5 (11) | 5 (11) | 0 | 20 (7) |
| Global deterioration | 0 | 0 | 1 (1.7) | 3 (4.6) | 2 (4.3) | 2 (4.3) | 0 | 8 (2.9) |
| Objective progression | 4 (13) | 2 (7) | 14 (23) | 22 (34) | 15 (33) | 13 (28) | 1 (33) | 71 (26) |
| Patient died | 0 | 1 (3.7) | 2 (3.3) | 2 (3.1) | 2 (4.3) | 1 (2.1) | 0 | 8 (2.9) |
| Refused participation | 0 | 1 (3.7) | 0 | 2 (3.1) | 2 (4.3) | 5 (11) | 0 | 10 (3.6) |
| Protocol violation | 0 | 0 | 0 | 1 (1.5)[a] | 0 | 0 | 0 | 1 (0.4) |
| Other | 0 | 0 | 0 | 1 (1.5) | 0 | 0 | 0 | 1 (0.4) |

[a] Machine read QTc interval of > 500 msec for patient (b) (6)

Table 45 shows the patient disposition of patients in the primary efficacy population.

**Table 45: Disposition of Patients in the Primary Efficacy Population**

| | **Overall** |
|---|---|
| N | 215 |
| **Ongoing (%)** | 120 (56) |
| **Withdrawn (%)** | 95 (44) |
| Adverse Event | 14 (15) |
| Death | 8 (8) |
| Protocol Violation | 1 (1) |
| Other | 1 (1) |
| No Longer Willing to Participate in Study | 5 (5) |
| Objective Progression or Relapse | 59 (62) |
| Global Deterioration or Relapse | 7 (7) |

Data cut-off date: 3/15/2017

**Protocol Violations/Deviations**

Pfizer reported a total of 339 protocol violations for Study B7461001 as of the database lock, most of which were minor and had no impact on safety or efficacy. Of these, 99 (29%) were

considered important, and Pfizer did not believe that these deviations impacted the interpretation of study results. In the dose escalation portion of Study B7461001, 6 patients had deviations involving eligibility criteria, including one patient who did not submit either archival tissue or a de novo biopsy sample, one patient who did not have confirmation of ALK-positive status after source document review (patient (b) (6), and four patients who did not meet one of the other inclusion or exclusion criteria. Three patients received a systemic anticancer therapy prior to documented disease progression per RECIST v1.1, the serious adverse event (SAE) report was not submitted to the Sponsor within the protocol required timeframe for submission in 11 patients, and three patients did not sign one of the amendment-associated informed consent documents. Aside from patient (b) (6) who did not have local confirmation of either ALK or ROS1 at study entry, none of the protocol deviations had an impact on the analysis populations or the risk/benefit assessment of lorlatinib.

In the dose expansion and Japanese lead-in cohort portions of Study B7461001, 52 patients had deviations involving eligibility criteria as follows: 9 patients did not provide either the archival tissue or the de novo biopsy sample at screening, 1 patient did not have confirmation of ALK-positive status after source document review (patient (b) (6), 14 patients had local confirmation of ALK/ROS1 status but use the protocol required testing method, and 31 patients did not meet one of the other inclusion or exclusion criteria. One patient received anticancer therapy prior to documenting disease progression per RECIST v1.1, the SAE report was not submitted to the Sponsor within the protocol required timeframe for submission in 12 patients, 6 patients did not sign one of the amendment-associated informed consent documents, and 2 patients did not receive timely notification of a special safety concern letter informing patients of the potential risk of PR interval prolongation. Aside from patient (b) (6) who did not have either ALK or ROS1 local confirmation at study entry, none of the other protocol deviations had an impact on the analysis populations or the risk/benefit assessment of lorlatinib.

*Reviewer's comment: Patient (b) (6) was enrolled in the 35 mg twice daily (BID) cohort in the dose expansion portion of Study B7461001 and therefore was not included in the primary efficacy population that included all patients with ALK-positive NSCLC enrolled in Study B7461001 who received at least one prior ALK TKI and received lorlatinib at the RP2D of 100 mg daily. Patient (b) (6) who was enrolled in cohort EXP-3 in the dose expansion portion of Study B7461001, was excluded by Pfizer from the primary efficacy population, but was included in FDA's analysis of efficacy, as ALK-positivity was confirmed for this patient during the course of treatment. Both patients were included in the safety analyses of all treated patients on Study B7461001. Therefore, the clinical reviewer agrees that the protocol deviations described for Study B7461001 are unlikely to impact the interpretation of the safety and efficacy results.*

**Table of Demographic Characteristics**

The demographic characteristics of the primary safety populations in Study B7461001 are summarized in Table 46 **Summary demographics of patients in the primary safety populations in Study B7461001**.



Reference ID: 4344794

**Table 46 Summary demographics of patients in the primary safety populations in Study B7461001**

| Demographic Parameters | 100 mg QD pooled group (N=295) n (%) | All treated (N=332) n (%) |
|---|---|---|
| **Sex** | | |
| Male | 125 (42) | 141 (42) |
| Female | 170 (58) | 191 (58) |
| **Age** | | |
| Mean years (SD) | 53.3 (12.1) | 53.3 (12.2) |
| Median (years) | 53 | 53 |
| Min, max (years) | 19, 85 | 19, 85 |
| **Age group** | | |
| < 65 years | 241 (82) | 270 (81) |
| ≥ 65 years | 54 (18) | 62 (19) |
| **Race** | | |
| White | 145 (49) | 169 (51) |
| Black or African American | 3 (1.0) | 6 (1.8) |
| Asian | 108 (37) | 113 (34) |
| Other | 13 (4.4) | 13 (3.9) |
| Unspecified[a] | 26 (8.8) | 31 (9.3) |
| **Region** | | |
| United States | 100 (34) | 121 (36) |
| Rest of the World | 195 (66) | 211 (64) |
| Canada | 7 (2.4) | 7 (2.1) |
| Europe | 92 (31) | 96 (29) |
| Asia | 78 (26) | 85 (26) |
| Australia | 18 (6.1) | 23 (6.9) |

Table 47 shows the demographic characteristics of patients in the primary efficacy population.

**Table 47: Demographic Characteristics of Patients in the Primary Efficacy Population**

| | Overall |
|---|---|
| N | 215 |
| Age (Mean (Sd)) | 53.0 (11.7) |
| **Age (%)** | |
| <65 | 177 (82) |
| >=65 | 38 (18) |
| **Sex (%)** | |
| Female | 127 (59) |
| Male | 88 (41) |
| **Race (%)** | |
| White | 109 (51) |
| Asian | 74 (34) |
| Missing | 23 (11) |
| Other | 9 (4) |

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Table 48 shows other baseline characteristics for patients in the primary efficacy population.

**Table 48: Other Baseline Characteristics in the Primary Efficacy Population**

| | Overall |
|---|---|
| n | 215 |
| Stage IV (%) | 214 (100) |
| **Histology (%)** | |
| ADENOCARCINOMA NOS | 176 (82) |
| OTHER[1] | 39 (18) |
| **ECOG (%)** | |
| 0 | 95 (44) |
| 1 | 112 (52) |
| 2 | 8 (4) |
| **CNS at Baseline (per IRC) (%)** | |
| No | 66 (31) |
| Yes | 149 (69) |
| With measurable disease (per IRC) | 89 (60) |
| **Number of disease sites involved at baseline (%)** | |
| 1 | 15 (7) |
| 2 | 57 (27) |
| 3 | 70 (33) |
| 4+ | 73 (34) |

[1] Includes other adenocarcinomas such as bronchoalveolar carcinoma or acinar adenocarcinoma. A total of 95% patients were found to have any adenocarcinoma.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

There were 13 patients in the dose escalation portion of Study B7461001 and 44 patients in the dose expansion portion of Study B7461001 who had protocol deviations due to an investigational product dosing or administration error. However, no patients were removed from the study or excluded from analyses due to poor compliance. According to Pfizer, the median relative dose intensity (actual dose / intended dose) was 99.2% in the dose escalation portion of the study and 98.5% in the dose expansion portion of the study. Four patients in the dose escalation portion of the study and 11 patients in the dose expansion portion of the study took more than 100 mg QD on one or more single-day episodes due to patient error; this resulted in relative dose intensities exceeding 100%.

*Reviewer's comment: Given the high median relative dose intensities for patients enrolled in*

*both portions of the study, missed doses of lorlatinib or poor treatment compliance are unlikely to have affected the efficacy analyses or the overall risk:benefit assessment of lorlatinib.*

During the study, 331 of 332 patients enrolled on Study B7461001 received at least one concomitant medication. The most common types of medications used were agents affecting the cardiovascular system (92% of patients), of which the most common class of medication was lipid-modifying agents (83% of patients); agents affecting the gastrointestinal tract and metabolism (87% of patients); and agents affecting the CNS (e.g. benzodiazepines, analgesics, and medications for neuropathy, including gabapentin and pregabalin) (82% of patients).

**Selection of the Recommended Phase 2 Dose (RP2D)**

After enrollment into the dose-finding phase of Study B7461001 was complete, the CNS effects observed at the 150 mg QD and 200 mg QD dose level were intolerable for some patients and were a cause for dose modification. As a result, doses lower than 200 mg QD were further investigated, and 100 mg QD was chosen as the RP2D since no patients in the dose-finding portion of the study who received 100 mg QD required a dose reduction and, based on the PK data observed, simulated patient exposure suggested that the 100 mg QD dose was the lowest dose that would exceed the lorlatinib effective concentration ($C_{eff}$) of 150 ng/mL during the majority of the dosing cycle once steady-state was reached. The $C_{eff}$ of 150 ng/mL was the concentration predicted to result in >80% tumor growth inhibition of the ALK G1202R resistance mutation.

**Data Quality and Integrity**

The initial data submission was based on a data cut-off date of March 15, 2017. This submission contained a folder for pooled analyses and a folder for analyses by part.

The initial data submission did not contain flags for “prior chemotherapy in the metastatic setting” or “number of prior TKIs received”. On April 18, 2018, Pfizer submitted a data set which contained additional data, including a variable indicating which pre-defined cohort each patient was part of (including Part 1 and Japanese LIC patients). This data also contained flags for the variables which were noted as missing above. The reviewer was able to replicate the analyses in the label after this submission.

On April 24, 2018, Pfizer submitted an updated data set based on a data cut-off date of September 15, 2017. This update included updated data on ORR and IC-ORR, as well as the duration of response for both endpoints. The update did not include updated data on any other efficacy endpoints. The data set which contained the IC-ORR data only contained data for 147 patients, while the original submission identified 149 patients who had brain metastases at baseline. This discrepancy was due to change in independent reader for these two patients. In Study B7461001, there were two independent readers who assessed response for each patient.



Reference ID: 4344794

Change in reader was implemented by an adjudicator after the CSR cutoff date, for reasons discussed below. For the two patients who were excluded from the IC-ORR analysis in the safety update, the updated reader had not identified the patients as having CNS metastases at baseline.

FDA requested that Pfizer provide a detailed rationale for why primary readers were changed for individual patients after the CSR cut-off date of March 15, 2017, and how such a change affected each patient's response values. In a teleconference on June 7, 2018, FDA communicated to Pfizer that a review of the details surrounding such a practice, as well as the accompanying data, may necessitate a major amendment. A communication confirming a major amendment was sent on July 6, 2018, following Pfizer's submission of this additional information to the sBLA.

In a response sent July 3, 2018 to an information request (IR) from FDA, Pfizer identified key dates in the central imagine read process. Table 49 shows dates from this response which are relevant to this review. To be included in the efficacy analysis at either the CSR or Safety Update cutoff, images had to have been collected no later than the respective cutoff dates.

**Table 49: Important Dates in the Central Imaging Read Process**

| Event | Date |
|---|---|
| CSR data cutoff date | 03/15/2017 |
| Receipt cutoff date at (b) (4) for imaging materials from the sites to be included in the CSR efficacy analysis | 04/12/2017 |
| Safety Update cutoff date | 09/15/2017 |
| Receipt cutoff date at (b) (4) for imaging materials from the sites to be included in the SU efficacy analysis | 12/05/2017 |

Source: Adapted from Pfizer's response sent 07/03/2018 to FDA's IR.

Pfizer identified five reasons for why readers were changed between the CSR cut-off and the safety update. These were described in their response sent July 3, 2018 to the IR as follows:

- *"Discordance in lesion measurement or lesion selection between two readers" describes cases where the derived Best Response (BR) from the respective readers were not identical, or discordant. This result always led to adjudication.*
- *"Change in the designation of response or progression" describes cases where either Reader 1 or Reader 2 updated his or her respective BR between the CSR data cutoff date and the Safety Update data cutoff date.*
- *"Change in assessment of a scan prior to the CSR database lock" describes cases where Reader 1 or Reader 2 or both updated tumor measurements on scans performed earlier than the CSR cutoff date.*
- *"Additional, earlier data having been submitted" describes cases where scans performed earlier than the CSR cutoff date, or other pertinent clinical information, were submitted to (b) (4) after the receipt data cutoff date to be included in the CSR analyses. These scans were then included in the Safety Update efficacy analyses.*



Reference ID: 4344794

- *"Update to other derivation input".*

Table 50 shows how many patients for which the reader was changed between the CSR cutoff date and safety update, organized by reason. For some patients, multiple reasons for change in reader were given.

**Table 50: Reasons for Change in Reader after the CSR Cutoff**

| Reason for Change in Reader | Number of Patients for Whom the Reader of Response was Changed N = 28 |
|---|---|
| Discordance in lesion measurement or lesion selection between two readers | 28 |
| Change in the designation of response or progression | 11 |
| Change in assessment of a scan prior to the CSR database lock | 5 |
| Additional, earlier data having been submitted | 2 |
| Update to other derivation input | 5 |

Source: Adapted from Pfizer's response sent 07/03/2018 to FDA's IR.

"Update to other derivation input" refers to information that was updated which was not lesion measurement information. In these cases, no additional imaging media was received for the respective patients. Specifically, on May 2, 2017, the start date for the derivation of the value "days on-study" was changed from the day of randomization to the day of Cycle 1 Day 1. This change was applied to all 215 patients in the primary efficacy population, and for 105 patients the start date was changed (the maximum change in date from the original start date was 12 days). This update triggered an adjudication in patients whose best response (ORR or IC-ORR) was different between the two readers. In 4 cases, the reader was changed upon this adjudication. The reader was changed via the same process for a fifth patient who had a date other than start date updated.

Response data from before the CSR cutoff date was changed for five patients. This was due to a "global review of all scans" which was defined in Pfizer's charter with (b) (4) in the following way:

> *"If a change is required to a time point that has previously been read (either on the basis of a correction identified during read QC or because of a "hindsight" change initiated by the independent reviewer based on additional information), the change will be made. The data in the reading application and in the study database will be concordant. Audit trails will reflect the change."*



Reference ID: 4344794

In their response to the IR, Pfizer submitted responses for all patients based on the safety update cutoff based on 1) the reader chosen at CSR and 2) the reader chosen at the safety update. The reviewer was able to replicate all of Pfizer's results.

**Reader of Response in Efficacy Results**

In the efficacy results that follow, results from the CSR data cutoff date and the safety update data cutoff date are presented. Unless otherwise noted, all efficacy results discussed below will be based on the independent review reader who was chosen at the time of the CSR cutoff, if adjudication was necessary. Although the charter with (b) (4) defined procedures for change in reader, FDA did not agree to re-adjudication of readers after the CSR data cutoff. The analyses below which were conducted at the safety cutoff reflect updated data based on responses as they were determined at the time of the CSR cutoff.

**Efficacy Results – Primary Endpoint**

Table 51 presents the confirmed ORR and IC-ORR as assessed by IRC for all patients in the primary efficacy population. In the analyses below, the presence of CNS metastases was confirmed by the IRC.

**Table 51: Confirmed ORR and IC-ORR per IRC in the Primary Efficacy Population**

| | Overall N = 215 | Intracranial N = 149 |
|---|---|---|
| Response Rate | 46% | 53% |
| (95% CI)[1] | (39%, 53%) | (45%, 61%) |
| CR | 2% | 29% |
| PR | 44% | 24% |

[1] Estimated using the Clopper-Pearson method
Data cut-off date: 3/15/2017

The median DOR was not reached for either ORR or IC-ORR. Table 52 summarizes the DOR by 6, 9, and 12-month landmarks.

**Table 52: Duration of Response per IRC for Responders in the Primary Efficacy Population**

| | Overall N = 99 | Intracranial N = 79 |
|---|---|---|
| Duration of response | | |
| ≥ 6 months | 48% | 60% |
| ≥ 9 months | 16% | 25% |
| ≥ 12 months | 9% | 19% |

Data cut-off date: 3/15/2017

Patients who obtained an overall response were followed for a median of 8.2 months. Patients who obtained an intracranial response were followed for a median of 8.3 months.

*Updated Data*

Table 53 presents the confirmed ORR and IC-ORR as assessed by IRC for all patients in the primary efficacy population based on a data cut-off date of September 15, 2017. In the analyses below, the presence of CNS metastases was confirmed by the IRC.

**Table 53: Updated Confirmed ORR and IC-ORR per IRC in the Primary Efficacy Population**

| | **Overall N = 215** | **Intracranial N = 149** |
|---|---|---|
| Response Rate | 48% | 54% |
| (95% CI)[1] | (42%, 55%) | (45%, 62%) |
| CR | 4% | 31% |
| PR | 44% | 22% |
| Duration of response | | |
| Median in months (95% CI) | 12.5 (8.4, 23.7) | 19.6 (14.5, NE[2]) |

[1] Estimated using the Clopper-Pearson method.
[2] NE = not estimable.
Data cut-off date: 9/15/2017

Patients who obtained an overall response were followed for a median of 12.5 months. Patients who obtained an intracranial response were followed for a median of 13.4 months. The DOR for ongoing intracranial responses was censored on the date of initiation of new anti-neoplastic therapy at the time of systemic disease progression, which occurred in 14% of the IC responders.

**Efficacy Results – Secondary and other relevant endpoints**

*ORR per INV*

Table 54 presents the confirmed ORR and IC-ORR as assessed by INV for all patients in the primary efficacy population. In the analyses below, the presence of CNS metastases was confirmed by the investigator.



Reference ID: 4344794

**Table 54: Confirmed ORR and IC-ORR per INV in the Primary Efficacy Population**

| | Overall N = 215 | Intracranial N = 139 |
|---|---|---|
| Response Rate (95% CI)[1] | 44% (37%, 51%) | 31% (23%, 39%) |
| CR | 1% | 17% |
| PR | 42% | 14% |

[1] Estimated using the Clopper-Pearson method.
Data cut-off date: 3/15/2017

The median DOR as assessed by INV was not reached for either ORR or IC-ORR. Table 55 summarizes the DOR by 6, 9, and 12-month landmarks.

**Table 55: Duration of Response per INV for Responders in the Primary Efficacy Population**

| | Overall N = 94 | Intracranial N = 43 |
|---|---|---|
| Duration of response | | |
| ≥ 6 months | 54% | 44% |
| ≥ 9 months | 23% | 21% |
| ≥ 12 months | 16% | 16% |

Data cut-off date: 3/15/2017

Patients who obtained an overall response were followed for a median of 8.3 months. Patients who obtained an intracranial response were followed for a median of 8.2 months.

*Reviewer's Comment: The intracranial response rate per INV (31%) was lower than the intracranial response rate per IRC (53%). Refer to Section 19.5 for evaluation of discordance.*

*PFS per IRC & OS*

At the time of the initial data cut-off, March 15, 2017, 111 PFS events as assessed by IRC had occurred, with 97 deaths. Median OS and PFS are documented in Section 19.5.

*Reviewer's Comment: Time-to-event endpoints are not interpretable in a single-arm trial.*

**Dose/Dose Response**

The primary efficacy population in this study included only patients who received lorlatinib 100 mg daily. However, responses were observed in patients treated at other dose levels in the dose escalation portion of the study.

**Durability of Response**

Duration of response and CNS duration of response are secondary endpoints; these results are

discussed in this section under the subheading of "Efficacy results – Primary endpoint."

**Persistence of Effect**

The available data does not permit an analysis of the effect of drug over time after treatment is stopped or withheld.

**Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

The EORTC QLQ-C30 and QLQ-C13 were both administered in Part 1 and Part 2 of Study B761001. No primary analysis method was specified for either instrument. The SAP specified that each instrument would be scored based on the EORTC scoring manual. Additionally, the SAP specified that tables would be used to summarize completion rates, as well as the mean score and mean change from baseline for all questions. In Section 19.6, the main summary measure for EORTC QLQ-C30, the Global Health Status / QoL measure, as well as graphs of each category of the EORTC QLQ-C13, are presented.

*Reviewer's Comment: Many of the PRO graphs show a change between the baseline visit and the second visit, with little change in score subsequently. As this is an open-label trial, this may suggest a placebo effect; however, there is no comparator arm so we are unable to draw any conclusion.*

**Additional Analyses Conducted on the Individual Trial**

*ORR per IRC in Patients who had Previously Received Alectinib as Their Only ALK TKI*

Table 56 presents the confirmed ORR as assessed by IRC for patients in the primary efficacy population who had previously received alectinib as their only ALK TKI (with or without chemotherapy). Of the two patients who had CNS disease at baseline in this subpopulation, neither had an intracranial response.

**Table 56: Confirmed ORR per IRC in Patients Who Had Previously Received Alectinib as Their Only ALK TKI**

| | **Overall N = 13** |
|---|---|
| Response Rate (95% CI)[1] | 31% (9%, 61%) |
| CR | 8% |
| PR | 23% |

[1] Estimated using the Clopper-Pearson method
Data cut-off date: 9/15/2017



Reference ID: 4344794

*ORR per IRC in Patients who had Previously Received Ceritinib as Their Only ALK TKI*

Table 57 presents the confirmed ORR as assessed by IRC for patients in the primary efficacy population who had previously received ceritinib as their only ALK TKI (with or without chemotherapy). Of the seven patients who had CNS disease at baseline in this subpopulation, four had an intracranial response.

**Table 57: Confirmed ORR per IRC in Patients Who Had Previously Received Ceritinib as Their Only ALK TKI**

| | Overall N = 13 |
|---|---|
| Response Rate | 46% |
| (95% CI)[1] | (19%, 75%) |
| CR | 0% |
| PR | 46% |

[1] Estimated using the Clopper-Pearson method
Data cut-off date: 9/15/2017

*ORR per IRC in Patients who had Previously Received Crizotinib and at Least One Other ALK TKI*

Table 58 presents the confirmed ORR as assessed by IRC for patients in the primary efficacy population who had previously received crizotinib and at least one other ALK TKI.

**Table 58: Confirmed ORR per IRC in Patients Who Had Previously Received Crizotinib and at Least One Other ALK TKI**

| | Overall N = 119 | Intracranial N = 93 |
|---|---|---|
| Response Rate | 39% | 48% |
| (95% CI)[1] | (30%, 48%) | (38%, 60%) |
| CR | 3% | 31% |
| PR | 36% | 17% |
| Duration of response | | |
| Median in months (95% CI) | 9.9 (5.6, 13.8) | 14.5 (8.3, NE[2]) |

[1] Estimated using the Clopper-Pearson method
[2] Not estimable
Data cut-off date: 9/15/2017

*Intracranial Response for Patients with Measurable Disease*

Table 59 presents the confirmed IC-ORR as assessed by IRC for all patients in the primary efficacy population who had measurable intracranial disease as assessed by IRC. In the analyses below, the presence of CNS metastases was confirmed by the IRC.

**Table 59: Confirmed IC-ORR per IRC in Patients with Measurable Intracranial Disease per IRC in the Primary Efficacy Population**

| | Intracranial N = 89 |
|---|---|
| Intracranial Response Rate | 61% |
| (95% CI)[1] | (50%, 71%) |
| CR | 20% |
| PR | 40% |

[1] Estimated using the Clopper-Pearson method
Data cut-off date: 3/15/2017

The median DOR was not reached for IC-ORR. Table 60 summarizes the DOR by 6, 9, and 12 month landmarks.

**Table 60: Duration of Response per IRC in the Primary Efficacy Population**

| | Intracranial N = 54 |
|---|---|
| Duration of response | |
| ≥ 6 months | 56% |
| ≥ 9 months | 24% |
| ≥ 12 months | 20% |

Data cut-off date: 3/15/2017

*Reviewer's Comment: The IC-ORR is similar to the IC-ORR reported in the primary analysis.*

*Updated Intracranial Response for Patients with Measurable Disease*

Table 61 presents the confirmed IC-ORR as assessed by IRC for all patients in the primary efficacy population based on a data cutoff date of September 15, 2017. In the analyses below, the presence of CNS metastases was confirmed by the IRC.

**Table 61: Updated Confirmed IC-ORR per IRC in Patients with Measurable Disease per IRC in the Primary Efficacy Population**

| | Intracranial N = 89 |
|---|---|
| Response Rate (95% CI)[1] | 60% (49%, 70%) |
| CR | 21% |
| PR | 38% |
| Duration of response | |
| Median in months (95% CI) | 19.5 (12.4, NE[2]) |

[1] Estimated using the Clopper-Pearson method
[2] NE = not estimable.
Data cut-off date: 9/15/2017

*Difference in Response Between the CSR Cutoff and the Safety Update Cutoff*

The safety update allowed for longer duration of follow-up of responders than the CSR cutoff. In addition, the ORR and IC-ORR was slightly different, as some responders responded after the CSR cutoff and some response information from prior to the CSR cutoff was updated after the CSR cutoff. Table 62 shows the number of patients whose intracranial response data was different at the safety update cutoff than the CSR cutoff. This includes changes in response or start date of response.

**Table 62: Number of Patients Whose Intracranial Response Data Was Different at the Safety Update Cutoff than the CSR Cutoff**

| IC-ORR at CSR Cutoff | IC-ORR at Safety Cutoff | N |
|---|---|---|
| No Response | Response | 2 |
| Response | No Response | 1 |

Both patients who had an intracranial response at the safety cutoff date but not the CSR cutoff date began response after the CSR cutoff date. One patient was recorded as having an intracranial response at the CSR cutoff but not having a response at the safety update cutoff. The reader chosen at the CSR cutoff assessed this patient to have a partial response at the CSR cutoff date but progressive disease at the safety update cutoff date. The reader had assessed a lesion on the occipital lobe to be absent on September 28, 2016, resulting in a partial response, and had assessed this same lesion to be present at the safety update cutoff.

Table 63 shows the number of patients whose overall response data was different at the safety update cutoff than the CSR cutoff. This includes changes in response or start date of response.



Reference ID: 4344794

**Table 63: Number of Patients Whose Overall Response Data Was Different at the Safety Update Cutoff than the CSR Cutoff**

| ORR at CSR Cutoff | ORR at Safety Cutoff | N |
|---|---|---|
| No Response | Response | 6 |
| Response | No Response | 1 |
| Response | Response | 3 |

Five of the six patients who did not have an overall response at the CSR cutoff but did have a response at the safety update cutoff responded after the CSR cutoff date, March 15, 2017. One began responding at February 6, 2017. For the three patients who were responders at both cutoff dates and had their start date of response change, the change in response was 1 day, 10 days, and 126 days. The patient who had a response at the CSR cutoff but no response at the safety update cutoff is the same patient discussed above who had these findings for intracranial response.

**Integrated Review of Effectiveness**

### 8.1.3. Assessment of Efficacy Across Trials

Study B7461001 is the only study supporting the efficacy claim in this NDA; therefore, no integrated review of effectiveness was performed. As such, all subsections have been deleted.

**Subpopulations**

*Response by Age, Sex, and Race*

Table 64 presents the confirmed ORR as assessed by IRC by age, sex, and race for all patients with ALK-positive NSCLC who received 100 mg of lorlatinib.



Reference ID: 4344794

**Table 64: Confirmed ORR per IRC by Age, Sex, and Race**

| | | N | ORR | 95% CI |
|---|---|---|---|---|
| Age | <65 | 177 | 49% | (42%, 57%) |
| | ≥65 | 38 | 45% | (29%, 62%) |
| Sex | Male | 88 | 48% | (37%, 59%) |
| | Female | 127 | 49% | (40%, 58%) |
| Race[2] | White | 109 | 42% | (33%, 52%) |
| | Asian | 74 | 51% | (39%, 63%) |
| | Other | 9 | 33% | (7%, 70%) |

Data cutoff date: 9/15/2017

*Response by Pre-Defined Cohort*

Table 65 presents the confirmed ORR as assessed by IRC by pre-defined cohort for all patients in the primary efficacy population. Although these cohorts were only defined for Part 2, we include patients from Part 1 and the Japanese LIC and assign them to these cohorts based on their baseline prior therapy. Demographic and baseline characteristics for these cohorts can be found in Section 19.5.

**Table 65: Confirmed ORR per IRC by Prior Therapy Cohorts Defined in Protocol**

| Cohort | N | ORR | 95% CI |
|---|---|---|---|
| EXP-2: Prior crizotinib only | 29 | 79% | (60%, 92%) |
| EXP-3A: Prior crizotinib + chemotherapy | 35 | 71% | (54%, 85%) |
| EXP-3B: Prior non-crizotinib TKI +/- chemotherapy | 28 | 36% | (19%, 56%) |
| EXP-4: Two Prior TKIs | 75 | 36% | (25%, 50%) |
| EXP-5: Three Prior TKIs | 48 | 40% | (26%, 55%) |

Data cutoff date: 9/15/2017

*Intracranial Response by Age, Sex, and Race*

Table 66 presents the confirmed IC-ORR as assessed by IRC by age, sex, and race for all patients with ALK-positive NSCLC who received 100 mg of lorlatinib.

[2] Race was missing for 23 patients.



Reference ID: 4344794

**Table 66: Confirmed IC-ORR per IRC by Age, Sex, and Race**

| | | N | ORR | 95% CI |
|---|---|---|---|---|
| Age | <65 | 130 | 53% | (44%, 62%) |
| | ≥65 | 19 | 58% | (33%, 80%) |
| Sex | Male | 60 | 48% | (35%, 62%) |
| | Female | 89 | 57% | (46%, 68%) |
| Race[3] | White | 84 | 46% | (35%, 58%) |
| | Asian | 44 | 55% | (39%, 70%) |
| | Other | 5 | 60% | (15%, 95%) |

Data cutoff date: 9/15/2017

*Intracranial Response by Pre-Defined Cohort*

Table 67 presents the confirmed IC-ORR as assessed by IRC by pre-defined cohort for all patients in the primary efficacy population. Although these cohorts were only defined for Part 2, the table below includes patients from Part 1 and the Japanese LIC, assigned to these cohorts based on their baseline prior therapy. Demographic and baseline characteristics for these cohorts can be found in Section 19.5.

**Table 67: Confirmed IC-ORR per IRC by Prior Therapy Cohorts Defined in Protocol**

| Cohort | N | ORR | 95% CI |
|---|---|---|---|
| EXP-2: Prior crizotinib only | 19 | 63% | (38%, 84%) |
| EXP-3A: Prior crizotinib + chemotherapy | 22 | 77% | (55%, 92%) |
| EXP-3B: Prior non-crizotinib TKI +/- chemotherapy | 13 | 38% | (14%, 68%) |
| EXP-4: Two Prior TKIs | 55 | 49% | (35%, 63%) |
| EXP-5: Three Prior TKIs | 40 | 48% | (32%, 64%) |

Data cut-off date: 9/15/2017

*Intracranial Response by Prior Brain Radiation*

Table 68 presents the confirmed IC-ORR as assessed by IRC by prior brain radiation therapy for all patients who were ALK positive and received 100 mg of lorlatinib. In Table 68, patients were confirmed to have CNS disease by the IRC.

[3] Race was missing for 16 patients.



Reference ID: 4344794

**Table 68: IC-ORR per IRC by Prior Brain Radiation Therapy**

| Cohort | N | ORR | 95% CI |
|---|---|---|---|
| No prior brain radiation | 60 | 68% | (55%, 80%) |
| Prior brain radiation | 89 | 44% | (33%, 55%) |

Data cut-off date: 9/15/2017

*Reviewer's Comment: There does not seem to be any differential effects on ORR or ORR-IC according to baseline demographic characteristics.*

**Additional Efficacy Considerations**

None.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The clinical reviewer confirmed Pfizer's safety analyses of Study B7461001, conducting analyses of primary data using the MedDRA Adverse Event Diagnosis Service (MAED) and JMP programs. Key safety issues identified for more detailed review include hepatotoxicity with concomitant CYP3A inducers (see clinical pharmacology section for details), CNS toxicity, hyperlipidemia, pneumonitis/interstitial lung disease, atrioventricular (AV) block, peripheral neuropathy, vision disorders, and edema.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

A total of 332 patients were exposed to lorlatinib in Study B7461001 at a range of doses from 10 mg daily (QD) to 200 mg daily (in single or divided doses). In the dose escalation portion of the study, 54 patients received lorlatinib in dosing cohorts summarized in the table below. In the dose expansion portion of the study, 275 patients received lorlatinib at the RP2D of 100 mg QD. Three patients enrolled in the Japanese lead-in cohort also received lorlatinib at 100 mg QD. Overall, 295 patients (including 275 dose expansion cohort patients, 3 Japanese lead-in cohort patients, and 17 dose escalation cohort patients) received lorlatinib 100 mg QD. The clinical review of the adverse events experienced by patients receiving lorlatinib in Study B7461001 primarily focused on the all-treated population (332 patients), as well as the subpopulation of 295 patients enrolled across both portions of the study and in the Japanese lead-in cohort who received lorlatinib at the RP2D ("100 mg QD pooled group").



Reference ID: 4344794

**Table 69 Dosing cohorts in the dose expansion portion of Study B7461001 (Reviewer table)**

| Dose level | Number of patients |
|---|---|
| 10 mg QD | 3 |
| 25 mg QD | 3 |
| 50 mg QD | 3 |
| 75 mg QD | 12 |
| 100 mg QD | 17 |
| 150 mg QD | 3 |
| 200 mg QD | 3 |
| 35 mg BID | 3 |
| 75 mg BID | 3 |
| 100 mg BID | 4 |

At the time of the data cut-off for the 120-day Safety Update Report (September 15, 2017), the median duration of treatment for the 100 mg QD pooled group was 12.5 months (range 0.03, 35.1 months). At the time of the data cut-off used for the original NDA submission (March 15, 2017), the median duration of treatment for the 100 mg QD pooled group was 8.3 months (range 0.03, 29.1), with a median relative dose intensity of 98.6%.

**Table 70 Exposure for Study B7461001, 100 mg QD pooled group (Reviewer table)**

| | 100 mg QD pooled group N=295 |
|---|---|
| **Duration of exposure in months** | |
| Median | 12.5 |
| Range | (0.03, 35.1) |
| **Duration of exposure, n (%)** | |
| Less than 3 months | 58 (20%) |
| 3 - < 6 months | 33 (11%) |
| 6 - < 12 months | 50 (17%) |
| ≥ 12 months | 154 (52%) |
| **Relative dose intensity (%)** | |
| Median | 98% |

Data cut-off September 15, 2017

**Table 71 Safety population (Reviewer table)**

| Safety Database for Lorlatinib 100 mg QD<br>Individuals exposed to lorlatinib 100 mg QD in this development program for the indication under review<br>N=295 | | | |
|---|---|---|---|
| Clinical Trial Groups | Dose escalation | Dose expansion | Japanese lead-in cohort |
| Study B7461001 | 17 | 275 | 3 |

**Relevant characteristics of the safety population:**

**Table 72 Patient characteristics of the safety population (Reviewer table)**

| Patient characteristic | 100 mg QD pooled group (N=295) n (%) | All treated (N=332) n (%) |
|---|---|---|
| **Sex** | | |
| Male | 125 (42) | 141 (42) |
| Female | 170 (58) | 191 (58) |
| **Age** | | |
| Mean (years) (SD) | 53.3 (12.1) | 53.3 (12.2) |
| Median (years) | 53 | 53 |
| Min, max (years) | 19, 85 | 19, 85 |
| **Age Group** | | |
| < 65 years | 241 (82) | 270 (81) |
| ≥ 65 years | 54 (18) | 62 (19) |
| **Race** | | |
| White | 145 (49) | 169 (51) |
| Black or African American | 3 (1.0) | 6 (1.8) |
| Asian | 108 (37) | 113 (34) |
| Other | 13 (4.4) | 13 (3.9) |
| Unspecified[a] | 26 (8.8) | 31 (9.3) |
| **ECOG performance status** | | |
| 0 | 125 (42) | 140 (42) |
| 1 | 159 (54) | 180 (54) |
| 2 | 11 (3.7) | 11 (3.3) |
| > 2 | 0 | 1 (0.3) |

[a] Data on race and/or ethnicity were not collected at some sites because of local regulations.

**Table 73 Baseline disease characteristics of the safety population (Reviewer table)**

| Disease characteristic | 100 mg QD pooled group (N=295) n (%) | All treated (N=332) n (%) |
|---|---|---|
| **Stage** | | |
| IV | 294 (99.7) | 331 (99.7) |
| Missing | 1 (0.3) | 1 (0.3) |

| Disease characteristic | 100 mg QD pooled group (N=295) n (%) | All treated (N=332) n (%) |
|---|---|---|
| **Histology** | | |
| Adenocarcinoma[a] | 293 (99.3) | 330 (99.4) |
| Large cell | 1 (0.3) | 1 (0.3) |
| Other[b] | 1 (0.3) | 1 (0.3) |
| **Tumor genomic alteration** | | |
| ALK | 245 (83) | 271 (82) |
| ROS1 | 50 (17) | 60 (18) |
| Missing[c] | 0 | 1 (0.3) |
| **CNS metastases** | | |
| CNS metastases at baseline | 184 (62) | 212 (64) |
| Measurable CNS metastases at baseline | 102 (35) | 119 (36) |
| **Prior therapy** | | |
| Crizotinib only | 38 (13) | 45 (14) |
| Crizotinib with or without chemotherapy | 95 (32) | 107 (32) |
| Alectinib with or without chemotherapy | 13 (4.4) | 14 (4.2) |
| One prior ALK TKI +/- chemotherapy | 123 (42) | 139 (42) |
| Two prior ALK TKIs +/- chemotherapy | 77 (26) | 86 (26) |
| Three prior ALK TKIs +/- chemotherapy | 47 (16) | 52 (16) |
| Other | 15 (5.1) | 20 (6.0) |
| None | 33 (11) | 35 (11) |
| **Prior radiotherapy** | | |
| Any radiotherapy for NSCLC | 168 (57) | 192 (58) |
| Radiation therapy to brain | 115 (69) | 133 (69) |

[a] Includes adenocarcinoma not otherwise specified, solid adenocarcinoma with mucin production, bronchioalveolar carcinoma, adenosquamous carcinoma, acinar adenocarcinoma, papillary adenocarcinoma, signet ring adenocarcinoma, micropapillary adenocarcinoma, glandular adenocarcinoma, and bronchial adenocarcinoma
[b] Histology not reported
[c] Patient not confirmed as either ALK- or ROS1-positive

**Adequacy of the safety database:**

The safety data from Study B7461001 is adequate to assess safety with reference to the overall U.S. target population. The safety database does not include a sufficient number of patients aged 65 and older to determine whether they respond differently from younger patients.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

The submission was of adequate quality for clinical review. There are no concerns regarding the integrity of the submission.

**Categorization of Adverse Events**

The definitions of AE and SAE provided in the protocol were appropriate. The active reporting period for SAEs began at the time informed consent was provided through and including 28 calendar days after the last administration of the investigational product. AEs (serious and non-serious) were recorded from the time the patient took at least one dose of lorlatinib through the patient's last study visit. SAEs occurring after the active reporting period ended were reported indefinitely, if the investigator was aware of them.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 and were assessed by frequency; preferred terms were assigned by the Sponsor to the original terms entered on case report forms. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used to grade AEs.

Pfizer summarized AEs by preferred term. Overall, this is appropriate for this application, although this method may create a splitting effect for some AE terms. The potential for splitting was mitigated in Pfizer's analyses of select AEs (AEs of special interest) according to System Organ Class (SOC), Standardized MedDRA Queries (SMQs), combined higher level group terms (HGLTs), or combined preferred terms to define these selected AEs. The safety adverse event data set for all patients who received lorlatinib 100 mg QD on Study B7461001 contains 1,758 individual adverse event listings considered to be treatment emergent. Pfizer coded the 1,758 TEAEs to 607 preferred terms; selected clinically significant adverse events were analyzed using an SMQ or a unique set of preferred terms defined by Pfizer, as above.

*Reviewer's comment: Review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no apparent instances of grossly inacc urate coding. In addition, case report forms (CRFs) from 10% of patients enrolled in Study B7461001 were reviewed (10% of the patients for whom CRFs were submitted) to determine if verbatim terms, toxicity grading, intervention, and characterization of seriousness of adverse events were accurately entered into the database. No major discrepancies were noted by the reviewer.*

Based on potential risks identified from non-clinical and clinical studies of lorlatinib, as well as known safety data from other ALK inhibitors, selected AEs were defined in the protocol for Study B7461001. The majority of these AEs were based on grouping AE terms by SMQs and/or SOCs and included the following:

- Hyperlipidemia, which included the following cluster terms:
    - Hypercholesterolemia, which included preferred terms blood cholesterol increased and hypercholesterolemia



Reference ID: 4344794

    - Hypertriglyceridemia, which included preferred terms blood triglycerides increased and hypertriglyceridemia
- Edema, which included preferred terms edema peripheral, peripheral swelling, edema, swelling, generalized edema
- Fatigue, which included fatigue and asthenia
- Peripheral neuropathy, SMQ peripheral neuropathy (broad)
- CNS effects, which included the following cluster terms:
    - Cognitive effects, which included HLGTs mental impairment disorders, cognitive and attention disorders and disturbances, and deliria (including confusion)
    - Mood Effects, which included HLGTs mood disorders and disturbances NEC, anxiety disorders and symptoms, depressed mood disorders and disturbances, personality disorders and disturbances in behavior, manic and bipolar mood disorders and disturbances
    - Speech effects, which included higher level terms (HLTs) speech and language abnormalities
- Weight gain
- Vision disorder, which included preferred terms diplopia, photopsia, vision blurred, visual impairment, vitreous floaters, visual acuity reduced, visual brightness, photophobia, halo vision, chromatopsia, and visual perseveration
- Hepatic enzymes increased
- QT interval prolongation
- Pneumonitis
- AV block
- Pancreatitis

The safety assessment methods used by Pfizer were adequate for the population, disease, and indication being investigated.

**Routine Clinical Tests**

The tests conducted as part of routine clinical testing and the frequency of such testing are detailed in the Study Calendar, included in Section 8.1.1 of this review. Relevant to this review, in the dose escalation portion of the study, the Mini Mental State Exam (MMSE) was collected to assess mental status; administration of the MMSE was subsequently removed as a study assessment under Amendment 6 (July 15, 2016) to the protocol and was not required for the dose expansion portion of the study. In the dose expansion portion of the study, an assessment of cognitive function was performed via a computerized test developed and validated by a central vendor (b) (4) The test was used to assess cognitive function via a 5-part battery consisting of verbal learning, psychomotor function, attention, working memory, and delayed recall. Also, in the dose expansion portion of the study, an assessment of mood was administered to patients via the Beck Depression Inventory-II (BDI-II) scale, to be analyzed by (b) (4). Finally, for patients in the dose expansion portion of the study, an assessment of suicidal ideation behaviors via the Columbia Suicide Severity Rating Scale (C-SSRS) was



Reference ID: 4344794

administered, to be analyzed by (b) (4)

Per protocol, abnormal test findings, including laboratory abnormalities, were to be reported as AEs if they met the following criteria:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in study dosing outside of protocol-stimulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the investigator or Sponsor

In addition to providing information on laboratory test abnormalities reported as AEs, Pfizer provided laboratory shift tables for clinically relevant laboratory results, with data available for approximately 284-293 of the 295 patients included in the primary safety population.

The safety assessment methods and time points described in the protocol are adequate for the population, disease, and indication being studied.

### 8.2.4. Safety Results

**Deaths**

Overall, 111 of 332 patients (33%) treated on Study B7461001 at any dose of lorlatinib had died by the time of the data cut-off for the 120-Day Safety Update Report. Of these deaths, 41 were reported as grade 5 AEs (e.g. occurring within 28 days of the last dose of lorlatinib); however, 6 of these deaths, all attributed to disease progression, were reported as AEs although they occurred greater than 28 days from the last dose of lorlatinib. Overall, 31 of the 41 (76%) grade 5 AEs were due to disease progression, and 100 of 111 (90%) of the deaths overall were due to disease progression, with one unknown cause of death. None of the 10 deaths among the 332 treated patients were attributed by the investigator as related to lorlatinib; the causes of death in these patients were reported as myocardial infarction (0.7%, including event terms “acute myocardial infarction” and “myocardial infarction”), pneumonia (0.7%, including event terms “pneumonia” and “lung infection”), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), respiratory distress (0.3%), and hypoxia (0.3%). Patient (b) (6) experienced the grade 5 AE of “general physical health deterioration”; however, the narrative summary for this event describes death due to disease progression. Therefore, fatal adverse reactions excluding disease progression occurred in 9 of 332 patients (2.7%) enrolled on Study B7461001. Additional details obtained from Pfizer’s narrative summaries for these 9 patients are described below.

<u>Acute myocardial infarction (patient</u> (b) (6)
Death due to acute myocardial infarction occurred in a 61-year-old male with a past medical history of pulmonary embolism, hyperlipidemia, and anemia. Concomitant medications included rosuvastatin, atorvastatin, fenofibrate, enoxaparin, acetyl salicylic acid, and Lisinopril.



Reference ID: 4344794

He had not received any prior systemic or local therapy for advanced NSCLC; at the time of the event he was receiving lorlatinib 100 mg QD. On cycle 18 day 2, he developed breathlessness. On cycle 18 day 3, he was found unresponsive at home and was brought to the hospital via ambulance. An ECG demonstrated significant ST elevations in leads V1-3. The patient died at the hospital on cycle 18 day 3 and was diagnosed with a fatal myocardial infarction; any additional relevant laboratory results and/or imaging results are pending at the time of this review.

Acute pulmonary edema (patient (b) (6)
Death due to acute pulmonary edema occurred in a 69-year-old male with a past medical history of peripheral motor neuropathy, hypercholesterolemia, and hypertension. Concomitant medications included lorazepam, deanxit, dexamethasone, tramadol, pravastatin, amiloride hydrochloride, hydrochlorothiazide, calcium carbonate/cholecalciferol, and magnesium and potassium supplementation. He had received prior cisplatin, gemcitabine, bevacizumab, pemetrexed, and crizotinib for ALK-positive NSCLC. At the time of the event he was receiving lorlatinib 100 mg QD. The patient began having decreased lower extremity strength, ataxia, and worsening cognitive function (reported as Grade 3 cognitive disorder) on cycle 4, day 14, for which he was hospitalized. During his hospitalization, he became dyspneic (Grade 3) with bilateral wheeze and decreased breath sounds; a chest x-ray was performed showing signs of cardiac overload. He was treated with furosemide and ipratropium and salbutamol. He also received acetylcysteine, glyceryl trinitrate, modurectic, and amoxicillin-clavulanic acid for pulmonary edema. However, his dyspnea worsened; he was treated with morphine and died on cycle 4, day 17. No autopsy was performed.

Embolism (patient (b) (6)
Death due to suspected thromboembolism occurred in a 78-year-old female with a past medical history of hypertension, hypercholesterolemia, and osteoarthropathy. Her concomitant medications included rosuvastatin, melatonin, and magnesium and potassium supplementation. She had received prior therapy for ALK-positive NSCLC with crizotinib, cisplatin, pemetrexed, ceritinib, and brigatinib, and was receiving treatment with lorlatinib 100 mg QD at the time of the event. During cycle 9 of therapy, a CT chest showed disease progression, with a new lesion in the lung; three weeks later she developed suspected thromboembolism with worsening dyspnea and fatigue and died due to this event. An autopsy was not performed. Relevant laboratory imaging and/or laboratory results were requested but are not available at the time of this review.

Hypoxia (patient (b) (6)
Death due to hypoxia was reported in a 44-year old female in the dose escalation portion of the study who received lorlatinib 150 mg QD, with a past medical history of diabetes mellitus, deep vein thrombosis, hypertension, hypothyroidism, anxiety, and depression. Her concomitant medications included hydrocodone bitartrate/paracetamol, warfarin sodium, propranolol, hydrochlorothiazide, metoprolol, lisinopril, clonidine, allopurinol, metformin, levothyroxine sodium, alprazolam, sertraline hydrochloride, pantoprazole, prochlorperazine edisylate,



Reference ID: 4344794

intramuscular medroxyprogesterone acetate, temazepam, rosuvastatin, and guaifenesin. On cycle 31, day 13, the patient was found by her family to be unresponsive and not breathing at home. She was pronounced dead on the arrival of a medical team, and no treatment measures were taken. Her death was attributed to multiple comorbidities including hypertension, supplemental oxygen dependency, morbid obesity, and diabetes. No autopsy was performed.

Lung infection (patient (b) (6)
Death due to probable lung infection occurred in a 58-year-old female with a past medical history of sinus tachycardia, hypothyroidism, hypercholesterolemia, and left femur fracture. Her concomitant medications included enoxaparin, levothyroxine, ondansetron, metoclopramide, oxycodone, paracetamol, ambroxol, prednisone, bisoprolol, ranitidine, rosuvastatin, and ursodeoxycholiacid. She received prior therapy for ALK-positive NSCLC with chemotherapy, crizotinib, and ceritinib. At the time of the event she was receiving treatment with lorlatinib 100 mg QD. At an unknown date, the daughter of the patient called the investigational site to report fever, cough, and cognitive deterioration; the patient was hospitalized and the event was reported as a probable lung infection. Lorlatinib was permanently discontinued, and the patient died on cycle 14 day 22; according to the investigator, due to influenza complicated by pneumonia. No laboratory or imaging reports are available from the time of the event; however, according to the investigator, the patient had radiologically stable disease on the last CT scan performed at the investigational site (reportedly performed the same month as the fatal event).

Myocardial infarction (patient (b) (6)
Death due to myocardial infarction occurred in a 71-year-old male with a past medical history of coronary artery disease (status post stent placement), hypercholesterolemia, hypertension, asthma, chronic renal insufficiency, and iron deficiency. His concomitant medications included atenolol, clopidogrel, lomotil, doxazosin, losartan potassium, furosemide, paracetamol combinations, potassium supplementation, and pravastatin. He was initially enrolled in cohort EXP-6 to receive lorlatinib 100 mg QD, but at the time of the event of myocardial infarction he was receiving lorlatinib 75 mg QD. After 6 months of receiving lorlatinib the patient collapsed at home; paramedics who arrived confirmed he had a myocardial infarction and had died. No relevant laboratory tests were available.

Peripheral artery occlusion (patient (b) (6)
Death due to peripheral artery occlusion occurred in a 55-year-old female with a past medical history of deep vein thrombosis, bilateral lower extremity lymphedema, and hypertriglyceridemia. Her concomitant medications included atorvastatin and fondaparinum sodium. After receiving lovenox for 4 months and 13 days, she developed worsening right lower extremity edema and pain. An ultrasound revealed that there was no flow in the right popliteal artery; a follow-up arterial ultrasound one day later showed an occlusion in the proximal right popliteal artery with minimal flow, and she was hospitalized for further management. She was also found to have left renal vein thrombosis and right lower lung pulmonary embolism. She underwent bilateral lower extremity angiography with placement of a fountain catheter for



Reference ID: 4344794

catheter-directed thrombolysis, followed by a second attempt at thrombectomy and a surgical exploration resulting in a right lower extremity fasciotomy. Her post-operative course was complicated by recurrent lower of perfusion to the lower extremity, and she ultimately underwent right knee disarticulation with primary closure. Lorlatinib was continued throughout these events at a dose of 100 mg QD but was discontinued due to disease progression on hospital day 29. She died on hospital day 32 due to progressive clot burden and progression of disease. An autopsy was not performed.

Pneumonia (patient (b) (6)
Death due to pneumonia occurred in a 52-year-old female patient whose past medical history included asthma, hypertension, cataracts, allergic rhinitis, and glaucoma. Her concomitant medications included bimatoprost, bisoprolol fumarate, cetirizine hydrochloride, dicycloverine, dorzolamide hydrochloride, calcium supplementation, loperamide hydrochloride, ondansetron, prednisolone, salbutamol sulfate, seretide, and levofloxacin. The patient was reported to have ongoing pneumonia at the time of study screening (on levofloxacin). On cycle 1, day 9 she received additional treatment with doxycycline and piperacillin/tazobactam, and vancomycin. In cycle 5 she was reported to have grade 3 pneumonia. A chest x-ray revealed a well-expanded left lung and limited aeration of the right lung. She was treated with vancomycin, piperacillin/tazobactam, cefepime, amoxicillin, levofloxacin, and linezolid. She also began prednisone 10 mg daily beginning on cycle 5, day 18, and she was subsequently discharged from the hospital. However, on cycle 6, day 6, the pneumonia worsened, and she died of pneumonia on cycle 6, day 17. She was initially enrolled to receive lorlatinib 100 mg QD, but at the time of her death was receiving lorlatinib 50 mg QD after dose reductions for events of QTc prolongation and bilateral hand swelling.

Respiratory distress (patient (b) (6)
Death due to respiratory distress occurred in a 52-year-old male patient whose relevant past medical history was not provided. His concomitant medications included metoprolol tartrate, acetylsalicyclic acid, rosuvastatin calcium, midazolam, and naloxone hydrochloride/oxycodone hydrochloride. He was enrolled in the dose expansion portion of the study to receive lorlatinib 100 mg QD. After receiving lorlatinib for 6 months and 1 day, the patient developed disease progression with an increase in size of subcarinal lymph nodes; lorlatinib was continued beyond progression. A stent of the main left bronchus was implanted and palliative radiotherapy was performed. Thirty-four days after the initial disease progression was detected, the patient developed dyspnea (grade 4) and hemoptysis (grade 4); he was hospitalized and died one day later due to respiratory distress.

*Reviewer's comment: The causes of death due to AEs in Study B7461001 are consistent with those that would be expected in a population of patients with metastatic NSCLC; none of the deaths due to AEs appear to be related to treatment with lorlatinib.*

**Serious Adverse Events**



Reference ID: 4344794

Among the 295 patients enrolled in Study B7451001 who received lorlatinib 100 mg QD, 95 patients (32%) experienced 173 SAEs, excluding events of disease progression. Table 74 Serious adverse events occurring in >2 patients (Reviewer table) lists SAEs by preferred term that occurred in >2 patients. Potential drug-relatedness of these SAEs will not be discussed since this report is from a single arm trial.

**Table 74 Serious adverse events occurring in >2 patients (Reviewer table)**

| Preferred term | n (%) |
|---|---|
| Pneumonia[a] | 10 (3.4) |
| Dyspnea | 8 (2.7) |
| Pyrexia | 6 (2.0) |
| Mental status changes | 4 (1.4) |
| Respiratory failure[b] | 4 (1.4) |
| Cognitive effects[c] | 3 (1.0) |
| Fall | 3 (1.0) |
| Pericardial effusion | 3 (1.0) |
| Pleural effusion | 3 (1.0) |
| Pneumonitis[d] | 3 (1.0) |
| Pulmonary embolism | 3 (1.0) |

[a] Includes pneumonia, lower respiratory tract infection, and lung infection
[b] Includes acute respiratory failure and respiratory failure
[c] Includes cognitive disorder, confusional state, and delirium
[d] Includes pneumonitis and interstitial lung disease

In addition to the above, there was one SAE of acute leukemia reported in the 120-day Safety Update Report that was not reported in the original NDA submission. A patient narrative for this case is provided below.

<u>Acute leukemia (patient</u> (b) (6)
Acute myeloid leukemia occurred in a 79-year-old female with a past medical history of hypertension, heart palpitations, cerebral meningioma, and anxiety. She was diagnosed with endometrial cancer (well-differentiated adenocarcinoma, International Federation of Gynecology and Obstetrics [FIGO] stage IB) and treated with total hysterectomy in (b) (6) . She was diagnosed with stage IIIA NSCLC in (b) (6), and initially underwent surgery (wedge resection), followed by carboplatin and gemcitabine from (b) (6) and radiotherapy in (b) (6). In (b) (6) she relapsed in the right lower lobe; molecular studies revealed a ROS1 rearrangement. She received stereotactic radiotherapy in (b) (6) and began treatment with lorlatinib 100 mg QD in (b) (6); baseline sites of disease were the lung, lymph nodes, and a pleural effusion. Her concomitant medications included nebivolol, zolpidem, rosuvastatin, zestoretic, and paracetamol.

On cycle 28 day 1 (b) (6) the patient was found to have Grade 4 thrombocytopenia, Grade 3 leukopenia, Grade 3 neutropenia, and Grade 3 asthenia, leading to temporary discontinuation of lorlatinib. Due to persistent pancytopenia, a peripheral blood smear was

done two weeks later, showing a monomorphic lymphocytic population. On (b) (6), the patient was hospitalized and the immunophenotyping of the peripheral blood showed a population of blasts (CD34+). Subsequently, a diagnosis of acute myeloid leukemia (AML) t (11, 19) was confirmed. Lorlatinib was permanently discontinued on (b) (6).

*Reviewer's comment: AML t (11, 19) is typically considered to be a therapy-related leukemia, with prior treatment with topoisomerase II inhibitors leading to translocations involving chromosome bands 11q23 or 21q22. These therapy-related leukemias are rarely preceded by myelodysplastic syndrome (MDS) and often occur with a shorter latency than alkylating agent-associated therapy-related AML (2-3 years vs. 5-7 years). However, this patient did not receive prior treatment with topoisomerase II inhibitors, and overall, therapy-related AML is rare in patients with a primary diagnosis of lung cancer; in a retrospective analysis of 306 patients with therapy-related AML at a single US center, 9 had a primary diagnosis of lung cancer, of whom 5 had received chemotherapy only, 2 received radiotherapy only, and 2 received combined chemoradiotherapy.[27] These translocations can occur in de novo AML, and, given that preclinical studies of lorlatinib (as well as other agents in its class) have not demonstrated leukemogenic potential, this likely represents a de novo case of AML.*

**Dropouts and/or Discontinuations Due to Adverse Effects**

The prespecified safety withdrawal criteria for Study B7461001 were reasonable; please see the study design in Section 8.1.1 of this review. A total of 23 patients (8%) who received lorlatinib 100 mg QD discontinued study drug due to AEs. The table below lists AEs by preferred term leading to discontinuation of lorlatinib.



Reference ID: 4344794

**Table 75 Adverse events leading to discontinuation of lorlatinib (n=295) (Reviewer table)**

| Preferred term | n (%) |
|---|---|
| Respiratory failure[a] | 4 (1.4) |
| Dyspnea | 2 (0.7) |
| Myocardial infarction[b] | 2 (0.7) |
| Cognitive effects[c] | 2 (0.7) |
| Mood effects[d] | 2 (0.7) |
| Acute leukemia | 1 (0.3) |
| Brain compression | 1 (0.3) |
| Embolism | 1 (0.3) |
| Hallucinations[e] | 1 (0.3) |
| Headache | 1 (0.3) |
| Hydrocephalus | 1 (0.3) |
| Hypoxia | 1 (0.3) |
| Leukocytosis | 1 (0.3) |
| Loss of consciousness | 1 (0.3) |
| Lung infection | 1 (0.3) |
| Mental status changes | 1 (0.3) |
| Parkinsonian gait | 1 (0.3) |
| Peripheral swelling | 1 (0.3) |
| Thrombocytopenia | 1 (0.3) |
| Tinnitus | 1 (0.3) |
| Vomiting | 1 (0.3) |

*Some patients discontinued lorlatinib for more than one of the above events
[a] Includes cases of acute respiratory failure and respiratory failure
[b] Includes cases of acute myocardial infarction and myocardial infarction
[c] Includes cases of cognitive disorder and confusional state
[d] Includes cases of affect lability and anxiety
[e] Includes preferred terms auditory hallucinations and visual hallucinations occurring in the same patient

**Significant Adverse Events**

For a listing of treatment-emergent AEs (TEAEs), including a listing of Grade ≥ 3 TEAEs, see the section below. The following tables list AEs by preferred term that led to dose reduction or dose interruption of lorlatinib in ≥1% of patients. Dose reductions due to AEs occurred in 71 of 295 patients (24%) receiving lorlatinib 100 mg QD, and at the time of the data cut-off for the 120-Day Safety Update (September 15, 2017), the median time to dose reduction was 84 days (range 1-681 days).

**Table 76 Adverse events leading to dose reduction of lorlatinib in ≥ 1% of patients (n=295) (Reviewer table)**

| Preferred term | n (%) |
|---|---|
| Edema[a] | 19 (6) |
| Peripheral neuropathy[b] | 14 (4.7) |
| Cognitive effects[c] | 12 (4.1) |
| Mood effects[d] | 9 (3.1) |
| Hypertriglyceridemia | 5 (1.7) |
| Arthralgia | 3 (1.0) |
| Dizziness | 3 (1.0) |
| Hallucinations[e] | 3 (1.0) |
| Weight increased | 3 (1.0) |

[a] Includes cases of face edema, generalized edema, localized edema, edema, peripheral edema, and peripheral swelling
[b] Includes cases of gait disturbance, hypoesthesia, neuralgia, peripheral neuropathy, neurotoxicity, paresthesia, peripheral sensory neuropathy
[c] Includes cases of amnesia, cognitive disorder, disorientation, and memory impairment
[d] Includes cases of affect lability, anxiety, depression, irritability, mood swings, and personality changes
[e] Includes cases of hallucinations, auditory hallucinations, and visual hallucinations

Dose interruption due to AEs occurred in 142 of 295 patients (48%) receiving lorlatinib 100 mg QD. At the time of the data cut-off for the 120-Day Safety Update (September 15, 2017), the median time to dose interruption was 125 days (range 1-769 days).



Reference ID: 4344794

**Table 77 Adverse events leading to dose interruption of lorlatinib in ≥1% of patients (n=295) (Reviewer table)**

| Preferred term | n (%) |
|---|---|
| Edema[a] | 20 (7) |
| Hypertriglyceridemia[b] | 17 (6) |
| Peripheral neuropathy[c] | 15 (5) |
| Cognitive effects[d] | 13 (4.4) |
| Increased blood lipase | 11 (3.7) |
| Hypercholesterolemia[e] | 10 (3.4) |
| Mood effects[f] | 9 (3.1) |
| Dyspnea | 8 (2.7) |
| Pneumonia[g] | 8 (2.7) |
| Hypertension | 6 (2.0) |
| Increased blood amylase | 5 (1.7) |
| Diarrhea | 5 (1.7) |
| Fatigue[h] | 5 (1.7) |
| Dizziness | 4 (1.4) |
| Fall | 4 (1.4) |
| Hyperglycemia | 4 (1.4) |
| Pyrexia | 4 (1.4) |
| Increased ALT | 3 (1.0) |
| Anemia | 3 (1.0) |
| Arthralgia | 3 (1.0) |
| Atrial fibrillation | 3 (1.0) |
| Back pain | 3 (1.0) |
| Decreased ejection fraction | 3 (1.0) |
| Mental status changes | 3 (1.0) |
| Pericardial effusion | 3 (1.0) |
| Pleural effusion | 3 (1.0) |
| Respiratory failure[i] | 3 (1.0) |
| Vomiting | 3 (1.0) |
| Weight increased | 3 (1.0) |

[a] Includes cases of face edema, generalized edema, localized edema, edema, peripheral edema, peripheral swelling, and swelling
[b] Includes cases of blood triglycerides increased and hypertriglyceridemia
[c] Includes cases of carpal tunnel syndrome, gait disturbance, hypoesthesia, neuralgia, peripheral neuropathy, neurotoxicity, paresthesia, and peripheral sensory neuropathy
[d] Includes cases of amnesia, cognitive disorder, confusional state, disorientation, disturbance in attention, and memory impairment
[e] Includes cases of blood cholesterol increased and hypercholesterolemia
[f] Includes cases of affect lability, affective disorder, agitation, anxiety, depression, irritability, and personality



Reference ID: 4344794

change
[g] Includes cases of lower respiratory tract infection, lung infection, and pneumonia
[h] Includes cases of fatigue and asthenia
[i] Includes cases of acute respiratory failure and respiratory failure

Selected AEs were presented by Pfizer as "Adverse Events of Special Interest" (AESIs) (see Section 8.2.3 for additional details). Many of these are addressed in other sections of this review, as noted in the following list. Those not addressed in other sections of this review will be discussed here. AESIs per Pfizer were: liver tests increased (Section 8.2.5.1), CNS effects (including the cluster terms mood effects, cognitive effects, and speech effects) (Section 8.2.5.2), hyperlipidemia (including hypercholesterolemia and hypertriglyceridemia) (Section 8.2.5.3), interstitial lung disease/pneumonitis (Section 8.2.5.4), AV block (Section 8.2.5.5), vision disorders, edema, weight gain, QTc prolongation, and pancreatitis.

Vision disorders

Vision disorders, including the preferred terms blindness, diplopia, photophobia, photopsia, blurred vision, visual acuity reduced, visual impairment, and vitreous floaters, were reported in 45 of 295 patients (15%) receiving lorlatinib 100 mg QD. The majority of these events were Grade 1 or 2 in severity, with a Grade 3 event of diplopia reported in one patient (0.3%). The most commonly reported vision disorder AEs (all grades) in ≥ 2% of patients by preferred term were blurred vision (5.0%) and visual impairment (4.7%). Lorlatinib was both interrupted and dose reduced for one event (0.3%) of Grade 1 visual impairment; no other study drug actions were taken with the other vision disorder events. Events of vision disorders occurred at a median of 86 days after starting lorlatinib (range 1-444 days).

*Reviewer's comment: The preferred term blindness was not included by Pfizer in the cluster term "Vision disorders" and was added by the clinical reviewer upon review of the safety database.*

Edema

Edema, including the preferred terms eyelid edema, face edema, generalized edema, localized edema, edema, periorbital edema, peripheral edema, peripheral swelling, and swelling, was reported in 168 of 295 patients (57%) who received lorlatinib 100 mg QD. The majority of these events were Grade 1 or 2 in severity, with 9 (3.1%) Grade 3 events. The most commonly reported events of edema (all grades) in ≥ 5% of patients by preferred term were peripheral edema (45%), edema (8%), and peripheral swelling (6%). Lorlatinib was permanently discontinued in one patient (0.3%) for the AE of Grade 3 peripheral swelling, dose reduced in 19 patients (6%) for edema and interrupted in 20 patients (7%). Events of edema occurred at a median of 64 days after the start of lorlatinib (range 1-681 days).

*Reviewer's comment: The preferred terms eyelid edema, face edema, and periorbital edema were included by the clinical reviewer in the cluster term "edema" after review of the safety database. There were three events of ascites reported in the safety database, but on further review of the case narratives for these events, two of the patients for whom ascites was reported had liver and/or peritoneal metastases which may have contributed to the ascites, and*



Reference ID: 4344794

*one patient had ascites present at baseline. Therefore, the reviewer agrees with Pfizer's assessment that these three cases of ascites are likely due to an alternative etiology from the additional cases of edema that are more likely due to lorlatinib and should not be grouped with the cases of edema described in this cluster term.*

Weight gain

Weight gain was reported in 71 of 295 patients (24%) who received lorlatinib 100 mg QD. The majority of these events were Grades 1 and 2 in severity; 13 patients (4.4%) had Grade 3 events. Lorlatinib was reduced in 3 patients (1.0%) and interrupted in 3 patients (1.0%) for weight gain. Weight gain occurred at a median of 98 days after the start of lorlatinib (range 1-702 days).

QTc prolongation

There were 19 (6%) of 295 patients who received lorlatinib 100 mg QD with an event of electrocardiogram QT prolonged; of these, 2 events (0.7%) were Grade 3 in severity. One patient (0.3%) required treatment interruption of lorlatinib. One patient (0.3%) had a shift to QT interval corrected for heart rate using Fridericia's correction (QTcF) ≥ 500 msec post baseline and one patient (0.3%) had a QTcF of ≥ 500 msec at baseline. A maximum QTcF increase from baseline of ≥ 60 msec was observed in 5 (1.7%) patients. The FDA Interdisciplinary Review Team for QT studies (QT-IRT) was consulted for this NDA and determined that of the 275 patients enrolled in the dose expansion portion of Study B7461001, the maximum mean change from baseline for QTcF was 10.1 msec (2-sided 90% upper CI: 12.1 msec). Refer to the review by the QT-IRT team for further details.

*Reviewer's comment: The maximum mean change from baseline for QTcF is considered not clinically significant; no large mean increases in the ΔQTc interval (i.e. 20 msec) are anticipated with the proposed therapeutic dosing regimen of lorlatinib (100 mg QD).*

Pancreatitis

Among the 295 patients receiving lorlatinib 100 mg QD, one patient (0.3%) had an event of preferred term pancreatitis that was Grade 3 in severity; lorlatinib was both interrupted and dose reduced in response to this event. Forty patients (14%) had increased lipase by preferred term and 26 patients (9%) had events that were Grade 3-4 in severity. The dose of lorlatinib was reduced for 4 patients (1.4%) with increased lipase, and treatment with lorlatinib was interrupted for 11 patients (3.7%) with increased lipase. Nineteen patients (6%) had increased amylase by preferred term and 9 patients (3.1%) had events that were Grade 3-4 in severity. The dose of lorlatinib was reduced for 2 patients (0.7%) with increased amylase, and treatment with lorlatinib was interrupted for 5 patients (1.7%) with increased amylase. A narrative for the event of pancreatitis (by preferred term) is provided below.

Pancreatitis (patient (b) (6)

The event of Grade 3 pancreatitis occurred in a 56-year-old female receiving lorlatinib 100 mg QD with a past medical history of asthma, chronic obstructive pulmonary disease, sciatica, and



Reference ID: 4344794

hypertension. Her concomitant medications included salbutamol, acetylsalicylic acid, folic acid, ergocalciferol, alprazolam, atorvastatin calcium, amlodipine besylate, prednisone, spironolactone, and budesonide/fomoterol fumarate. The patient was admitted to the hospital 2 months after the start of treatment with lorlatinib with upper abdominal and back pain. A CT scan with contrast demonstrated mild peri-pancreatic inflammation; her lipase was 497 (1.3 x upper limit of normal [ULN], Grade 1); she was diagnosed with Grade 3 pancreatitis. Lorlatinib was interrupted and dose reduced. She received intravenous fluids and pain control and recovered.

*Reviewer's comment: The cases of increased amylase and lipase described above for whom narrative summaries were provided in the NDA submission were not associated with signs or symptoms of pancreatitis (e.g. abdominal pain, vomiting, imaging findings characteristic of pancreatitis), therefore these laboratory abnormalities were likely not clinically significant. Increases in amylase and lipase based on laboratory shift data are included in this review under* Table 78*.*

**Treatment Emergent Adverse Events and Adverse Reactions**

The most common TEAEs (≥ 25%) reported for lorlatinib administered at a dose of 100 mg QD were edema (including the terms ascites, eyelid edema, face edema, generalized edema, localized edema, edema, peripheral edema, periorbital edema, peripheral swelling, and swelling), peripheral neuropathy (composite term defined by Pfizer), cognitive effects (composite term defined by Pfizer), dyspnea, and fatigue (composite term defined by Pfizer). Table 78 lists TEAEs occurring in ≥ 10% (all Grades) or ≥ 2% (Grade 3-5) of patients receiving lorlatinib 100 mg QD; for definitions of composite terms, see footnotes below the table.

*Reviewer's comment: The cluster term edema was defined by Pfizer to include preferred terms peripheral edema, peripheral swelling, edema, swelling, and generalized edema. The clinical reviewer determined that it would be more appropriate to include the terms eyelid edema, face edema, localized edema, and periorbital edema to this cluster term.*



Reference ID: 4344794

**Table 78 Treatment-emergent adverse events occurring in ≥ 10% (all Grades) or ≥ 2% (Grades 3-5) of patients receiving lorlatinib 100 mg QD (n=295) (Reviewer table)**

| Preferred term or composite term | All grades (%) | Grade 3-5 (%) |
|---|---|---|
| Edema[a] | 57 | 3.1 |
| Peripheral neuropathy[b] | 47 | 2.7 |
| Cognitive effects[c] | 27 | 2.0 |
| Dyspnea | 27 | 5.4 |
| Fatigue[d] | 26 | 0.3 |
| Weight gain | 24 | 4.4 |
| Mood effects[e] | 23 | 1.7 |
| Arthralgia | 23 | 0.7 |
| Diarrhea | 22 | 0.7 |
| Cough | 18 | 0 |
| Headache | 18 | 0.7 |
| Nausea | 18 | 0.7 |
| Myalgia[f] | 17 | 0 |
| Dizziness | 16 | 0.7 |
| Vision disorder[g] | 15 | 0.3 |
| Constipation | 15 | 0 |
| Rash[h] | 14 | 0.3 |
| Back pain | 13 | 0.7 |
| Pain in extremity | 13 | 0.3 |
| Vomiting | 12 | 1.0 |
| Pyrexia | 12 | 0.7 |
| Speech effects[i] | 12 | 0.3 |
| Upper respiratory tract infection[j] | 12 | 0 |
| Sleep effects[k] | 10 | 0 |

[a] Includes preferred terms eyelid edema, face edema, generalized edema, localized edema, edema, peripheral edema, periorbital edema, peripheral swelling, swelling
[b] Includes preferred terms burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, peripheral neuropathy, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance
[c] Includes preferred terms amnesia, attention deficit/hyperactivity disorder, cognitive disorder, confusional state, delirium, dementia, disorientation, disturbance in attention, memory impairment, mental impairment, reading disorder
[d] Includes preferred terms fatigue and asthenia
[e] Includes preferred terms affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, altered mood, mood swings, personality change, stress, suicidal ideation
[f] Includes preferred terms myalgia and musculoskeletal pain
[g] Includes preferred terms blindness, diplopia, photophobia, photopsia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters
[h] Includes preferred terms dermatitis acneiform, rash, maculopapular rash, pruritic rash
[i] Includes preferred terms aphasia, bradyphrenia, dysarthria, slow speech, speech disorder
[j] Includes preferred terms upper respiratory infection, fungal upper respiratory infection, and viral upper



Reference ID: 4344794

respiratory infection
[k] Includes preferred terms abnormal dreams, insomnia, nightmare, sleep disorder, sleep talking, and somnambulism

It is appropriate to include all of these TEAEs in the Adverse Reactions section of the prescribing information for lorlatinib since these data are derived from a single arm trial.

**Laboratory Findings**

Table 79 lists treatment-emergent laboratory abnormalities, based on laboratory shift tables, occurring in >20% of patients treated with lorlatinib 100 mg QD. Laboratory shift results were available for 290-293 of the 295 patients included in the ISS except for amylase, for which laboratory shift results were available for 284 patients.

**Table 79 Worsening laboratory values occurring in >20% of patients (n=295) (Reviewer table)**

| Parameter | All grades (%) | Grade 3-4 (%) |
|---|---|---|
| **Chemistry** | | |
| Hypercholesterolemia[a] | 96 | 18 |
| Hypertriglyceridemia[a] | 90 | 18 |
| Hyperglycemia[b] | 52 | 5 |
| Increased AST[a] | 37 | 2.1 |
| Hypoalbuminemia[c] | 33 | 1.0 |
| Increased ALT[a] | 28 | 2.1 |
| Increased lipase[d] | 24 | 10 |
| Increased alkaline phosphatase[a] | 24 | 1.0 |
| Increased amylase[e] | 22 | 3.9 |
| Hypophosphatemia[a] | 21 | 4.8 |
| Hyperkalemia[b] | 21 | 1.0 |
| Hypomagnesemia[a] | 21 | 0 |
| **Hematology** | | |
| Anemia[b] | 52 | 4.8 |
| Thrombocytopenia[b] | 23 | 0.3 |
| Lymphopenia[a] | 22 | 3.4 |

N=number of patients with at least one on-study assessment
[a] N=292
[b] N=293
[c] N=291
[d] N=290
[e] N=284

Among patients with elevations of liver function tests, two potential Hy's law cases were identified by Pfizer, one in a patient in the dose escalation portion of the study and one in a patient in the dose expansion portion of the study. Narratives for these two patients are



Reference ID: 4344794

presented below.

Potential Hy's law case (patient (b) (6)
A potential Hy's law case occurred in a 36-year-old female who was initially enrolled to receive lorlatinib 100 mg BID but was receiving lorlatinib 75 mg QD at the time of the event. Her past medical history included hypercholesterolemia. Her concomitant medications included paracetamol ((b) (6) docusate sodium/sennoside A+B, gabapentin, morphine sulfate, pantoprazole, furosemide, and rosuvatstatin (b) (6) On cycle 14 day 21, the patient developed Grade 3 increased AST and ALT, Grade 4 increased gamma-glutamyl transferase (GGT), Grade 2 increased bilirubin (2.2 mg/dL [normal range 0-1.2 mg/dL]), and Grade 1 increased alkaline phosphatase (AP) (210 IU/L [normal range 30-130 IU/L]). These laboratory findings did not meet Hy's law criteria; lorlatinib treatment was interrupted, and on cycle 15 day 5, the patient's ALT decreased to Grade 1 in severity, the AST level decreased to Grade 2 in severity, and the GGT decreased to Grade 2 in severity.

On cycle 30 day 21 (day 632 of the study), the patient's AST and ALT levels began to increase again (see table below), while the AP level remained normal. However, lorlatinib was permanently discontinued due to the increased AST/ALT. She was hospitalized; a liver ultrasound demonstrated a fatty liver without cirrhosis, portal hypertension, or liver metastases. Fourteen days later (day 646), her AST, ALT, and GGT levels increased to Grade 3 in severity, with Grade 1 AP elevation. Autoimmune and infectious screens were conducted with negative results; a liver biopsy was performed sixteen days (day 648) after her initial presentation. The biopsy demonstrated moderate to heavy inflammatory infiltrates in the portal tracts, consisting mainly of small lymphocytes. The bile ducts showed minimal epithelial damage. The acini showed numerous acidophil bodies and moderate focal necrosis, with moderate to mixed macrovesicular and microvesicular steatosis. According to the biopsy report, the histologically appearance would be consistent with drug-induced liver injury in the appropriate clinical setting. On day 652, the elevations of AST/ALT and total bilirubin met potential Hy's law criteria and on day 654, her liver function test results improved and she was discharged from the hospital. The concomitant medications paracetamol (discontinued on day 633) and rosuvastatin (discontinued on day 638) were considered to have potentially contributed to this event.

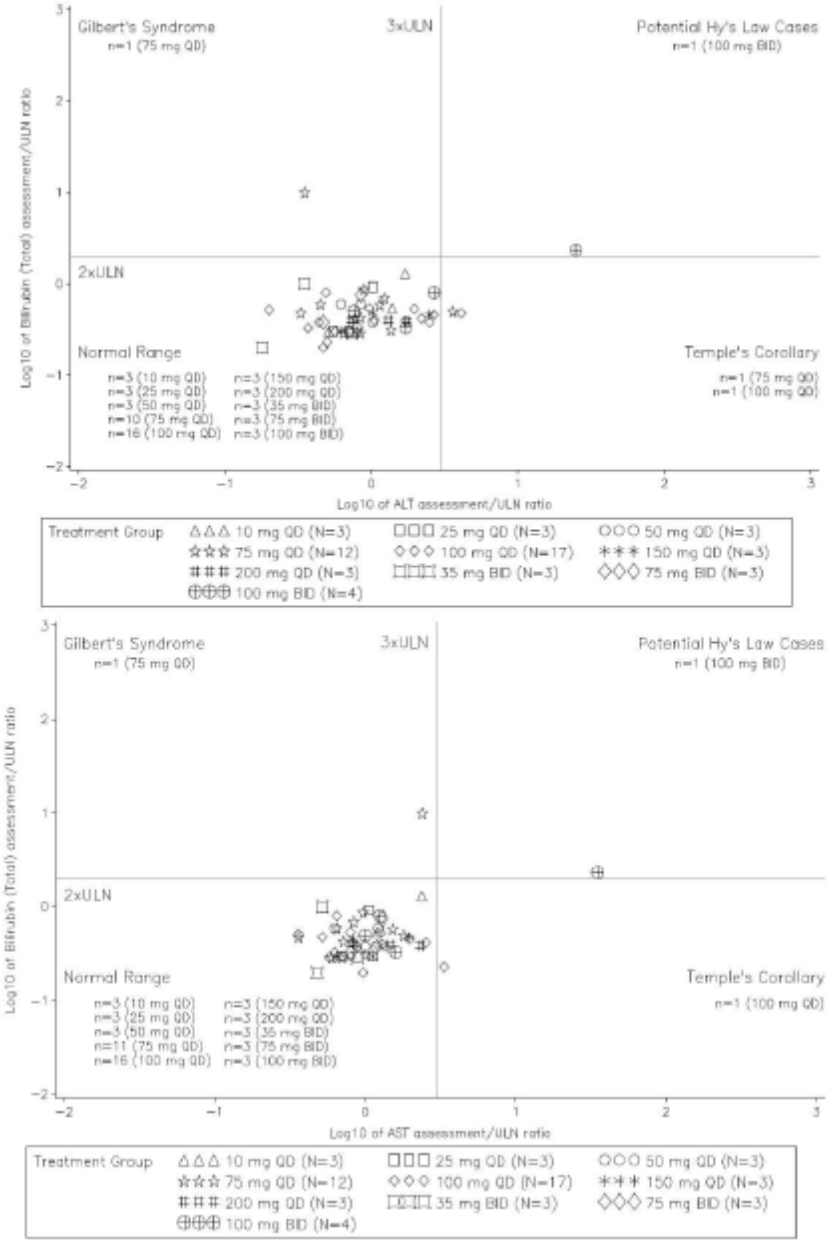
**Table 80 Liver function testing for patient (b) (6) (Reviewer table)**

| **Study day** | **632** | **646** | **648** | **652** | **654** | **677** |
|---|---|---|---|---|---|---|
| ALT (range 5-55 IU/L) | 195 | 953 | 1367 | 787 | 544 | 263 |
| AST (range 5-55 IU/L) | 277 | 1448 | 1896 | 650 | 451 | 242 |
| GGT (range 0-35 IU/L) | N/A | 361 | 569 | 518 | 392 | 103 |
| Total bili (range 0-1.2 mg/dL) | 0.2 | 0.6 | 1.2 | 2.9 | 1.7 | 0.6 |
| AP (range 30-130 IU/L) | 56 | 153 | 255 | 257 | 249 | 114 |



Reference ID: 4344794

**Figure 9 eDISH analysis for patient (b) (6) (Applicant figure)**




*Reviewer's comment: Although the patient met Hy's law criteria on study day 652 with Grade 3 AST and ALT elevations and Grade 2 elevation in total bilirubin, she also had a mildly elevated AP (Grade 2) as well as elevated GGT (Grade 3), which are suggestive of cholestasis. She was taking paracetamol and rosuvastatin which can cause liver injury, both of which were discontinued shortly after lorlatinib was discontinued. However, the liver biopsy was consistent with drug-induced liver injury (DILI). It is possible that lorlatinib may have contributed to or been the primary cause of DILI in this case, but this is difficult to determine given all the factors involved.*

Potential Hy's law case (patient (b) (6))

A potential Hy's law case occurred in a 47-year-old male receiving lorlatinib 100 mg QD. His medical history was not reported. His concomitant medications includes pravastatin, dexamethasone, levetiracetam, and midazolam. Prior to the event of potential Hy's law, lorlatinib was temporarily withheld beginning cycle 18 day 3 for the SAE of influenza. On cycle 18 day 13 the patient was found to have a significant increase in AST, ALT, amylase, and lipase (all reported as Grade 4 in severity; see Table 81 below). Hy's law criteria were met on cycle 18 day 22. The patient was also found to have progression of disease in the pleura, peritoneum, and pancreas. Lorlatinib was not restarted and the patient died due to disease progression on cycle 19 day 6.

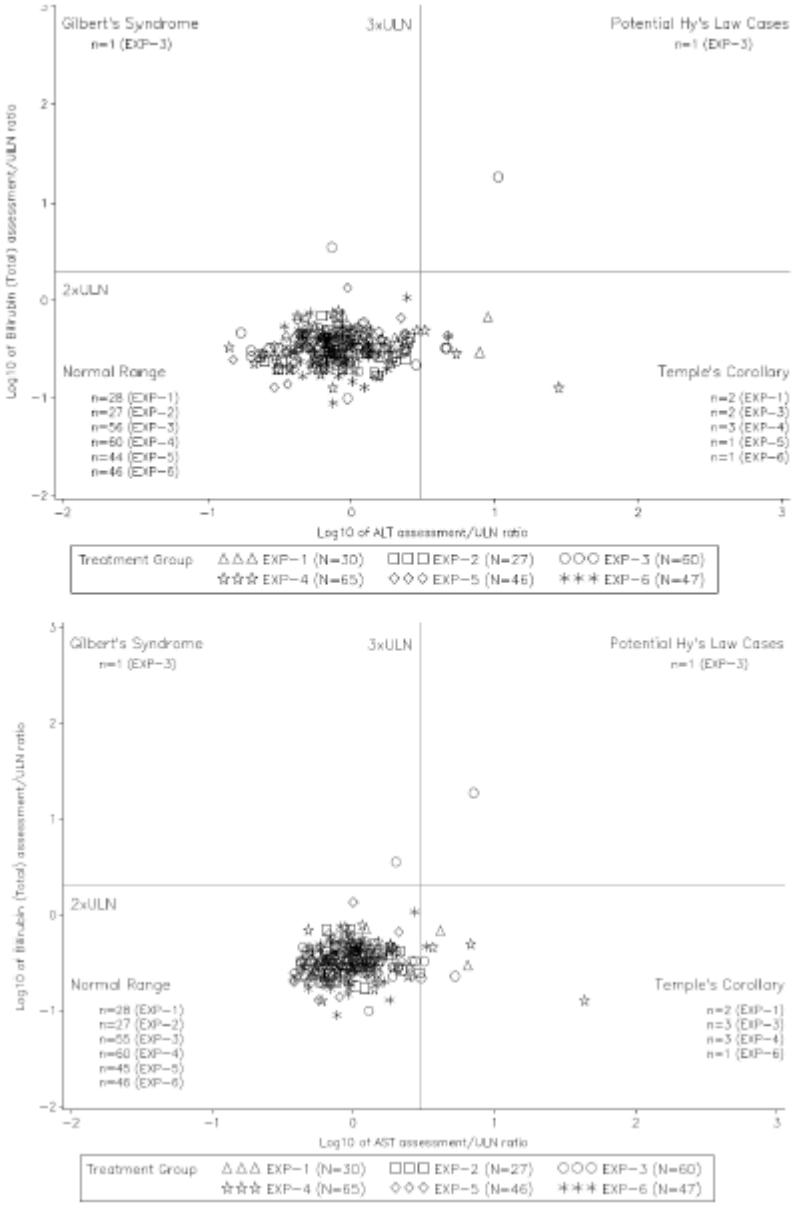
**Table 81 Liver function testing for patient (b) (6) (Reviewer table)**

| Study day | C18D1 | C18D13 | C18D22 |
|---|---|---|---|
| ALT (range 8-50 IU/L) | 29 | 1158 | 529 |
| AST (range 12-50 IU/L) | 26 | 1186 | 357 |
| AP (range 30-120 IU/L) | 89 | N/A | 1952 |
| Total bili (range 0.3-1.2 mg/dL) | 0.5 | N/A | 22.5 |
| Amylase (< 350 IU/L) | 69 | 769 | N/A |
| Lipase (range 21-67 IU/L) | 18 | 910 | N/A |



Reference ID: 4344794

**Figure 10 eDISH analysis for patient (b) (6) (Applicant figure)**




*Reviewer's comment: The concurrent imaging findings of disease progression in the peritoneum and pancreas were the likely cause of the liver function test abnormalities; thus, this case does not represent DILI due to lorlatinib treatment.*

**Vital Signs**

In the group of 295 patients who received lorlatinib 100 mg QD, 26 (9%) of patients had increases in their systolic blood pressure (SBP) ≥ 40 mmHg. One (0.3%) patient had an SBP increase ≥ 60 mmHg. Diastolic blood pressure (DBP) was increased by ≥ 20 mmHg in 26% of

patients, and three patients (1.0%) had DBP increases of ≥ 40 mmHg. Decreases in SBP and DBP were also observed, with the most prominent change being a decrease of ≥ 20 mmHg in DBP in 15% of patients.

A pulse rate of > 120 beats per minute (bpm) was reported in 6.5% of patients; a maximum increase from baseline of ≥ 30 bpm occurred in 19% of patients.

As of the data cutoff for the 120-day Safety Update Report, the all-causality AE of hypertension was reported in 9% of patients, including one case of preferred term hypertensive crisis; of these 4.1% of patients had an event that was Grade 3 in severity. Lorlatinib was dose reduced in one (0.3%) patient and interrupted in 2.0% of patients due to hypertension. One patient (0.3%) had an AE of hypotension.

*Reviewer's comment: A narrative for the event of hypertensive crisis in patient* (b) (6) *was not provided; however, the patient was a 77-year-old male in treatment group EXP-4 of the dose expansion portion of the study who had a significant past medical history that included hypertension, atrial fibrillation, gout, and Parkinson's disease. At study entry, he was receiving the anti-hypertensive medications nicardipine hydrochloride and valsartan. Lorlatinib was dose reduced due to the event of hypertensive crisis, but the event was attributed to disease under study by the investigator. Given his medical history of hypertension and the investigator's attribution of the event, the etiology of the hypertensive crisis was likely multifactorial.*

Weight gain is discussed above as a clinically significant adverse event.

**Electrocardiograms (ECGs)**

For detailed information on ECG findings from Study B7461001, refer to the review by the FDA QT-IRT team, which was consulted for this NDA. The QT-IRT team concluded that the QT interval was not affected to any clinically significant extent; findings related to the PR interval are discussed in Section 8.2.5 of this review.

**QT**

The ability of lorlatinib to prolong the QT interval was assessed in 275 patients in the dose expansion portion of Study B7461001. Lorlatinib did not prolong the QTc interval to any clinically relevant extent. Treatment-related QT interval prolongation events were reported for 16 (5.8%) patients. There were no SAEs of prolonged QT. One patient had a Grade 3 AE of prolonged QT which required temporary discontinuation of lorlatinib; however, this patient had a history of baseline prolonged QTc interval (QTcF > 500 ms) and was enrolled in violation of the protocol, and she was ultimately discontinued from the study given this protocol violation.

The QT-IRT was consulted; see their review for full details. Based on data from the 275 patients enrolled in the dose expansion portion of the study, the QT-IRT concluded that no large mean increases in the QTc interval (i.e. > 20 ms) are anticipated with the proposed therapeutic dosing



Reference ID: 4344794

regimen of lorlatinib (100 mg QD), based on a central tendency analysis (largest 90% CI upper bound of 12.1 ms with a mean of 10 ms). Furthermore, the QTc effects did not appear to have any direct relationship with lorlatinib exposures.

**Immunogenicity**

This subsection is not relevant to this review, as lorlatinib is not associated with a concern for immunogenicity.

### 8.2.5. Analysis of Submission-Specific Safety Issues

**Hepatotoxicity**

Hepatotoxicity occurred in all twelve healthy subjects enrolled on Study B7461011, a single site, open label, two-period, two-treatment, fixed sequence cross-over study to estimate the effect of multiple dose rifampin administration on the single dose pharmacokinetics (PK) of lorlatinib. See the Clinical Pharmacology section (Section 6) of this review for detailed information regarding the lorlatinib plasma PK evaluation data from Study B7461011. In this study, twelve healthy subjects received rifampin, a strong CYP3A inducer that also activates pregnane X receptor (PXR), 600 mg once daily for 8 days (Days 1 to 8) and a single oral dose of lorlatinib 100 mg on Day 8. The primary objective of the study was to estimate the effect of multiple dose rifampin on plasma PK of a single oral dose of lorlatinib under fasting conditions in healthy adult subjects; the secondary objective was to assess the safety and tolerability of a single 100 mg dose of lorlatinib in healthy adult subjects under fasting conditions when administered alone and following multiple doses of rifampin. The study consisted of two periods: Period 1, in which a single 100 mg dose of lorlatinib was administered in a fasted state on Day 1, followed by a washout period of at least 10 days, followed by Period 2, in which rifampin 600 mg once daily was planned to be administered from Day 1 to Day 12, with a single 100 mg dose of lorlatinib administered concurrently with rifampin on Day 8.

In Period 2, rifampin was to be administered 1 hour before or 2 hours after a meal from Day 1 to Day 12, except for the rifampin dose on Day 8, which was to be administered simultaneously with lorlatinib 100 mg. All subjects were to refrain from lying down (except when required for blood pressure, pulse, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after lorlatinib dosing. Safety evaluations included monitoring for AEs and SAEs, potential cases of drug-induced liver injury, safety laboratory measurements, physical exams, vital signs, and ECGs.

A total of 12 subjects were assigned to study treatment. Subject (b) (6) voluntarily withdrew from the study during Period 2 due to Grade 3 nausea and vomiting on day 9, one day after receiving the co-administered doses of lorlatinib and rifampin. All subjects were analyzed for safety and PK data. The median age was 43 (range 21-55 years), 11 subjects (92%) were female, 6 subjects (50%) were Black, and 2 subjects (17%) were White.

Eleven of 12 subjects in Period 2 had normal liver function test (LFT) values while they were receiving rifampin alone; Subject (b) (6) ad a mildly elevated (Grade 1) ALT and AST during the period of rifampin dosing. After receiving lorlatinib co-administered with rifampin on Day 8, increases in AST and ALT were observed in all subjects; therefore, further dosing of rifampin was halted beginning on Day 10. There were no bilirubin increases in any subject. Five subjects were hospitalized for observation; no intervention was required. Grade 4 ALT or AST elevations occurred in 50% of subjects, Grade 3 ALT or AST elevations occurred in 33% of subjects, and Grade 2 ALT or AST elevations occurred in 8% of subjects. ALT or AST elevations occurred within 3 days of co-administration of lorlatinib and rifampin and returned to within normal limits after a median of 15 days (range 7-34 days). The median time to recovery was 18 days in subjects with Grade 3 or 4 ALT or AST elevations and 7 days in the subject with Grade 2 ALT or AST elevations. Table 82 below provides liver function testing reports for the 12 subjects enrolled on Study B7461011.

**Table 82 Liver function testing in Study B7461011 (Reviewer table)**

| Subject ID | Baseline ALT (IU/L) | Baseline AST (IU/L) | Number of days to first ALT/AST elevation | Maximum ALT (IU/L) (ULN 41) | Maximum AST (IU/L) (ULN 50) | Number of days to recovery | Maximum grade ALT or AST elevation |
|---|---|---|---|---|---|---|---|
| (b) (6) | 16 | 24 | 2 | 207 | 186 | 10 | 3 |
| | 13 | 16 | 3 | 851 | 1140 | 20 | 4 |
| | 13 | 21 | 3 | 863 | 1198 | 25 | 4 |
| | 14 | 15 | 3 | 118 | 80 | 15 | 1 |
| | 25 | 24 | 2 | 129 | 85 | 7 | 2 |
| | 13 | 23 | 2 | 283 | 335 | 11 | 3 |
| | 11 | 19 | 2 | 262 | 246 | 15 | 3 |
| | 25 | 31 | 1 | 262 | 228 | 11 | 3 |
| | 17 | 20 | 2 | 695[a] | 576 | 11 | 4 |
| | 19 | 21 | 1 | 1338 | 1307 | 27 | 4 |
| | 16 | 20 | 2 | 1126 | 1258 | 34 | 4 |
| | 27 | 18 | 3 | 1261 | 1086 | 25 | 4 |

U it of normal
[a] ULN 34 IU/L

Subject (b) (6) had Grade 1 elevation in alkaline phosphatase at Day -8; this mild elevation persisted throughout the study period and did not increase higher than Grade 1. Subjects (b) (6) had Grade 1 elevations in GGT beginning from the day prior to co-administration of rifampin and lorlatinib (Subject (b) (6), to between 1 and 5 days after co-administration of rifampin and lorlatinib.

Because of the results of Study B7461011, FDA requested that Pfizer perform an analysis of any hepatic events occurring in any patients who received a strong CYP3A4 inducer in violation of



Reference ID: 4344794

the protocol while enrolled on Study B7461001 and in all patients receiving a moderate CYP3A4 inducer while enrolled on Study B7461001. The protocol for Study B7461001 excluded patients with current use or anticipated need for drugs that are known strong CYP3A4 inducers including their administration within 12 days prior to the first lorlatinib dose. Use of drugs known to be moderate CYP3A4 inducers was permissible; however, concomitant medications with a suspected CYP3A4 inductive effect must have been approved by the Sponsor.

Two patients were identified who received a strong CYP3A4 inducer (phenytoin) while enrolled on Study B7461001; narratives for these patients are provided below.

Strong CYP3A4 inducer (patient (b) (6)
This patient was a 44-year-old female with ALK-positive NSCLC with a past medical history of hypertension, diabetes, hypothyroidism, anxiety, and depression. Her concomitant medications included hydrocodone bitartrate/paracetamol, warfarin sodium, propranolol, hydrochlorothiazide, metoprolol, lisinopril, clonidine, allopurinol, metformin, levothyroxine sodium, alprazolam, sertraline hydrochloride, pantoprazole, prochlorperazine edisylate, medroxyprogesterone acetate, temazepam, rosuvastatin, and guaifenesin. She was enrolled in the dose escalation portion of the study in the 150 mg QD cohort. Lorlatinib treatment was initiated on (b) (6) and was held from (b) (6) for Grade 2 hallucinations and resumed at 100 mg QD on (b) (6). She was admitted to the hospital on (b) (6) for Grade 3 altered mental status and developed Grade 2 partial seizures requiring intubation on (b) (6) This event is discussed in further detail in Section 8.2.5.2 of this review; during this hospitalization she received phenytoin 100 mg QD for seizure control from (b) (6) to (b) (6) there was one day of concomitant treatment of phenytoin with lorlatinib . No laboratory measurements were drawn on (b) (6) and no adverse events related to hepatoxicity were reported.

Strong CYP3A4 inducer (patient (b) (6))
This patient was a 36-year-old female with ROS1-positive NSCLC with a past medical history of hypercholesterolemia, headaches, and constipation. Her concomitant medications were paracetamol, docusate sodium/sennoside A+B, gabapentin, morphine sulfate, pantoprazole, and furosemide. She was enrolled in the dose escalation portion of the study in the 100 mg BID cohort. Lorlatinib treatment was initiated on (b) (6) and was dose reduced to 75 mg BID on (b) (6) for Grade 3 lower respiratory tract infection. Lorlatinib was held from (b) (6) to (b) (6) following an episode of Grade 2 seizures for which she was hospitalized and received treatment with phenytoin 300 mg QD from (b) (6) No safety laboratory measurements were drawn during this period and no adverse events related to hepatotoxicity were reported during this time.

In Study B7461001, three patients received a moderate CYP3A4 inducer while receiving lorlatinib; all of these patients received modafinil, which has lower PXR activation compared to rifampin (Fahmi et al 2012). Narratives for these three patients are provided below.



Reference ID: 4344794

Moderate CYP3A4 inducer (patient (b) (6))

This patient was a 46-year-old female with ALK-positive NSCLC with a past medical history of Wernicke's aphasia and seizures. Her concomitant medications included acyclovir, ibuprofen, lamotrigine, estradiol, Premarin, and Tri-Luma cream. She was enrolled in the dose escalation portion of the study in the 200 mg QD cohort and began treatment with lorlatinib on (b) (6) The lorlatinib dose was reduced to 100 mg QD on (b) (6) for hypercholesterolemia. She received modafinil 100 mg QD from (b) (6). There were no hepatic associated laboratory abnormalities or hepatic adverse events reported during this concurrent treatment period. Results from safety laboratory measurements performed during co-administration of lorlatinib and modafinil are reported in Table 83 below.

**Table 83 Hepatic function testing during co-administration of lorlatinib and modafinil, patient (b) (6) (Applicant table)**

| | (b) (6) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 |
| Total bili (range 0-1 mg/dL) | 0.3 | 0.3 | 0.3 | 0.2 | 0.4 | 0.2 | 0.2 | 0.3 |
| AST (range 9-32 U/L) | 23 | 25 | 21 | 18 | 30 | 28 | 31 | 27 |
| ALT (range 7-30 U/L) | 16 | 19 | 14 | 11 | 25 | 23 | 28 | 24 |
| AP (range 30-100 U/L) | 57 | 56 | 60 | 53 | 68 | 61 | 75 | 68 |

Moderate CYP3A4 inducer (patient (b) (6)

This patient was a 59-year-old male with ALK-positive NSCLC. His past medical history included pulmonary embolism, dyspepsia, chronic kidney disease, hypertension, seizure, spinal compression fracture, spinal column stenosis, peripheral edema, hypothyroidism, osteopenia, asthma, hyperlipidemia, and constipation. His concomitant medications included salbutamol sulfate, fluticasone/vilanterol, dexamethasone, duonase, fondaparinux, guaifenesin, ibuprofen, levetiracetam, pantoprazole, prednisone, propranolol hydrochloride, and rosuvastatin. He was enrolled in the dose escalation portion of the study as part of the 100 mg QD cohort and started treatment with lorlatinib on (b) (6). He received modafinil 100 mg QD from



Reference ID: 4344794

(b) (6) until the time of the clinical study report, which included laboratory measurements until (b) (6). During the period of concomitant modafinil and lorlatinib administration, he experienced one ALT elevation on (b) (6) to 46 U/L (reference range 0-44 U/L). The ALT returned to below the upper limit of normal on the next laboratory measurement on (b) (6) There were no hepatic related adverse events or abnormal liver function tests reported during the concomitant treatment period.

Moderate CYP3A4 inducer (patient (b) (6)

This patient was a 54-year-old male with ALK-positive NSCLC. His past medical history included hypothyroidism and hypercholesterolemia. His concomitant medications included levothyroxine, calciferol, lorazepam, mematine, olanzapine, and atorvastatin. He was enrolled in the dose expansion portion of lorlatinib and received lorlatinib 100 mg QD. Lorlatinib treatment began on (b) (6) and modafinil 200 mg QD was started prior to study entry on (b) (6). The patient received both medications concomitantly from (b) (6) until the patient discontinued the study on (b) (6) On (b) (6), prior to the start of lorlatinib, the patient had Grade 1 AST elevation (102 U/L [reference range 10-40 U/L]), ALT elevation (58 U/L [reference range 10-55 U/L]), and alkaline phosphatase (151 U/L [reference range 45-115 U/L]). During the period of concurrent administration of modafinil and lorlatinib, the patient continued to experience Grade 1 AST elevations (42-52 U/L) and alkaline phosphatase elevations (157-171 U/L), with one instance of Grade 1 ALT elevation (69 U/L). There were no reported hepatic adverse events during the concomitant treatment period. Results from safety laboratory measurements performed during co-administration of lorlatinib and modafinil are reported in Table 84 below.

**Table 84 Hepatic function testing during co-administration of lorlatinib and modafinil, patient (b) (6) (Applicant table)**

| | (b) (6) | | | | |
|---|---|---|---|---|---|
| Total bili (range 0-1 mg/dL) | 0.3 | 0.6 | 0.2 | 0.3 | 0.2 |
| AST (range 10-44 U/L) | 102 | 42 | 52 | 55 | 52 |
| ALT (range 10-55 U/L) | 58 | 36 | 55 | 69 | 53 |
| AP (range 45-115 U/L) | 151 | 157 | 140 | 130 | 171 |

*Reviewer's comment: The mild elevations in AST, ALT, and alkaline phosphatase are likely not related to the concurrent administration of lorlatinib and modafinil as they began prior to the start of lorlatinib, while the patient was receiving modafinil only, and did not worsen once lorlatinib treatment was started.*

Overall, amongst the 332 patients treated with lorlatinib on Study B7461001, adverse events



Reference ID: 4344794

associated with hepatotoxicity were relatively uncommon, with 3.6% of patients experiencing at least one all-causality hepatic adverse event (including preferred terms biloma, cholecystitis, abnormal hepatic function, hepatic hemorrhage, hepatic steatosis, hepatocellular injury, hepatosplenomegaly, and jaundice, as well as the two cases that met Hy's law criteria discussed in Section 8.2.4). Of these events, four (1.2%) were Grade 3-4 in severity. Lorlatinib was temporarily interrupted for one case of jaundice and was permanently discontinued for both cases of possible drug-induced liver injury. Laboratory shift abnormalities in AST were reported in 34% of patients receiving lorlatinib 100 mg QD (1.7% were Grade 3-4 in severity); laboratory shift abnormalities in ALT were reported in 24% of patients receiving lorlatinib 100 mg QD (1% were Grade 3-4 in severity); and laboratory shift abnormalities in alkaline phosphatase were reported in 20% of patients receiving lorlatinib 100 mg QD (1.7% were Grade 3-4 in severity).

**CNS effects**

Pfizer grouped three categories of CNS effects classified as adverse events of special interest (AESIs) by the cluster terms cognitive effects, mood effects, and speech effects. Cognitive effects included all preferred terms comprising the higher level group terms of mental impairment disorders, cognitive and attention disorders and disturbances, and deliria (including confusion). Mood effects included all preferred terms comprising the higher level group terms of mood disorders and disturbances NEC, anxiety disorders and symptoms, depressed mood disorders and disturbances, personality disorders and disturbances in behavior, and manic and bipolar mood disorders and disturbances. Speech effects included all preferred terms comprising the high level term of speech and language abnormalities. To evaluate these effects, the mini mental state exam (MMSE) was collected in the dose escalation portion of the study. The MMSE is a 30-item questionnaire that tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall and language. Of the 54 patients treated in the dose expansion portion of the study, 47 were included in the evaluable analysis set for MMSE, defined as all enrolled patients who received at least one dose of study medication who completed a baseline (last assessment prior to first dose of lorlatinib), and at least one post-baseline assessment. The MMSE assessment was removed under Amendment 6 of the study protocol and was not required for the dose expansion portion of the study.

In the dose expansion portion of Study B7461001, an assessment of cognitive function (b) (4) was performed via a computerized test developed and validated by a central vendor, (b) (4). This test included a 5-part battery test consisting of verbal learning, psychomotor function, attention, working memory, and delayed recall; the following specific tests were administered: Detection Test; Identification Test; One Back Test; International Shopping List Test; and International Shopping List Test-Delayed Recall. These tests are intended to evaluate the following interrelated cognitive domains: psychomotor speed, attention, working memory, episodic memory, and verbal learning. Of the 275 patients who were treated as part of the dose expansion portion of the study, 213 patients were included in the (b) (4) evaluable analysis set, defined as all enrolled patients who received study treatment, had a baseline test assessment, and at least one on-study test assessment.



Reference ID: 4344794

An assessment of mood was also administered to patients via the Beck Depression Inventory-II (BDI-II) scale and was analyzed by (b) (4) The BDI-II includes items describing mood (loss of pleasure, sadness, and irritability), suicidal ideation, and cognitive dysfunction (punitive thoughts, self-criticism, self-dislike, pessimism, and poor concentration), as well as somatic symptoms including appetite, fatigue, sleep, and libido changes. The BDI-II uses 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

Finally, an assessment of suicidal ideation behaviors was performed via the Columbia Suicide Severity Rating Scale (C-SSRS) which was analyzed by (b) (4) The C-SSRS assesses both behavior and ideation, providing a summary of suicidality. It assesses the lethality of attempts and other features of ideation, including its frequency, duration, controllability, reasons for ideations, and deterrents. It 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 Study B7461001 was one year.
2. The Since Last Visit (SLV) version rates suicidal ideation and behavior that emerged since the last assessment.

In the C-SSRS, higher counts indicate more intense and frequent suicidal ideation and behavior, as follows:

- Level 1: Wish to be dead
- Level 2: Non-specific active suicidal thoughts
- Level 3: Active suicidal ideation with any methods (not plan) without intent to act
- Level 4: Active suicidal ideation with some intent to act, without specific plan
- Level 5: Specific plan and intent
- Level 6: Preparatory acts or behavior
- Level 7: Aborted attempt
- Level 8: Interrupted attempt
- Level 9: Non-fatal suicide attempt
- Level 10: Completed suicide

In the dose expansion portion of Study B7461001, 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 obtained on Day 1 of Cycle 1. The results from the (b) (4) BDI-II, and C-SSRSS were reported by Pfizer in a separate analysis performed by (b) (4) The number of patients with evaluable BDI-II and C-SSRS data available in the NDA



Reference ID: 4344794

submission were 196 and 200, respectively.

In addition to the preferred terms that comprised the three main cluster terms of cognitive effects, mood effects, and speech effects defined by Pfizer, FDA proposed the addition of other preferred terms to fully characterize the extent of the CNS effects experienced by patients enrolled in both portions of Study B7461001. All included terms are presented in Table 85 below.

**Table 85 Preferred terms included as CNS effects (Reviewer table)**

| Cluster term | Preferred term |
|---|---|
| Cognitive effects | Amnesia |
| | Attention deficit/hyperactivity disorder |
| | Cognitive disorder |
| | Confusional state |
| | Delirium |
| | Dementia |
| | Disorientation |
| | Disturbance in attention |
| | Memory impairment |
| | Mental impairment |
| | Reading disorder |
| Mood effects | Affect lability |
| | Affective disorder |
| | Aggression |
| | Agitation |
| | Anxiety |
| | Depressed mood |
| | Depression |
| | Euphoric mood |
| | Irritability |
| | Mania |
| | Mood altered |
| | Mood swings |
| | Personality change |
| | Stress |
| | Suicidal ideation[a] |
| Speech effects | Aphasia[a] |
| | Dysarthria |
| | Slow speech |
| | Speech disorder |
| Sleep effects[b] | Abnormal dreams |
| | Insomnia |



Reference ID: 4344794

| Cluster term | Preferred term |
|---|---|
| | Nightmare |
| | Sleep disorder |
| | Sleep talking |
| | Somnambulism |
| Miscellaneous | Abnormal behavior |
| | Altered state of consciousness |
| | Bradyphrenia |
| | Epilepsy |
| | Hallucination |
| | Hallucination auditory |
| | Hallucination visual |
| | Impulse-control disorder |
| | Mental status changes |
| | Nervous system disorder |
| | Partial seizures |
| | Psychomotor hyperactivity |
| | Seizures |

[a] Included in cluster term by reviewer
[b] Cluster term and corresponding preferred terms included as CNS effects by reviewer

A consultation from the Division of Psychiatry Products (DPP) was requested by the NDA clinical reviewer to address the validity of the instruments used to assess depressive symptoms and suicidal ideation and behavior and to comment on the clinical significance of the reported findings from Study B7461001. The consultative reviewer from DPP performed analyses using the following datasets that included patients in the dose expansion portion of Study B7461001:

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

Results from the consultative report were incorporated into the clinical safety review.

Overall, CNS effects occurred in 54% of the 332 patients treated in Study B7461001; 6% of patients had Grades 3-4 CNS effects. Lorlatinib was permanently discontinued in five patients (1.5%) due to a CNS effect, dose reduced in 8% of patients, and temporarily discontinued in 9% of patients. The median time to first onset of any CNS effect was 1.2 months (range: 1 day to 1.7 years). The subcategories of CNS effects as defined by Pfizer and the clinical reviewer are described in more detail below.

<u>Mood effects</u>



Reference ID: 4344794

Mood effects, defined by the preferred terms listed in Table 85, occurred in 24% of patients treated on Study B7461001; 1.8% of these events were severe (Grades 3-4). This includes two patients (patients (b) (6) and (b) (6)) for whom multiple instances of suicidal ideation were endorsed on either the BDI-II or the C-SSRS but were not captured as an adverse event. Two patients required permanent discontinuation of lorlatinib for mood effects; lorlatinib was dose reduced in 3.0% of patients and temporarily discontinued in 3.0% of patients due to a mood effect. Within the cluster term mood effects, the most commonly experienced adverse events were anxiety (6%) and irritability (5.7%).

<u>BDI-II findings</u>
According to the consultative reviewer's analysis of the data from the BDI-II, a total of 196 patients were included in the evaluable analysis set. At baseline, the mean BDI-II total score was 8.8 (range: 0 to 32). The distribution of total scores at baseline by overall symptom severity was:

- Minimal (0 to 13): N=149
- Mild (14 to 19): N=29
- Moderate (20-28): N=16
- Severe (29-63): N=2

The mean change from baseline in the BDI-II total score for all assessments was -2.8, indicating improved depressive symptoms on average. The range of changes was -32 to +39, with 13 patients (6.6%) having an increase in the total score of ≥ 10 on at least one assessment, suggesting a potentially clinically significant increase in overall depressive symptoms. Of these 13 patients, four had an increase of ≥ 10 on multiple study visits; all four had minimal depressive symptoms at baseline and none had a documented previous history of depression. One patient (ID (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. In Cycles 4, 5, and 12, he endorsed suicidal thoughts but had no intent to carry them out. At other visits, including the End of Treatment (EOT) visit, he denied any suicidal thoughts. Further details regarding the four patients in whom an increase of ≥ 10 on the BDI-II are summarized in Table 86.



Reference ID: 4344794

**Table 86: Patients with an increase in BDI-II total score ≥ 10 on multiple study visits (DPP Reviewer table)**

| Patient ID | Summary of changes from baseline |
|---|---|
| (b) (6) | Baseline score = 5. Changes from baseline were consistently ≥ +11 in 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 of +33 at the EOT. |
| | Baseline score = 7. Six of nine on treatment assessments revealed changes from baseline ≥ +10 with a maximum change of +32. The change at the EOT was -7. |
| | Baseline score = 3. Three of six on treatment assessments revealed changes from baseline ≥ +10, with a maximum change +25. |

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. Of the 13 patients (4.4%) with a TEAE of depression, the median duration of depressive events was approximately 9 weeks with a range of 2 weeks to 56 weeks; one patient (0.03%) had an AE of depression that was Grade 3 in severity. None of the 13 depression AEs were considered serious and no patients discontinued treatment due to depression. The mean on-treatment BDI-II total score for the 13 patients who reported depression as an AE was 6.1 (range 0 to 32); the mean change from baseline was -3.7 (range -16 to +7), indicating slight improvement on average. Five patients (1.7%) received medication for depressive symptoms and no patients received non-drug treatment (e.g. psychotherapy). Four of the 13 patients (31%) had a previous diagnosis of depression and 10 (77%) had brain metastases at baseline.

<u>C-SSRS findings</u>

According to the consultative reviewer, the C-SSRS evaluable analysis set consisted of 200 patients from the dose expansion portion of Study B7461001. Six patients (3%) reported suicidal ideation with in the last year on their baseline C-SSRS assessment; all six endorsed one item of the C-SSRS, i.e., a wish to be dead but no thoughts of acting on that wish. Four of these six patients reported no suicidal ideation during study treatment. The other two patients and five other patients reported suicidal ideation at some point during study treatment; for six of these seven patients, there was a wish to be dead but no thought of acting on it that was recorded at only one assessment. In one patient (ID (b) (6), a wish to be dead was reported at Cycles 5, 6, 8, and 12. At Cycle 5, the 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. The patient had a pre-study diagnosis of depression and the patient had a BDI-II total score of 20; changes from baseline during treatment were ≤ +6, with improvement relative to baseline documented at Cycles 2, 3, 4, 8, and 10.

Of note, no patient is reported as having engaged in suicidal behavior during treatment.

*Reviewer's comment: The DPP reviewer identified two patients, IDs* (b) (6),

*who were reported in the original* (b) (4) *study data as having committed suicide. The study sites were queried and confirmed that these were data entry errors which were corrected after the* (b) (4) *data cutoff date* (b) (6) (b) (4) *reported that as of that date, neither patient had committed suicide or attempted suicide. The clinical reviewer reviewed the case report forms (CRFs) for both patients. Patient* (b) (6) *was discontinued from the study on* (b) (6) *(reported date of death), with Cycle 6 (Day 1* (b) (6) *reported as the final dosing cycle; however, on the Cycle 3 tumor assessment, the patient is reported as having progressive disease (non-target lesion progression). On the C-SSRS assessment performed at the start of the last dosing cycle* (b) (6) *no elements of suicidal ideation were endorsed. On* (b) (6) *the patient elected to discontinue treatment and transition to hospice care and refused further follow up. Patient* (b) (6) *was enrolled on study on* (b) (6) *and was still receiving treatment as of the CRF submitted with the original NDA submission. The last dosing cycle date reported on the CRF was* (b) (6) *(Cycle 37) with the most recent C-SSRS assessment reported on* (b) (6)*, in which no suicidal ideation was endorsed.*

*Pfizer was also queried about the above two patients by the clinical reviewer and confirmed that while the date of death for patient* (b) (6) *was confirmed by the clinical site as being* (b) (6)*, the patient had declined further follow up as of* (b) (6)*, so the cause of death is unknown. Patient* (b) (6) *remains alive and receiving treatment with lorlatinib as of* (b) (6)*. Furthermore, Pfizer stated that no AE or SAE of suicide has been reported in the clinical database for Study B7461001 as of* (b) (6)*.*

Three patients of the 332 patients (0.9%) treated on Study B7461001 experienced suicidal ideation that was captured as an AE term; event narratives for the three patients for whom suicidal ideation was captured as an AE term are provided below.

<u>Suicidal ideation (patient (b) (6))</u>
The adverse event of Grade 2 suicidal ideation was reported in a 38-year-old male with ROS1-positive NSCLC with brain metastases, initially diagnosed in (b) (6). His past medical history included gastroesophageal reflux disorder (GERD), myopathy, and seizures. His concomitant medications included diphenhydramine hydrochloride, rosuvastatin calcium, dexamethasone, levetiracetam, nystatin, pantoprazole, prednisone, vitamin B complex, and gemfibrozil. The patient began therapy with lorlatinib 100 mg QD on (b) (6). While still receiving study treatment, a physician note from a visit at his investigational site dated (b) (6) reported that the patient had "thoughts of suicide but no plan…Felt stressed at work as end of quarter close out of accounting. Recommend patient to relax and take time off which he is planning after the closeout quarter. Also advised the patient can hold lorlatinib if he feels stressed. Patient would like to continue lorlatinib and I agree." No action was taken with lorlatinib. On (b) (6) the patient had an additional event of poor impulse control and anger due to a long wait time for his visit; at that time the physician note stated that, "He has also had another episode of stress at work to a point he was thinking of suicide." Due to this event and to anger felt to be out of character for the patient, lorlatinib was temporarily discontinued after this visit; it is not clear



Reference ID: 4344794

when lorlatinib was restarted.

Suicidal ideation (patient (b) (6)
The adverse event of Grade 2 suicidal ideation was reported in a 52-year-old male with ALK-positive NSCLC with brain metastases, initially diagnosed in (b) (6). His past medical history included anemia, chronic pain, constipation, GERD, goat, hypertension, hypertriglyceridemia, and type 2 diabetes mellitus. He began treatment with lorlatinib 100 mg QD on (b) (6). On (b) (6) the patient reported suicidal ideation (Grade 2); he had been dose reduced to 25 mg QD due to hyperlipidemia and hypoxia at that time. A physician note dated (b) (6) states, "Questionnaire reveals Grade 2 fleeting suicidal ideation associated with pain before nerve block – not drug related," and further states, "Psychiatric: He has a normal mood and affect. His behavior is normal. Thought content normal." A physician note dated (b) (6) states, "Prior questionnaire revealed Grade 2 fleeting suicidal ideation associated with pain before nerve block – not drug related – grade 0 today." The patient received no treatment for this event and no action was taken with lorlatinib. An MRI brain performed on (b) (6) revealed numerous known metastatic lesions demonstrating decreased size and intensity of enhancement and improved surrounding edema, with no new or enlarging lesions.

*Reviewer's comment: Although the investigator assessed the fleeting suicidal ideation as being unrelated to lorlatinib given pain before a nerve block procedure, it is possible that treatment with lorlatinib contributed to the intensity of negative emotion experienced by the patient at the time of the procedure.*

Suicidal ideation (patient (b) (6)
The adverse event of Grade 1 suicidal ideation was reported in a 32-year-old female with ALK-positive NSCLC with brain metastases, initially diagnosed in (b) (6). Her past medical history included hyperlipidemia, cerebral edema, QTc prolongation, and allergic rhinitis. She began treatment with lorlatinib 100 mg QD on (b) (6) At the visit for cycle 24 day 1 (b) (6), the patient answered "yes" to the question, "Wish to be dead since last visit," on the suicidal ideation questionnaire. The following conversation between the patient and the study coordinator was documented in the medical record: "I was depressed because my father-in-law mentioned that I slacked off the meal preparation. However, now I'm soothed by making myself heard. I realize that I feel distress because my disease condition is getting better and I'm recharging. So I'm OK." A brain MRI performed on (b) (6) revealed no new or worsening brain metastases. The event of suicidal ideation was considered resolved on (b) (6) when the patient stated, in a conversation with the study coordinator, "I have been free from my distress and completely recovered…".

*Reviewer's comment: It is not possible to rule out the contribution of lorlatinib to the passive suicidal ideation experienced by the patient after a family altercation.*

*Reviewer's comment: The events of suicidal ideation in patients (b) (6) may have been captured only in the setting of this clinical trial due to the use of the C-SSRS, and*



Reference ID: 4344794

*otherwise may not have been reported as an adverse event given their transient nature. However, in the context of the mood effects experienced by approximately 20% of the patients enrolled on Study B7461001, the reviewer considers the inclusion of the AEs of suicidal ideation in these two patients in the overall reported CNS effects to be appropriate, regardless of the extenuating circumstances surrounding the event (nerve block and family altercation). Furthermore, the reactions of suicidal ideation and "wishing to be dead" are likely out of proportion to the inciting event, which may be a result of the overall effect of lorlatinib on the patients' mood.*

A summary of the patients who experienced suicidal ideation during Study B7461001 is provided in Table 87.

**Table 87 Patients with suicidal ideation in Study B7461001 (Reviewer table)**

| Patient ID | Group | Where SI was captured | | | Other CNS effects and grade |
|---|---|---|---|---|---|
| | | AE term and grade | BDI-II | C-SSRS | |
| (b) (6) | | Yes, Grade 2 | No | No | Aggression, Grade 1<br>Agitation, Grade 1<br>Amnesia, Grade 1<br>Seizure, Grade 3 |
| | | Yes, Grade 2 | No | Yes, Level 1 | No |
| | | Yes, Grade 1 | No | No | Amnesia, Grade 1 |
| | | No | Yes | No | No |
| | | No | No | Yes, Level 1 | Hallucination, Grade 1 |
| | | No | No | Yes, Level 1 | No |
| | | No | No | Yes, Level 1 | Anxiety, Grade 1 |
| | | No | No | Yes, Level 1 | Euphoric mood, Grade 1<br>Hallucination visual, Grade 1 |
| | | No | No | Yes, Level 1 | Depression, Grade 2 |
| | | No | No | Yes, Level 3 | Dysarthria, Grade 1<br>Memory impairment, Grade 1 |

*Included as patient with suicidal ideation in CNS effects aggregate term

*Reviewer's comment: Of the patients for whom suicidal ideation was captured only in the screening tests administered per the protocol, patients* (b) (6) *were considered by the reviewer to have more clinically significant suicidal ideation than those for whom Level 1 suicidal ideation ("wish to be dead") was reported on the C-SSRS on only one occasion during the study (patients* (b) (6)*). Patient* (b) (6) *had multiple instances in which he endorsed suicidal ideation including one instance in which he stated that he would kill himself if he had the chance, and patient* (b) (6) *endorsed Level 3 suicidal ideation on the C-SSRS, indicating active thoughts of suicide but no plan, as well as multiple other instances of Level 1 suicidal ideation. Therefore, of these*



Reference ID: 4344794

*patients, only patients* (b) (6) *were included in the group of patients with CNS effects in the Warnings and Precautions section of the USPI. Patient* (b) (6) *had additional CNS effects (dysarthria, memory impairment) captured as AEs during the study.*

*In summary, the findings reported from the BDI-II and C-SSRS, as well as an evaluation of other psychiatric adverse events described below, indicate that most patients had no or minimal levels of depression, suicidal ideation, and most other psychiatric adverse events. A small fraction of patients (1-2%) had a more significant level of symptomatology. Limitations of these analyses include the extent to which these findings are attributable to lorlatinib as opposed to other causes (such as reactions to disability or a shortened life span, or to brain metastases) as this was a single arm trial with no control group. Furthermore, patients with severe psychiatric illnesses were excluded from the trial and may be more vulnerable to developing psychiatric adverse events than the patients enrolled on study. Finally, DPP recommends C-SSRS assessments at every protocol visit which did not occur in Study B7461001, raising the possibility that some instances of suicidal ideation or behavior may have been undetected.*

Cognitive effects

Cognitive effects, defined by the preferred terms listed in Table 85, occurred in 29% of patients treated on Study B7461001; 2.1% of these events were severe (Grade 3). Two patients required permanent discontinuation of lorlatinib for cognitive effects; lorlatinib was dose reduced in 4.2% of patients and temporarily discontinued in 4.8% of patients due to a cognitive effect. Within the cluster term cognitive effects, the most commonly experienced adverse events (e.g. occurring in ≥ 5% of patients) were memory impairment (11%), cognitive disorder (9%), and amnesia (6%).

*Reviewer's comment: In the dose expansion portion of Study B7461001, group mean performance on the Identification Test portion of the* (b) (4) *battery is reported to have declined from baseline over the course of the study. Group mean scores on the other four 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 Study B7461001 had any relationship to the administration of lorlatinib.*

Speech effects

Speech effects, defined by the preferred terms listed in Table 85, occurred in 14% of patients treated on Study B7461001; 0.3% of these events were severe (Grade 3). Lorlatinib was not permanently discontinued for any patient due to a speech effect; lorlatinib was dose reduced for 0.9% of patients and temporarily discontinued in 0.6% of patients due to a speech effect. The most commonly experienced adverse event within the cluster term of speech effects was dysarthria (4.2%).

Sleep effects

Sleep effects, defined by the preferred terms listed in Table 85, occurred in 10% of patients



Reference ID: 4344794

treated on Study B7461001; none of these events were severe. No actions were taken with lorlatinib due to a sleep effect. The most commonly experienced adverse event within the cluster term of speech effects was insomnia (7.8%).

Miscellaneous

Other significant CNS effects not included in the predefined cluster terms cognitive effects, mood effects, and speech effects, were hallucinations (including preferred terms hallucinations, hallucinations auditory, and hallucinations visual) and seizures (including preferred terms seizures, partial seizures, and epilepsy). Hallucinations occurred in 6.9% of patients treated on Study B7461001; two of these events (0.6%) were severe (Grade 3). Lorlatinib was permanently discontinued in one patient (0.3%) due to hallucinations, and was dose reduced in 0.9% of patients and temporarily discontinued in 2.1% of patients.

Seizures were reported in 3.0% of patients treated on Study B7461001; Grade 3 event severity occurred in one patient (0.3%). No patients discontinued lorlatinib due to seizures, and two patients (0.6%) had both a dose reduction and a temporary discontinuation in lorlatinib due to these events. Although seizures are a potential effect of brain metastases, in many cases, the events described occurred in the setting of additional neurologic symptoms not attributed to CNS metastases and without progression or change in existing brain lesions. Narratives for patient experiencing an adverse event of seizures are provided below.

Seizure (patient (b) (6)

The event of Grade 2 seizure occurred in a 36-year-old female with ROS1-positive NSCLC initially diagnosed in (b) (6), with CNS metastases and a history of whole brain radiation in (b) (6). She had a past medical history of hypercholesterolemia, headaches, and constipation. Her concomitant medications were paracetamol, docusate sodium/sennoside A+B, gabapentin, morphine sulfate, pantoprazole, and furosemide. She was enrolled in the dose escalation portion of the study in the 100 mg BID cohort. On cycle 5 day 4 (b) (6) she was admitted to the hospital following seizures with possible status epilepticus. Brain CT on the day of admission did not reveal any hemorrhage and MRI brain reported no features of leptomeningeal disease with overall improvement in the appearance of CNS metastases. Her hospitalization was prolonged for the serious adverse event of headaches and lorlatinib was withheld from (b) (6) and was resumed at a reduced dose of 50 mg BID. She received treatment for the seizures with levetiracetam and midazolam. On (b) (6) an electroencephalogram (EEG) revealed no epileptiform activity, and no further episodes of seizures were observed during her hospitalization.

Seizure (patient (b) (6)

The event of Grade 2 seizure occurred in a 50-year-old female with ALK-positive NSCLC with CNS metastases, initially diagnosed in (b) (6) She received stereotactic radiosurgery (SRS) to six brain lesions in (b) (6), to the left parietal lobe in (b) (6), to two brain lesions in (b) (6), gamma knife radiosurgery to five brain lesions in (b) (6) and whole brain radiation therapy ending in 9/2013. Her past medical history included anxiety, endometriosis, spinal compression fracture,



Reference ID: 4344794

nephrolithiasis, pulmonary embolism, and right-sided hemiparesis. Her concomitant medications included paracetamol, acetylsalicylic acid, prochlorperazine, dexamethasone, diphenoxylate/atropine, enoxaparin, folic acid, levetiracetam, lorazepam, magnesium oxide, metoclopramide hydrochloride, ondansetron hydrochloride, pantoprazole, sennoside A+B, cholecalciferol, oxycodone, Vicodin, morphine, and hydromorphone hydrochloride. She was enrolled in the dose expansion portion of the study and began treatment with lorlatinib 150 mg QD on (b) (6). The patient was hospitalized on cycle 10 day 22 (b) (6) for abrupt onset altered mental status and weakness. An EEG showed seizure activity. One week prior to this presentation the patient had completed a corticosteroid taper given as treatment for radiation necrosis. Lorlatinib was withheld beginning on (b) (6) and a head CT on that date was stable compared with a prior head CT from (b) (6). Treatment for seizure included levetiracetam, methylprednisolone 12 mg, lacosamide, and oral corticosteroids. The patient's mental status returned to baseline and she was considered to have recovered from the event of seizure on (b) (6) Lorlatinib was resumed at the reduced dose of 75 mg QD on cycle 11 day 1 (b) (6). The investigator concluded that the seizure activity was due to radiation necrosis after completion of the steroid wean one week prior to the event.

<u>Seizure (patient (b) (6))</u>
The event of Grade 1 seizure occurred in a 53-year-old male with ALK-positive NSCLC with CNS metastases, initially diagnosed in (b) (6) Whole brain radiation was completed in (b) (6) (b) (6) and brain radiotherapy was performed on 10 lesions on (b) (6). He had a past medical history of diabetes, dysarthria, occasional gait instability, hypercholesterolemia, memory impairment, and deep vein thrombosis of the right lower extremity. His concomitant medications included atorvastatin, sulfmethaoxazole/trimethoprim, denosumab, docusate sodium, enoxaparin, insulin aspart, insulin glargine, levetiracetam, meloxicam, omeprazole, pioglitazone, sennoside A+B, gemfibrozil, and prednisone. On cycle 50 day 1 (b) (6), the patient reported the AE of seizure. Lacosamide 200 mg was started as treatment. No action was taken with lorlatinib. The investigator assessed the event as related to disease.

<u>Partial seizures (patient (b) (6)</u>
The event of Grade 2 partial seizure occurred in a 44-year-old female with ALK-positive NSCLC initially diagnosed in (b) (6), with CNS metastases. She had a past medical history of hypertension, diabetes, hypothyroidism, anxiety, and depression. Her concomitant medications included hydrocodone bitartrate/paracetamol, warfarin sodium, propranolol, hydrochlorothiazide, metoprolol, Lisinopril, clonidine, allopurinol, metformin, levothyroxine sodium, alprazolam, sertraline hydrochloride, pantoprazole, prochlorperazine edisylate, medroxyprogesterone acetate, temazepam, rosuvastatin, and guaifenesin. She was enrolled in the dose escalation portion of the study in the 150 mg QD cohort. Lorlatinib treatment was initiated on (b) (6) She presented to the ER on (b) (6) for hallucinations; a head CT on that date was reported as being negative and a chest x-ray was read as suggestive of bronchitis. Oral antibiotics were started and she was not admitted to the hospital. On (b) (6) her family brought her to the outpatient clinic where she was found to be altered, demonstrating perseveration and echolalia, and was not answering questions appropriately. She was sent to



Reference ID: 4344794

the ER for further evaluation where she was found to be hypotensive with a blood pressure of 79/66. A lumbar puncture was performed and revealed clear cerebrospinal fluid (CSF) with a red blood cell (RBC) count of 4 (units not provided), lymphocytes 86, monocytes 14, glucose 77, and protein 36 (units and reference ranges not provided). A gram stain revealed no white blood cells or organisms and a bacterial meningitis screen was negative. The CSF pathology report was also negative as were CSF cultures and blood cultures. A repeat head CT on (b) (6) revealed no significant intracranial abnormality changes and an MRI brain was obscured by motion artifact. The patient was admitted to the intensive care unit (ICU) with Grade 3 altered mental status, where she developed Grade 2 partial (focal) seizures on (b) (6) requiring intubation. Continuous video EEG monitoring was performed from (b) (6) and demonstrated moderately severe diffuse background slowing, with slowing most prominent in the right hemisphere with intermixed epileptiform discharge phase reversing at P4. A repeat MRI brain was performed on (b) (6) and did not show any evidence of solid metastases but could not rule out leptomeningeal disease. Repeat lumbar puncture on (b) (6) revealed blood and rare degenerated cells, with no features diagnostic of malignancy. She was treated with levetiracetam, propofol, and a phenytoin taper which was completed prior to her discharge. The AE of partial seizure was considered resolved on (b) (6)

On (b) (6), a repeat MRI brain revealed no evidence of leptomeningeal disease and a repeat lumbar puncture revealed no evidence of malignancy. She was extubated on (b) (6) and her mental status improved and returned to baseline; she was discharged to a skilled nursing facility on (b) (6) after a CT chest on (b) (6) revealed stable disease. Lorlatinib was held from (b) (6) and resumed at 100 mg QD on (b) (6)

<u>Partial seizures (patient (b) (6))</u>
The event of partial seizures occurred in a 52-year-old male with ROS1-positive NSCLC with CNS metastases, initially diagnosed in (b) (6) His past medical history included attention deficit hyperactivity disorder, anxiety, asthma, cervical spine stenosis, depression, hypercholesterolemia, hypertension, and insomnia. His concomitant medications included rosuvastatin calcium, guanfacine, naproxen, prochlorperazine, fenofibrate, zolpidem tartrate, amlodipine, testosterone, dexamethasone, levetiracetam, fish oil, lorazepam, prednisone, methylphenidate hydrochloride, montelukast sodium, Tylenol with codeine, and cholecalciferol. On cycle 1 day 1 the patient developed focal seizure was reported as a Grade 1 adverse event; no action was taken with lorlatinib and no treatment was given. The event resolved on the same day. The investigator assessed the causality of partial seizures as related to disease.

<u>Partial seizures (patient (b) (6)</u>
The event of Grade 2 partial seizures occurred in a 57-year-old male with ROS1-positive NSCLC with brain metastases, initially diagnosed in (b) (6) He had not received any prior radiation therapy. His past medical history included aortic arteriosclerosis, hearing loss, seasonal allergies, and probably venous thrombosis. His concomitant medications included beclomethasone diproprionate, polysaccharide-iron complex, allopurinol, bisoprolol, enalapril/hydrochlorothiazide, enoxaparin, acetylcysteine, fondaparinux, and prednisone. On



Reference ID: 4344794

cycle 3 day 10 (b) (6) the patient experienced partial seizures and was hospitalized on (b) (6) with Grade 3 diplopia and Grade 3 confusion. A head CT was reported as being normal. Levetiracetam 500 mg was administered for the event of partial seizures; no action was taken with lorlatinib. On cycle 4 day 11 (b) (6) the patient died due to dyspnea from disease progression; the last dose of lorlatinib was administered on (b) (6).

Epilepsy (patient (b) (6)
The event of Grade 1 epilepsy occurred in a 56-year-old female with ALK-positive NSCLC initially diagnosed in (b) (6) with CNS metastases. She received radiation therapy to left frontal and right parietal lesions in (b) (6) and underwent brain surgery in (b) (6) due to progression of a right frontal metastasis. Her medical history included paresthesia, seizure (last hospitalized in (b) (6) and epistaxis. Her concomitant medications included ranitidine hydrochloride, tinzapatin sodium, and levetiracetam (given (b) (6). She began treatment with lorlatinib 100 mg daily in (b) (6). On cycle 2 day 2, she was diagnosed with Grade 1 epilepsy (not described further). No action was taken with lorlatinib, and levetiracetam was resumed with no further recurrence of seizures.

Epilepsy (patient (b) (6)
The event of Grade 1 epilepsy occurred in a 77-year-old male with ALK-positive NSCLC initially diagnosed in (b) (6) with a history of radiation therapy to the left vermis in (b) (6) and (b) (6) and to the cerebellum from (b) (6). His past medical history included atrial fibrillation, gout, facial paralysis, hearing loss in the right ear, hypertension, and Parkinson's disease. His concomitant medications included prednisolone for brain metastases, valsartan, paracetamol, tinzaparin sodium, pravastatin sodium, and Bactrim. The patient began lorlatinib 100 mg daily in (b) (6) the drug was stopped temporarily from (b) (6) due to confusion and was resumed at a reduced dose of 50 mg daily beginning (b) (6) (cycle 2 day 17) due to a hypertensive crisis and dyspnea. A brain MRI performed on (b) (6) revealed new leptomeningeal metastases. On (b) (6) (cycle 3 day 10), the patient experienced Grade 1 epilepsy (not further described), which resolved on (b) (6). The investigator assessed the cause of epilepsy as related to lorlatinib, but no action was taken with lorlatinib in response to the event. Treatment with levetiracetam was initiated, and no further epileptic events have been reported.

Epilepsy (patient (b) (6)
The event of Grade 1 epilepsy occurred in a 52-year-old male with ALK-positive NSCLC initially diagnosed in (b) (6) with multiple brain lesions in the frontal, parietal, and temporal lobes; he underwent radiation therapy to the brain in (b) (6) His ongoing medical history included epilepsy. His concomitant medications included levetiracetam and oxcarbezapine. He began treatment with lorlatinib 100 mg daily in (b) (6). On cycle 23 day 12, he experienced Grade 1 epilepsy (not further described). The event was considered resolved on the same day. On cycle 30 day 2 the patient experienced a second seizure, considered to be Grade 1 in severity. No action was taken with lorlatinib in response to either of these events, and there are no reports of brain imaging from the time of the events provided in the narrative. No further



Reference ID: 4344794

episodes of seizures have been reported.

Epilepsy (patient (b) (6)
The event of Grade 3 epilepsy occurred in a 33-year-old male with ALK-positive NSCLC initially diagnosed in (b) (6). He received whole brain radiation therapy from (b) (6) then received radiation therapy to the left parietal lobe and right cerebellum in (b) (6) and further radiation to the brain in (b) (6) He had no past medical history. His concomitant medications included heparin prophylaxis. The patient began treatment with lorlatinib 100 mg daily in (b) (6). The first episode of Grade 3 epilepsy occurred on cycle 1 day 18 and was treated with diazepam, dexamethasone, and levetiracetam. The subsequent episodes, both Grade 2 in severity, occurred on cycle 3 day 15 and cycle 5 day 12 (b) (6). A brain MRI performed on (b) (6) revealed an increase in the parietal lesion and Grade 2 cerebral edema. No action was taken with lorlatinib in response to these events; it was permanently discontinued on (b) (6) for an adverse event of headache.

**Hyperlipidemia**

The safety issue of hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia, was assessed in detail by Pfizer. As of the data cutoff of September 17, 2017, 86% of patients treated on Study B7461001 experienced an event of hyperlipidemia, including the preferred terms blood cholesterol increased, blood triglycerides increased, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, lipids increased, low density lipoprotein increased, and non-high-density lipoprotein increased. Twenty-six percent of the events of hyperlipidemia by the preferred terms described above were severe (Grade 3 or 4); 17% of patients had a Grade 3 or 4 elevation in total cholesterol and 17% of patients had a Grade 3 or 4 elevation in triglycerides by laboratory assessment. Lorlatinib was not discontinued for any event of hyperlipidemia; however, 3.3% of patients required a dose reduction in lorlatinib for hyperlipidemia, and 7% of patients required a temporary discontinuation of lorlatinib. Of the 8% of patients for whom lorlatinib was either dose reduced or temporarily discontinued for hyperlipidemia, the adverse event of hyperlipidemia was considered to have been resolved in all patients. Eighty-three percent of patients had an AE of hypercholesterolemia (including preferred terms blood cholesterol increased, hypercholesterolemia, low density lipoprotein increased, and non-high-density lipoprotein increased) and 16% of patients had a severe AE of hypercholesterolemia; 64% of patients had an AE of hypertriglyceridemia (including preferred terms blood triglycerides increased and hypertriglyceridemia) and 15% of patients had a severe AE of hypertriglyceridemia.

According to the protocol for Study B7461001, lorlatinib was required to be held in the event of Grade 4 elevations in total cholesterol or triglycerides until toxicity was Grade ≤ 2 and then either dose reduced by one dose level or restarted at the same dose. For Grade 3 elevations in total cholesterol or triglycerides, lorlatinib was able to either be continued at the same dose without interruption or withheld until toxicity was Grade ≤ 2, then continued at the same dose. Of the 1945 events of hyperlipidemia in 286 (86%) patients for which lorlatinib was not held or

dose reduced, 699 (36%) were severe (Grade 3 or 4), and 6% were Grade 4 in severity.

The protocol's dose modification guidelines included consideration of introducing a statin or other lipid lowering agent as appropriate based on the investigator's medical judgment for Grade 1 elevations of total cholesterol or triglycerides and required introduction of a statin or other lipid lowering agent for Grade 2 elevations of total cholesterol or triglycerides. For Grades 3 or 4 elevations in total cholesterol or triglycerides, the protocol required introducing a statin or other lipid lowering agent, increasing the dose of an ongoing statin/lipid lowering agent, or changing to a new agent.

Overall, 80% of patients received a lipid lowering agent during treatment with lorlatinib; 10% of patients enrolled on the study were receiving a lipid lowering agent prior to treatment with lorlatinib. In 79 (11%) of the 699 severe events of hyperlipidemia, no treatment was given to the patient, and 9 (1.3%) of the events were considered to have been still present at the time of the data cutoff.

Table 88 provides the time to start of a lipid lowering agent for patients in the dose escalation (Phase 1), dose expansion (Phase 2), and Japan LIC portions of the study.

**Table 88 Time to start of medication to lower cholesterol and/or triglycerides (Reviewer table)**

| Time to start (days) | N (%) | Mean | SD | Median | Range |
|---|---|---|---|---|---|
| Phase 1 (N=54) | 39 (72) | 65 | 99.7 | 28 | (8, 580) |
| Phase 2 (N=275) | 222 (81) | 27 | 27.1 | 18 | (1, 190) |
| Japan LIC (N=3) | 3 (100) | 14 | 7.5 | 14 | (7, 22) |

SD: Standard deviation
Time to start of medication to lower cholesterol and/or triglycerides is calculated from Day -7 and/or cycle 1 day 1 if this is the first dose, to the start of the relevant medication

Laboratory abnormalities based on data from laboratory shift tables provided by Pfizer provide a more accurate estimation of toxicity. Based upon laboratory data available for 292 of the 295 patients receiving lorlatinib 100 mg QD, 95% of patients had a clinically significant laboratory shift in cholesterol level. Grade 3 or 4 elevations in cholesterol occurred in 17% of patients. Eighty-nine percent of patients had a clinically significant laboratory shift in triglyceride level; 17% of patients had a Grade 3 or 4 elevation in triglycerides.

Elevated cholesterol is a major risk factor for the development of cardiovascular disease and cerebrovascular accidents, including myocardial infarctions and ischemic stroke. Each year, approximately 735,000 people in the US have a myocardial infarction (incidence of 0.3%) and approximately 795,000 people in the US have a stroke (https://www.CDC.gov) (incidence of



Reference ID: 4344794

0.3%). Given the high incidence of hyperlipidemia in patients receiving treatment with lorlatinib, the clinical reviewer performed an analysis of the patients enrolled on Study B7461001 with an adverse event of myocardial infarction or stroke. Five patients (1.5%) experienced an event of acute myocardial infarction, cerebrovascular accident, ischemic stroke, lacunar stroke, myocardial infarction, and myocardial ischemia (1 event each); of these two events (acute myocardial infarction and myocardial infarction, described in detail in Section 8.2.4 of this review) were fatal, and two events (ischemic stroke and lacunar stroke) were Grade 3 in severity. The average age of the 5 patients was 64 years (SD 4.55), with a median age of 62 (range 59-71). No action was taken with lorlatinib in the four nonfatal events. All but one of the patients (patient (b) (6)) were on at least one lipid lowering agent during treatment with lorlatinib. Table 89 demonstrates the mean cholesterol and triglyceride levels recorded during treatment with lorlatinib and prior to the event of myocardial infarction or cerebrovascular accident for each of these patients.

**Table 89 Mean cholesterol and triglyceride levels preceding adverse event**

| Patient number | Preferred term | Mean cholesterol[a] (mg/dL) (range) | Grade | Mean triglycerides[b] (mg/dL) (range) | Grade |
|---|---|---|---|---|---|
| (b) (6) | Acute myocardial infarction | 300 (235-401) | 1 | 219 (119-371) | 1 |
| | Myocardial ischemia | 290 (250-401) | 1 | 160 (119-225) | 1 |
| | Cerebrovascular accident | NR | -- | NR | -- |
| | Ischemic stroke | 230 (192-276) | 1 | 227 (161-307) | 1 |
| | Lacunar stroke | 298 (255-460) | 1 | 150 (120-186) | 1 |
| | Myocardial infarction | 241 (192-286) | 1 | 111 (72-155) | 1 |

[a] Normal < 200 mg/dL
[b] Normal < 150 mg/dL

*Reviewer's comment: Overall, three patients (0.9%) had a cerebrovascular accident and two patients (0.6%) had a myocardial infarction. Although these incidences are slightly higher than the incidence of myocardial infarction and stroke in the general US population, this would be expected for this population of advanced cancer patients. Furthermore, the mean cholesterol and triglyceride levels for each patient preceding the event of myocardial infarction or stroke were only Grade 1 in severity; coupled with the relatively short duration of treatment with lorlatinib, the hypercholesterolemia and hypertriglyceridemia experienced by these patients during the course of treatment with lorlatinib is unlikely to have contributed to an increased risk of myocardial infarction or stroke.*



Reference ID: 4344794

### 8.2.5.4 Atrioventricular (AV) block

AV block, as described by the preferred terms atrioventricular block complete, atrioventricular block first degree, and electrocardiogram PR prolongation, occurred in five patients (1.5%) enrolled on Study B7461001; all five patients received lorlatinib 100 mg QD. One (0.3%) of these events (atrioventricular block complete) was Grade 3 in severity and required pacemaker placement. In the case of Grade 3 complete AV block, lorlatinib was temporarily discontinued; no other actions were taken with lorlatinib in the remaining four cases of AV block.

In the 275 patients enrolled in the dose expansion portion of Study B7461001, in which all patients received lorlatinib 100 mg QD, the maximum mean change from baseline for PR interval was 14.2 msec (2-sided 90% upper CI: 16.1 msec). Of the 265 patients with a baseline PR interval of less than 200 msec, 14% of patients had PR interval prolongation greater than 200 msec after starting treatment with lorlatinib. The prolongation of PR interval occurred in a concentration-dependent manner. See the QT-IRT consult for this NDA for further details.

### 8.2.5.5 Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) is considered a class effect of tyrosine kinase inhibitors, including ALK inhibitors, and was identified by Pfizer as an adverse event of special interest (AESI) for lorlatinib. Of the 332 patients treated on Study B7461001, four (1.5%) had an event reported as ILD (including preferred terms interstitial lung disease and pneumonitis). Three of the events (1.2%) were severe (Grade 3 or 4). Lorlatinib was permanently discontinued in one (0.3%) event of Grade 4 pneumonitis and temporarily discontinued in one event of Grade 3 pneumonitis; both events were considered to have been resolved at the time of the data cutoff for the 120 Day Safety Update Report. Of note, steroids were not reported as being administered for two of these four events of ILD; narratives for these two patients are provided below.

<u>Interstitial lung disease (patient</u> (b) (6)
The event of Grade 3 interstitial lung disease occurred in a 54-year-old male with ALK-positive NSCLC. His past medical history included hypercholesterolemia and hypertriglyceridemia and seizures. His concomitant medications included ibuprofen, lamotrigine, budesonide with formoterol fumarate, paracetamol, and denosumab. He began treatment with lorlatinib 100 mg QD on (b) (6). The patient traveled to and from the investigational site for purposes of clinical trial participation. On cycle 4 day 6 (b) (6), he was admitted to his local hospital by his local oncologist with shortness of breath and chest pain. A CT chest was performed and revealed bilateral air space opacities which could represent pulmonary edema, atypical pneumonia, or other etiologies; a dense opacity in the perihilar right upper and lower lobes worrisome for marked interval worsening of neoplasm; and no evidence of pulmonary embolus. His white blood cell (WBC) count on the day of admission was 6,200/mm$^3$ (reference range not provided, but not flagged as high). Because the patient was significantly hypoxic and required oxygen supplementation, the pulmonologist considered this to be a case of

pneumonitis; he was treated with IV levofloxacin and discharged two days later. It is unclear if steroids were prescribed. Lorlatinib was temporarily discontinued in response to this event; the duration of discontinuation is not clear from the narrative.

*Reviewer's comment: It is not possible to rule out drug-induced pneumonitis/interstitial lung disease due to lorlatinib as the cause of this patient's hypoxia and chest CT findings.*

Pneumonitis (patient (b) (6)
The event of Grade 3 pneumonitis occurred in a 42-year-old male with ALK-positive NSCLC. His past medical history included right jugular vein thrombosis and dysarthria. His concomitant medications included calcium carbonate, acetylcysteine, nefopam hydrochloride, amoxicillin, prednisone, cotrimoxazole, and potassium chloride. He began treatment with lorlatinib 100 mg QD on (b) (6). On cycle 6 day 2 (b) (6) he developed fever and dyspnea and presented to the ER. There his oxygen saturation was 89% and his temperature was 38.9°C. His WBC count was 11,200/mm$^3$ with 73% neutrophils (reference range not provided; WBC count and neutrophil percentage described as elevated). Antigen screen for legionella and pneumococcus was negative. He was treated with intravenous antibiotics followed by oral antibiotics with clinical improvement; a chest x-ray or CT chest was not performed. The investigator's final diagnosis was infectious pneumonitis. No action was taken with lorlatinib in response to this event.

*Reviewer's comment: Given the reported rapid improvement with antibiotics without the use of corticosteroids and without any action being taken with lorlatinib, this likely does not represent a case of drug-induced pneumonitis.*

In addition to the reported events of ILD and pneumonitis described above, the reviewer examined the case report forms (CRFs) and narratives for patients with respiratory AEs, including preferred terms pneumonia (n=18), lung infection (n=12), lower respiratory tract infection (n=7), acute respiratory failure (n=5), respiratory failure (n=5), and lung disorder (n=1), who had received corticosteroids (initiation or increase in baseline dose) as part of their treatment for the event in order to assess for missed cases of ILD. The reviewer requested that Pfizer perform the same analysis. Ten patients with one of the respiratory AEs listed above met criteria for further investigation (9 patients with initiation of corticosteroids and one patient with both initiation and dose increase in corticosteroids at the time of the event). Of these events, one event of acute respiratory failure and one event of pneumonia were due to disease progression with imaging supporting that diagnosis; corticosteroids were administered for respiratory symptom relief. In one event of lower respiratory tract infection and one event of respiratory failure, only one dose of corticosteroids was given, making the diagnosis of ILD unlikely. In one event of lower respiratory tract infection, the patient had a past medical history of asthma with a concurrent asthma exacerbation for which the steroids were prescribed, making the diagnosis of ILD less likely. In one event of acute respiratory failure, there was a concurrent adverse event of pneumonitis which was included in the cases of ILD/pneumonitis described above. In one event of lung infection, a tapering dose of prednisone was prescribed,



Reference ID: 4344794

however, a CT chest performed at the time of the event revealed an improvement in previously noted minimal ground glass opacities and an unchanged left lower lobe nodule. The patient was treated with antibiotics, and no action was taken with lorlatinib in response to the event, which resolved in approximately 8 days. Given the lack of progression of clinical symptoms with continued use of lorlatinib and the low dose of prednisone (10 mg QD tapered to 5 mg QD), this event is unlikely due to drug-induced ILD. The remaining three cases in which ILD/pneumonitis is a possible alternate diagnosis are described in narrative summaries below.

Lung infection (patient (b) (6))
The event of Grade 3 lung infection occurred in a 50-year-old female with ALK-positive NSCLC. Her past medical history included anxiety, dyspnea, endometriosis, and spinal compression fracture. Her concomitant medications included cholecalciferol, acetylsalicylic acid, enoxaparin, folic acid, hydromorphone, levetiracetam, lomotil, lorazepam, magnesium oxide, pantoprazole, paracetamol, prochlorperazine, sennoside A+B, and Vicodin. She was enrolled in the 150 mg QD cohort of the dose expansion portion of the study. On cycle 12 day 19 the patient presented to a local hospital with fever, cough, and shortness of breath. A CT chest reportedly revealed an infiltrate; the report is not available at the time of this review. The patient was treated with a tapering dose of prednisone (dose and length of treatment not specified) and with IV ceftriaxone. She was discharged two days later with oral antibiotics and a nebulizer (medication not specified). Lorlatinib was held in response to this event.

*Reviewer's comment: Given the lack of details regarding the CT chest report, laboratory data, length of treatment with and dose of prednisone and the fact that lorlatinib was held due to this event, it is not possible to exclude a diagnosis of drug-induced ILD in this patient.*

Pneumonia (patient (b) (6)
The event of Grade 3 pneumonia occurred in a 52-year-old female with ALK-positive NSCLC. Her past medical history included pneumonia, dyspnea, asthma, hypertension, cataracts, glaucoma, and allergic rhinitis. Her concomitant medications included multivitamins, bimatoprost, bisoprolol fumarate, cetirizine hydrochloride, dicycloverine, dorzolamide hydrochloride, levofloxacin for ongoing pneumonia at study entry, loperamide hydrochloride, ondansetron, prednisolone, salbutamol sulfate, and seretide. The patient initially began treatment in the dose expansion portion of the study with lorlatinib 100 mg QD; this was dose reduced twice to 50 mg QD for peripheral swelling in cycle 3. She was hospitalized at the beginning of cycle 5 for pneumonia and was treated with multiple IV antibiotics in addition to prednisone 10 mg QD beginning cycle 5 day 17 (duration of treatment not reported). She was discharged from the hospital on cycle 5 day 18, however, she worsened again on cycle 6 day 6 and she died due to the event of pneumonia on cycle 6 day 17. Imaging from the time of these events was not provided. Lorlatinib was held in response to this event.

*Reviewer's comment: Despite the ongoing respiratory symptoms resulting in the patient's death and absence of a definitive evidence of infectious cause or disease progression, the diagnosis of drug-induced ILD in this patient is considered less likely given the low reported starting dose of*



Reference ID: 4344794

*prednisone (10 mg) and the patient's significant past medical history of pneumonia and asthma.*

Respiratory failure (patient (b) (6))
The event of Grade 3 respiratory failure occurred in a 65-year-old female with ALK-positive NSCLC. Her past medical history included hypertension, migraines, allergic rhinitis, and sinus tachycardia. She was not taking any medications at the time of entry into the study. She was enrolled in the dose expansion portion of the study and was receiving lorlatinib 100 mg QD at the time of the event. On cycle 8 day 3 she experienced worsening shortness of breath and presented to an ER. A chest x-ray performed at the time of the event revealed right perihilar and basilar consolidation with small right pleural effusion and left central vascular congestion and atelectasis. She underwent IR-guided thoracentesis for a pleural effusion; 310 mL of fluid was drained with reportedly no malignant cells seen. She received a 23-day course of prednisone (70 mg QD to 5 mg QD), and lorlatinib was held in response to the event.

*Reviewer's comment: Although the chest x-ray findings are not consistent with ILD, they do not exclude a diagnosis of ILD, and in the absence of definitive evidence for infection or disease progression, it is not possible to exclude a diagnosis of drug-induced ILD in this patient.*

*Reviewer's comment: If the two additional cases (patients (b) (6)) described above are included in the total number of cases reported by the preferred terms ILD/pneumonitis, excluding patient (b) (6) who was diagnosed with infectious pneumonitis, the total incidence of ILD/pneumonitis in patients enrolled on Study B7461001 is 1.5%, with four events (1.2%) Grade 3 or 4 in severity. Lorlatinib was permanently discontinued in one event of Grade 4 ILD/pneumonitis, and temporarily discontinued in 3 events of Grade 3 ILD/pneumonitis. However, in the PI, providers are instructed to permanently discontinue lorlatinib in the event of any grade treatment-related pneumonitis as this is a known class effect of ALK inhibitors and because the data observed in 5 patients enrolled on Study B7461001 is insufficient to demonstrate the safety of temporarily withholding, rather than permanently discontinuing, lorlatinib for low grade pneumonitis.*

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

General health status was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30 version 3.0) and its lung cancer module, Quality of Life Questionnaire 13 (QLQ-LC13). These assessments are considered exploratory only and are difficult to interpret without comparison to a control arm. There were no COA analyses specifically addressing safety/tolerability.

### 8.2.7. Safety Analyses by Demographic Subgroups

**Age**

Of the patients who received lorlatinib 100 mg QD in Study B7461001, 54/295 (18%) were ≥ 65 years of age. Table 90 shows the incidence of TEAEs by age. In general, a substantive review of safety by age could not be conducted due to the limited number of patients 65 years of older.

**Table 90 Comparison of treatment-emergent adverse events by age in Study B7461001 (Reviewer table)**

| | Lorlatinib 100 mg QD N=295 | |
|---|---|---|
| | < 65 years N=241 | ≥ 65 years N=54 |
| Any TEAE, % | 99.6 | 100 |
| Grade 3-4 TEAEs | 68 | 72 |
| Grade 5 TEAEs | 10 | 19 |
| SAE, % | 33 | 50 |
| AEs leading to discontinuation, % | 7 | 13 |
| AEs by preferred term in ≥ 20% of patients, % | | |
| Edema[a] | 53 | 70 |
| Peripheral neuropathy[b] | 47 | 50 |
| Dyspnea | 25 | 35 |
| Fatigue[c] | 24 | 35 |
| Cognitive effects[d] | 25 | 28 |
| Arthralgia | 22 | 28 |
| Diarrhea | 21 | 26 |
| Mood effects[e] | 24 | 19 |
| Weight gain | 27 | 13 |

[a]Edema (including eyelid edema, face edema, localized edema, generalized edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling).
[b]Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance).
[c]Fatigue (including fatigue and asthenia).
[d]Cognitive effects (including amnesia, attention deficit/hyperactivity disorder, cognitive disorder, confusional state, delirium, dementia, disorientation, disturbance in attention, memory impairment, mental impairment, reading disorder).
[e]Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).

*Reviewer's comment: There is an increased proportion of Grade 5 AEs, SAEs, AEs leading to discontinuation, and edema in older patients; however, conclusions on the significance of these differences cannot be reached due to the small number of older patients.*

**Gender**

Of the patients who received lorlatinib 100 mg QD in Study B7461001, there were 125 men (42%) and 170 women (58%). Table 91 shows the incidence of TEAEs by gender; overall, there



Reference ID: 4344794

was no consistent pattern of TEAE differences between genders and no evidence that gender affects lorlatinib's tolerability.

**Table 91 Comparison of treatment-emergent adverse events by gender in Study B7461001 (Reviewer table)**

| | Lorlatinib 100 mg QD N=295 | |
|---|---|---|
| | Male N=125 | Female N=170 |
| Any TEAE, % | 99.2 | 100 |
| Grade 3-4 TEAEs | 67 | 69 |
| Grade 5 TEAEs | 14 | 10 |
| SAE, % | 39 | 50 |
| AEs leading to discontinuation, % | 9 | 7 |
| AEs by preferred term in ≥ 20% of patients, % | | |
| Peripheral neuropathy[a] | 48 | 47 |
| Edema[b] | 47 | 63 |
| Dyspnea | 30 | 25 |
| Cognitive effects[c] | 30 | 25 |
| Fatigue[d] | 29 | 24 |
| Weight gain | 26 | 22 |
| Arthralgia | 22 | 24 |
| Mood effects[e] | 22 | 23 |
| Diarrhea | 18 | 25 |

[a]Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance).
[b]Edema (including eyelid edema, face edema, localized edema, generalized edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling).
[c]Cognitive effects (including amnesia, attention deficit/hyperactivity disorder, cognitive disorder, confusional state, delirium, dementia, disorientation, disturbance in attention, memory impairment, mental impairment, reading disorder).
[d]Fatigue (including fatigue and asthenia).
[e]Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).

**Race**

Of the 295 patients enrolled on Study B7461001, 269 were categorized by race. Table 92 shows the incidence of TEAEs by race. Across all AEs, SAEs, and AEs leading to discontinuation, Asian patients appeared to experience less toxicity than non-Asian patients. Nevertheless, the limited number of patients and non-randomized nature of the subgroups to account for other baseline demographic factors precludes any definitive statements regarding safety across different racial/ethnic groups.



Reference ID: 4344794

**Table 92 Comparison of treatment-emergent adverse events by race in Study B7461001 (Reviewer table)**

| | Lorlatinib 100 mg QD N=295 | |
|---|---|---|
| | Asian N=108 | Non-Asian N=161 |
| Any TEAE, % | 99.1 | 100 |
| Grade 3-4 TEAEs | 64 | 71 |
| Grade 5 TEAEs | 11 | 14 |
| SAE, % | 29 | 43 |
| AEs leading to discontinuation, % | 4.6 | 11 |
| AEs by preferred term in ≥ 20% of patients, % | | |
| Edema[a] | 53 | 62 |
| Peripheral neuropathy[b] | 38 | 50 |
| Dyspnea | 19 | 29 |
| Arthralgia | 19 | 24 |
| Cognitive effects[c] | 15 | 32 |
| Diarrhea | 15 | 24 |
| Mood effects[d] | 13 | 27 |
| Weight gain | 12 | 26 |
| Fatigue[e] | 6 | 35 |

[a]Edema (including eyelid edema, face edema, localized edema, generalized edema, edema, edema peripheral, periorbital edema, peripheral swelling, swelling).
[b]Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance).
[c]Cognitive effects (including amnesia, attention deficit/hyperactivity disorder, cognitive disorder, confusional state, delirium, dementia, disorientation, disturbance in attention, memory impairment, mental impairment, reading disorder).
[d]Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).
[e]Fatigue (including fatigue and asthenia).

### 8.2.8. Specific Safety Studies/Clinical Trials

This subsection is not applicable to this review, as no separate studies have been conducted to evaluate specific safety concerns.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Please see the Nonclinical Pharmacology/Toxicology section of this review for details.



Reference ID: 4344794

**Human Reproduction and Pregnancy**

For full details, see the Pharmacology/Toxicology portion of this review. Based on its mechanism of action, lorlatinib may cause fetal harm when administered to pregnant women. In non-clinical studies, embryo-fetal toxicity was observed in rats and rabbits, including lower embryo-fetal viability, reduced fetal body weights, and congenital malformations. There is no clinical experience with lorlatinib in pregnant or lactating women, as these populations were excluded from participation in the lorlatinib clinical trial program. Patients were required to use adequate methods of contraception during treatment and for at least 90 days after the last dose of lorlatinib. No pregnancies were reported in the clinical studies included in the ISS. There is no data on the presence of lorlatinib or its metabolites in human milk, the effects of lorlatinib on the breast-fed infant, or its effects on milk production.

No animal studies have been performed to specifically evaluate the effect of lorlatinib on fertility. 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, but not a mutagen or clastogen.

A consult was obtained from the Division of Pediatric and Maternal Health (DPMH); for full details, see the DPMH Memorandum by Dr. Kristie Baisden. The recommendations were to include a pregnancy "Warning and Precaution for Embryo-Fetal Toxicity" in the lorlatinib labeling. Because of the potential for serious adverse reactions in breastfed infants from exposure to lorlatinib, DPMH recommended advising lactating women not to breastfeed during treatment and for 7 days after the final dose. In addition, DPMH recommended a verification of pregnancy status prior to initiation of treatment with lorlatinib and the use of an effective non-hormonal contraceptive method in females of reproductive potential as lorlatinib can render hormonal contraceptives ineffective. Finally, DPMH recommended that an infertility section be included in the lorlatinib USPI given the adverse effects of lorlatinib exposure on male reproductive organs in animals.

**Pediatrics and Assessment of Effects on Growth**

For details, please see the Nonclinical Pharmacology/Toxicology section of this review. This subsection has limited relevance for this NDA, as NSCLC is extremely rare in the pediatric population.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**



Reference ID: 4344794

No experience with overdose relevant to the recommended dose of lorlatinib is available. Four patients in the dose escalation portion of Study B7461001 took more than the intended dose of study drug due to patient error which resulted in relative dose intensities exceeding 100%; however, there were no AEs associated with any of these cases of overdose. There is no specific antidote for overdose with lorlatinib.

A Controlled Substance Staff (CSS) consultation was not obtained, as there are no concerns regarding the potential for abuse, withdrawal, or rebound with lorlatinib. On the basis of its pharmacological properties, the risk of abuse or misuse of lorlatinib is low.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Lorlatinib has not been approved for use anywhere in the world; therefore, no post-marketing data is available for this drug.

**Expectations on Safety in the Postmarket Setting**

The safety database does not include a sufficient number of patients aged 65 and older to determine whether they respond differently from younger patients. It is possible that CNS effects may be more significant in older patients and in patients with pre-existing psychiatric conditions. There are no safety concerns regarding potential differences in how the drug was administered and used in the clinical trials versus its expected use in the postmarket setting. Off-label use in patients with non-NSCLC tumors documented to have ALK rearrangement is anticipated, but there are no specific safety concerns expected from this potential off-label use.

### 8.2.11. Integrated Assessment of Safety

The safety of lorlatinib in patients with ALK-positive NSCLC who disease has progressed on a prior ALK inhibitor was primarily based on the 295 patients who received lorlatinib 100 mg QD in Study B7461001, a single arm, open-label, dose escalation/dose expansion study of lorlatinib. When assessed in the context of the treatment of a life-threatening disease, lorlatinib appears to have a reasonable safety profile. There was not an excess of unexplained deaths. Fatal adverse reactions occurred in 2.7% of patients, and review of these cases did not identify a specific safety concern related to lorlatinib. The most common adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; however, the most commonly experienced group of AE terms was CNS effects, encompassing mood effects, cognitive effects, speech effects, sleep effects, and miscellaneous CNS effects, occurring in approximately 50% of patients. The most common laboratory shift abnormalities were hypercholesterolemia and hypertriglyceridemia. Permanent discontinuation of lorlatinib due to an adverse reaction occurred in 8% of patients.

Safety issues (discussed in Section 8.2.5 of this review) recommended for inclusion in the Warnings and Precautions section of the USPI include hepatotoxicity, CNS effects,



Reference ID: 4344794

hyperlipidemia, atrioventricular block, and interstitial lung disease/pneumonitis.

# SUMMARY AND CONCLUSIONS

## 8.3. Statistical Issues

In the primary efficacy population, the confirmed ORR per IRC was 48% (95% CI: [42%, 55%]) and the IC-ORR was 54% (95% CI: [45%, 62%]) for patients who had CNS disease at baseline per IRC. The median duration of response was 12.5 months (95% CI: [8.4, 23.7]) and the median duration of intracranial response was 19.6 months (95% CI: [14.5, NE]). Lorlatinib appears to have anti-tumor activity when administered after ALK TKIs, other than crizotinib, that are approved for the first-line treatment of patients with ALK-positive NSCLC, with an ORR of 31% (95% CI: [9%, 61%]) in patients who had previously received alectinib as their only ALK TKI and an ORR of 40% (95% CI: [12%, 74%]) in patients who had previously received ceritinib as their only ALK TKI. Lorlatinib also demonstrated anti-tumor activity in patients who had previously received crizotinib and at least one other ALK TKI with an ORR of 39% (95% CI: [30%, 48%]). Patients in the latter subpopulation also achieved an IC-ORR of 48% (95% CI: [38%, 60%]).

## 8.4. Conclusions and Recommendations

NSCLC has a poor prognosis overall; patients with metastatic ALK-positive NSCLC whose disease has progressed on previous ALK inhibitor therapy have limited options for treatment, consisting primarily of single- or multi-agent chemotherapy with responses rates not exceeding 45% and median response durations of less than 6 months. Furthermore, there is an unmet medical need for this population based on the high rate of intracranial metastases.

Based on the data from 215 patients with previously treated ALK-positive NSCLC who received lorlatinib 100 mg QD enrolled on Study B7461001, the IRC-confirmed percentage of responders was 48% (95% CI: 42, 55). As of the data cutoff date of September 15, 2017, the IRC-confirmed median duration of response was 12.5 months (95% CI: 8.4, 23.7). The IRC-confirmed percentage of patients with measurable intracranial lesions at baseline with an intracranial response was 60% (95% CI: 49, 70), with a complete intracranial response rate of 21%. As of the data cutoff date of September 15, 2017, the IRC-confirmed median duration of intracranial response was 19.5 months (95% CI: 12.4, NR).

These results demonstrate a clinically meaningful improvement in ORR and DOR as compared to the results expected with available therapy. Furthermore, the intracranial response rate in this ALK inhibitor-pretreated population indicates CNS penetration at clinically effective concentrations.

Accelerated approval is recommended for lorlatinib at the dose of 100 mg daily until disease progression or unacceptable toxicity. Both alectinib and ceritinib were initially approved for use following progression on or intolerance to crizotinib and are currently approved for use as first-



Reference ID: 4344794

line treatment for patients with metastatic ALK-positive NSCLC. In the setting of the limited available clinical data for lorlatinib and considering the toxicity profile of lorlatinib when compared with the other agents in its class, the review team has determined that the most appropriate indication for the accelerated approval of lorlatinib is for the treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed on alectinib or ceritinib as first-line ALK inhibitor therapy for metastatic disease or has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease. Pfizer is conducting an ongoing randomized study assessing lorlatinib versus crizotinib as first-line treatment in patients with ALK-positive NSCLC, which is intended to serve as a confirmatory trial and verify the clinical benefit of lorlatinib.

| | |
|---|---|
| X | X |
| Jonathon Vallejo<br>Primary Statistical Reviewer | Kun He<br>Statistical Team Leader |
| X | X |
| Nicole Drezner,<br>Primary Clinical Reviewer | Erin Larkins<br>Clinical Team Leader |



Reference ID: 4344794

# 9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this NDA to the Oncologic Drug Advisory Committee (ODAC) because the safety profile is acceptable for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on crizotinib and one other ALK inhibitor or on alectinib or ceritinib as the first ALK inhibitor for metastatic disease, and the application did not raise significant public health questions regarding the role of lorlatinib for this indication. Outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.



Reference ID: 4344794

# 10 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted. NSCLC is a very rare disease in the pediatric population. The NDA is exempt from the requirement to assess safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.



Reference ID: 4344794

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

DOP2 made general revisions to labeling for brevity and clarity. Some information was moved to different sections of labeling (e.g. clinical pharmacology and toxicology). Such changes are not described below. The remainder of this section of the review will only focus on high-level issues regarding the amended label submitted by Pfizer.

- INDICATIONS AND USAGE
  - Change [redacted] (b) (4) to "whose disease has progressed on:
    - crizotinib and at least one other ALK inhibitor for metastatic disease; or
    - alectinib as the first ALK inhibitor therapy for metastatic disease; or
    - ceritinib as the first ALK inhibitor therapy for metastatic disease."

    *Reviewer's comment: Due to the limited efficacy data available for lorlatinib and the toxicity profile of lorlatinib compared to the other FDA-approved therapies in its class, the most appropriate indication was determined to be for use following prior treatment with alectinib or ceritinib, which are approved for the first-line treatment of ALK-positive NSCLC, or following crizotinib and at least one other ALK inhibitor, since alectinib and ceritinib were initially approved for use following crizotinib and are available treatment options for this patient population.*

- DOSAGE AND ADMINISTRATION
  - Add therapy discontinuation criteria for any grade treatment-related ILD/pneumonitis.

    *Reviewer's comment: ILD/pneumonitis is a class effect and this dose modification guidance is consistent with other ALK inhibitor prescribing information. There was not a sufficient number of patients in Study B7461001 who experienced an event of ILD/pneumonitis to adequately characterize risk stratification and specify dose modification guidelines based on grade of pneumonitis in patients taking lorlatinib.*

  - Include section 2.3 on concomitant use of strong or moderate CYP3A inducers stating that lorlatinib is contraindicated in patients taking strong CYP3A inducers and to avoid concomitant use of lorlatinib with moderate CYP3A inducers.

    *Reviewer's comment: This modification would make it clear that lorlatinib is contraindicated in patients taking strong CYP3A inducers given the severe hepatotoxicity observed in the healthy volunteer study in which lorlatinib was co-*



Reference ID: 4344794

*administered with rifampin.*

- WARNINGS AND PRECAUTIONS
  - Include a section on the risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers.

    *Reviewer's comment: This section was added to provide further detail for investigators on the hepatotoxicity observed in the study of healthy volunteers with specific descriptions of the type, severity, and length of hepatoxicity.*

  - Expand the section on central nervous system effects, which initially included only "changes in cognitive function, mood, and speech", to broaden the type and category of CNS effects observed in Study B7461001; to clarify that suicidal ideation was one of the mood effects observed; and to describe the proportion of patients who experienced each category of CNS effect.

    *Reviewer's comment: This recommendation is based on a review of the safety database with seizures, hallucinations, sleep effects, mental status changes, and suicidal ideation included in the broad CNS effects category.*

  - Add a section on interstitial lung disease/pneumonitis.

    *Reviewer's comment: This recommendation is based on ILD/pneumonitis being a serious ALK inhibitor class effect and provides descriptive information on the proportion of patients who experienced ILD/pneumonitis on Study B7461001 as well as guidelines for therapy discontinuation.*

  - Add information regarding the incidence of events for hyperlipidemia and atrioventricular block, categories which were included in the initial labeling submitted by Pfizer.

  - Revise section on embryo-fetal toxicity to state that females of reproductive potential should use an effective non-hormonal method of contraception, since lorlatinib can render hormonal contraceptives ineffective, during treatment and for at least 6 months, (b) (4), after the final dose.

    *Reviewer's comment: This modification was made based on clinical pharmacology recommendations; see Section 6 for further details.*

- ADVERSE REACTIONS
  - Add the following adverse reactions to the adverse reactions table: headache, dizziness, speech effects (composite term), sleep effects (composite term), dyspnea, cough, nausea, vomiting, myalgia (composite term), back pain, pain in



Reference ID: 4344794

extremity, pyrexia, upper respiratory tract infection (composite term), and rash (composite term).

*Reviewer's comment: These adverse reactions occurred in ≥ 10% of patients in Study B7461001 based on information included in the 120-day safety update for lorlatinib.*

— Delete [redacted] (b) (4) laboratory abnormalities from [redacted] (b) (4) .

*Reviewer's comment: Laboratory abnormalities based on laboratory shift tables, which are included in Table 3 in the label, provide a more accurate estimation of these toxicities.*

— Add the following laboratory shift values to the worsening laboratory values table: increased AST, hypoalbuminemia, increased ALT, increased alkaline phosphatase, hyperkalemia, [redacted] (b) (4) anemia, and thrombocytopenia.

*Reviewer's comment: These laboratory abnormalities occurred in ≥ 20% of patients in Study B7461001 based on information included in the 120-day safety update for lorlatinib.*

- CLINICAL PHARMACOLOGY
  — Add subsection "Clinical Studies," under "Drug Interaction Studies," to describe the effect of CYP3A inducers on lorlatinib.

  *Reviewer's comment: Provides additional details on hepatoxicity as described above.*

- CLINICAL STUDIES
  — Add table to describe the extent of prior therapy in the subgroup of patients with previously treated ALK-positive metastatic NSCLC in Study B7461001.

  *Reviewer's comment: This addition was made to inform investigators on the types and numbers of prior therapies administered to patients enrolled on Study B7461001 and to provide context for the exploratory analyses of ORR in patients grouped by extent of prior therapy included in this section of the label (see below).*

  — [redacted] (b) (4) include separate table of intracranial response rate in patients with measurable intracranial lesions in Study B7461001; also revised the number of patients included in the intracranial efficacy population to 89 from [redacted] (b) (4) to exclude



Reference ID: 4344794

patients without measurable intracranial lesions at baseline; included the Kaplan-Meier estimated durations of response rather than (b) (4)

*Reviewer's comment:* (b) (4) *intracranial efficacy population was revised according to the statistical review. Intracranial response data limited to patients with measurable intracranial metastases at baseline is considered most appropriate for inclusion in labeling.*

— Include results of exploratory analyses conducted in subgroups defined by prior therapy.

*Reviewer's comment: Included the ORRs for each subgroup specified in the indication statement to provide supportive data relevant to the proposed indication of treatment of patients who have progressed on alectinib or ceritinib as first ALK inhibitor therapy or on crizotinib and one other ALK inhibitor.*

- PATIENT COUNSELING INFORMATION
  — Revised to include sections on risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers and interstitial lung disease/pneumonitis for consistency with the Warnings and Precautions section.

# 12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend a risk evaluation and mitigation strategy (REMS) be required to ensure safe and effective use of lorlatinib for the indicated population. Recommendations for the safe and effective use of lorlatinib are made in labeling and a patientpackage insert. There are no additional risk management strategies required beyond the recommended labeling. Although lorlatinib can cause severe/serious toxicity, it will be prescribed by oncologists who, by training, understand how to monitor and manage such toxicities.



Reference ID: 4344794

# 13 Postmarketing Requirements and Commitment

(b) (4)

Clinical PMR: Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of lorlatinib in patients with locally advanced or metastatic non-small cell lung cancer without a history of prior systemic therapy for advanced disease and whose tumors harbor anaplastic lymphoma kinase (ALK) gene rearrangement.

Milestone dates:
Final protocol submission: November 29, 2016
Trial completion: December 31, 2020
Final report submission: September 30, 2021

A clinical pharmacology PMR has also been recommended to evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers. Pfizer has provided milestone dates for this PMR.

Clinical pharmacology PMR: Evaluate the risk for hepatotoxicity when lorlatinib is co-administered with CYP3A inducers (PXR agonists and non-PXR agonists) and non-CYP3A inducers (PXR agonists and non-PXR agonists) using a pharmacologically relevant animal model capable of demonstrating the clinically observed hepatoxicity signal. The study should be designed to inform the label regarding hepatoxicity.

Milestone date:
Final protocol submission: March 31, 2019
Trial completion: September 30, 2019
Final report submission: December 31, 2019

A clinical pharmacology PMR has been recommended to evaluate the appropriate dose of lorlatinib to minimize toxicity in patients with severe renal impairment; the final protocol for this study has already been submitted.

Clinical pharmacology PMR: Complete a pharmacokinetic trial to determine an appropriate dose of lorlatinib to minimize toxicity in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled, “Pharmacokinetics in Patients with Impaired Renal



Reference ID: 4344794

Function – Study Design, Data Analysis, and Impact on Dosing and Labeling," found at https://www.fda.gov/downloads/drugs/guidances/ucm204959.pdf.

Milestone dates:
Final protocol submission: April 12, 2018
Trial completion: May 31, 2020
Final report submission: January 31, 2021

A clinical pharmacology PMR has been recommended to determine the appropriate dose of lorlatinib to minimize toxicity in patients with moderate and severe hepatic impairment. The final protocol for this study has already been submitted.

Clinical pharmacology PMR: Complete a pharmacokinetic trial to determine an appropriate dose of lorlatinib to minimize toxicity in patients with moderate and severe hepatic impairment in accordance with the FDA Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling," found at https://www.fda.gov/downloads/drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf.

Milestone dates:
Final protocol submission: July 9, 2018
Study/Trial completion: March 31, 2023
Final report submission: February 28, 2024



Reference ID: 4344794

# 14 Division Director (DHOT)

X

Haleh Saber
Director, Division of Hematology, Oncology, Toxicology



Reference ID: 4344794

# 15 Division Director (OCP)

X

Nam Atiqur Rahman
Director, Office of Clinical Pharmacology



Reference ID: 4344794

# 16 Division Director (OB)

X

Rajeshwari Sridhara
Director, Office of Biometrics



Reference ID: 4344794

# 17 Division Director (Clinical)

I concur with the recommendations of the review team as summarized in this review and the Integrated Quality Assessment that LORBRENA (lorlatinib) tablets be approved with the agreed-upon labeling and required post-marketing commitments to verify clinical benefit and further investigate the mechanism of hepatotoxicity and dosage recommendations for patients with severe organ impairment. The application contained evidence of adherence to good manufacturing practices and no quality issues that precluded approval and substantial evidence of a clinically important and durable effect on tumor reduction that provides an advance of that reported with available therapy for this population (i.e., single- or multi-agent chemotherapy with or without an anti-PD1/anti-PDL1 antibody). In addition, there was evidence of a durable anti-tumor effect in tumor lesions in the brain parenchyma (CNS lesions), which is a sanctuary site and major site of disease recurrence in patients progressing on crizotinib. However, the clinical significance of isolated CNS response rates are otherwise difficult to interpret with a systemic therapy intended to treat all sites of disease; thus, only ORR incorporating all disease sites is considered an effect likely to predict clinical benefit.

Lorlatinib also carries the risks of significant hepatotoxicity (whose mechanism is poorly understood), a wide presentation of CNS toxicities, and interstitial pneumonitis, which appear to be manageable with dose modification, and hyperlipidemia, which appears to be manageable with medical management (generally initiation of or an increase in statin therapy). These risks are qualitatively different but do not appear to carry greater risk of mortality or permanent morbidity than the risks of available chemotherapeutic agents, as described in the review. Thus the benefit:risk profile is acceptable for the indicated population in whom the benefits of a more durable and likely higher response rate that achieved with chemotherapy outweighs the risks of the drug. This benefit:risk assessment will be re-evaluated when the results of the confirmatory study are available.

Review of this application was impacted by the submission of non-CDISC-compliant datasets, which precluded the reviewer's use of standardized tools for data quality assessment and identification of clinical review sites for inspection, that needed to be conducted manually. Additionally, a major amendment was required to understand the changes in patient outcomes in the efficacy update submitted to the application during review. Both issues substantially delayed completion of review by the clinical and statistical review team.

X _____

Patricia Keegan
Director, Division of Oncology Products 2 (DOP2)



Reference ID: 4344794

# 18 Office Director (or designated signatory authority)

*This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of lorlatinib was also assessed by Drs. Larkins and Drezner, and I concur with their recommendation to approve this drug. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.*

X _____

Office of Hematology and Oncology Products (OHOP)
Gideon Blumenthal, Acting Associate Office Director, OHOP, Deputy Director, OCE



Reference ID: 4344794

# 19 Appendices

## 19.1. References

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Reference ID: 4344794

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Reference ID: 4344794

## 19.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): B7461001, B7461004, B7461011, B7461012**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 418 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 10 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 13<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor of covered study: 0<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 405 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

## 19.3. Nonclinical Pharmacology/Toxicology

*No additional information.*



Reference ID: 4344794

## 19.4. OCP Appendices (Technical documents supporting OCP recommendations)

### 19.4.1. Summary of Bioanalytical Method Validation and Performance

**Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

Yes, plasma, feces and urine concentrations of lorlatinib and its main metabolite, M8 or PF-06895751, were measured in the clinical pharmacology trials. Based on results of human mass-balance Study B7461004, lorlatinib is the predominant circulating moiety in plasma accounting for 44% of the total radioactivity, whereas M8 accounts for approximately 21%. M8 is pharmacologically inactive, and therefore, M8 does not contribute to the clinical efficacy and safety. Pfizer also measured lorlatinib and M8 in cerebrospinal fluid (CSF) from three patients and 4β-hydroxycholesterol in human plasma. However, these assessments are considered exploratory and were not evaluated by FDA.

**For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The total plasma concentrations of lorlatinib and its metabolite, M8, were measured in the clinical trials. This is appropriate due to the concentration-independent plasma protein binding of both lorlatinib and M8. The average binding of lorlatinib and M8 is 66% and 79%, respectively.

**What bioanalytical methods are used to assess concentrations?**

The concentrations of lorlatinib and M8 were quantified in human plasma, cerebral spinal fluid and urine using liquid chromatography with tandem mass spectrometry (LC-MS/MS) detection methods. Similar methodology was used to quantify the serum concentration of concomitant drugs such as rifampicin, deacetyl rifampicin, itraconazole, and midazolam. Refer to Table 93, Table 94, and Table 95 for a complete list of the methods used in the clinical development of lorlatinib and their respective standard curve ranges. Overall the precision, accuracy, selectivity, and performance of the assays were acceptable and within FDA guidance recommended criteria. Incurred sample reanalysis met the acceptance criteria for most studies which require that at least two thirds of reanalyzed samples fall within (b) (4)% of the original measurement.

The assay accuracy and precision of the above bioanalytical methods are summarized in Table 93 below.



Reference ID: 4344794

**Table 93 Summary of the Validated Analytical Methods for Lorlatinib, Midazolam, Rifampicin, and Desacetyl Rifampicin**

| Pfizer Method Validation Report No. | Matrix | Assay Laboratory | LLOQ (ng/mL) | Calibration Range (ng/mL) | Inter-Assay Precision %CV | Inter-Run Accuracy %RE | Protocol No. |
|---|---|---|---|---|---|---|---|
| B7469001 Lorlatinib (primary validation) | Plasma | (b) (4) | 2.50 | 2.50-2500 | ≤9.0% | −0.5% to 6.8% | B7461001<br>B7461005<br>B7461007<br>B7461008<br>B7461011<br>B7461012<br>B7461016 |
| B7469001 Lorlatinib (Addendum) long-term stability | Plasma | | 2.50 | 2.50-2500 | ≤4.9% | −1.6% to 0.8% | B7461001<br>B7461004<br>B7461005<br>B7461007<br>B7461008<br>B7461011<br>B7461012<br>B7461016 |
| B7469004 Lorlatinib | Plasma | | 2.50 | 2.50-2500 | ≤5.0% | −2.8% to 1.6% | B7461004 |
| B7469002 Lorlatinib | Urine | | 2.50 | 2.50-2500 | ≤8.2% | −0.3% to 6.8% | B7461001 |
| B7469002 Lorlatinib (Addendum) long-term stability | Urine | | 2.50 | 2.50-2500 | ≤3.2% | −1.2% to 1.6% | B7461001<br>B7461004 |
| B7469005 Lorlatinib | Urine | (b) (4) | 2.50 | 2.50-2500 | ≤4.8% | −1.1% to 1.6% | B7461004 |
| B7469003 Lorlatinib | CSF | | 1.00 | 1.00-1000 | ≤5.5% | 0.0% to 2.3% | B7461001 |
| B7469003 Lorlatinib (Addendum) long-term stability | CSF | | 1.00 | 1.00-1000 | ≤3.7% | −1.0% to 2.4% | B7461001 |
| B7469011 (rifampin) | Plasma | | 50.0 | 50.0-35,000 | ≤8.4% | −3.6% to 6.0% | B7461011 |
| B7469011 (desacetyl rifampin) | Plasma | | 50.0 | 50.0-35,000 | ≤9.4% | -4.8% to 4.3% | B7461011 |
| (b) (4) | Plasma | | 0.100 | 0.100-100 | ≤8.6% | −6.4% to 4.0% | B7461001 |

%CV=percent coefficient of variation; %RE=percentage relative error; CSF=cerebrospinal fluid; ID=identification; LLOQ=lower limit of quantitation.



Reference ID: 4344794

Source: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods; Table 7; Pages 24-25

**Table 94 Summary of Bioanalytical Assay Performance**

| Clinical Study | Compound Analyzed | Matrix | Calibration Range (ng/mL) | LLOQ (ng/mL) | Inter-Run Precision %CV | Inter-Run Accuracy %RE | ISR Acceptable |
|---|---|---|---|---|---|---|---|
| B7461001 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤36.5 (include outliner) ≤9.0 (exclude outliner) | −8.8% to 3.7% (include outliner) −8.8% to 0.8% (exclude outliner) | Yes |
| B7461001 | Lorlatinib | Urine | 2.50-2500 | 2.50 | ≤6.3% | −4.0% to 4.7% | Yes |
| B7461001 | Lorlatinib | CSF | 1.00-1000 | 1.00 | ≤4.6% | 0.0% to 1.8% | Yes |
| B7461001 | Midazolam | Plasma | 0.100-100 | 0.100 | ≤5.4% | −1.3% to −0.3% | Yes |
| B7461004 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤3.9% | −1.6% to −0.8% | Yes |
| B7461004 | Lorlatinib | Urine | 2.50-2500 | 2.50 | ≤4.6% | −2.1% to 0.1% | Yes |
| B7461005 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤45.0% (include outliner) ≤4.0% (exclude outliner) | −7.2% to 9.3% (include outliner) −7.2% to 0.4% (exclude outliner) | Yes |
| B7461007 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤6.4% | −1.6% to 0.8% | Yes |
| B7461008 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤8.1% | −1.6% to 1.5% | Yes |
| B7461011 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤4.9% | −3.2% to 1.6% | Yes |
| B7461011 | Rifampin | Plasma | 50.0-35,000 | 50.0 | ≤5.1% | −1.8% to 4.0% | Yes |
| B7461011 | Desacetyl Rifampin | Plasma | 50.0-35,000 | 50.0 | ≤5.2% | −2.1% to 1.4% | Yes |
| B7461012 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤8.1% | 1.1% to 2.1% | Yes |
| B7461016 | Lorlatinib | Plasma | 2.50-2500 | 2.50 | ≤4.7% | 0.0% to 0.8% | Yes |

%CV=percent coefficient of variation; %RE=percentage relative error; CSF=cerebrospinal fluid; ISR=incurred sample reanalysis; LLOQ=lower limit of quantitation.

Source: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods; Table 8; Page 26

**Table 95 Summary of Bioanalytical Assay Performance for PF-06895751**

| Clinical Study | Compound Analyzed | Matrix | Calibration Range (ng/mL) | LLOQ (ng/mL) | Inter-Run Precision %CV | Inter-Run Accuracy %RE | ISR Acceptable |
|---|---|---|---|---|---|---|---|
| B7461001* | PF-06895751 | Plasma | 2.50-2500 | 2.50 | ≤6.0% | −5.5% to −1.1% | Yes |
| B7461007 | PF-06895751 | Plasma | 2.50-2500 | 2.50 | ≤6.2% | −8.1% to −5.8% | Yes |
| B7461011 | PF-06895751 | Plasma | 2.50-2500 | 2.50 | ≤4.6% | −6.5% to −4.7% | Yes |
| B7461012 | PF-06895751 | Plasma | 2.50-2500 | 2.50 | ≤9.9% | −3.3% to 0.5% | Yes |

* Long-term stability of PF-06895751 in frozen plasma was not established at the time of sample analysis.
%CV=percent coefficient of variation; %RE=percentage relative error; ISR=incurred sample reanalysis; LLOQ=lower limit of quantitation.

Source: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods; Table 12; Page 28

Clinical lorlatinib PK

Pfizer evaluated the dose proportionality properties of lorlatinib in Study B7461001 (b) (4) tablets). The dose proportionality assessment was evaluated over single and repeated daily doses of lorlatinib ranging from 10 mg to 200 mg. In general, the exposure of lorlatinib increased in an approximately dose proportional manner after single and repeated doses. After a single administration, the mean dose normalized ratio (90%CI) for $C_{max}$ and $AUC_{0\text{-}Inf}$ of lorlatinib was 1.036 (0.907, 1.166) and 0.953 (0.719, 1.186), respectively. For repeated doses, the dose normalized ratio (90% CI) for $C_{max}$ and $AUC_{0\text{-}tau}$ were 0.896 (0.763, 1.028) and 0.808 (0.678, 0.937), respectively. The lower regression slope of 0.808 for lorlatinib $AUC_{tau}$ was probably due to the net auto-induction of CYP3A by lorlatinib, which becomes more

pronounced with increasing lorlatinib doses. Thus, it is acceptable to conclude that lorlatinib exhibits approximately linear PK properties. The PK parameters after a single dose across the dose range from 10 to 200 mg are summarized in Table 96. PK parameters after multiple doses are summarized in Table 97.

**Table 96 Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following a Single Oral Dose of Lorlatinib**

| | Parameter Summary Statistics[a] by Dose | | | | |
|---|---|---|---|---|---|
| **Parameter [units]** | | | | | |
| **Day -7 Lead In:** ***QD Doses*** | *10 mg QD* | *50 mg QD* | *75 mg QD* | *100 mg QD* | *200 mg QD* |
| N, n | 3,1 | 2,2 | 12,11 | 16,15 | 3,3 |
| $AUC_{inf}$ [ng.hr/mL] | 698.0 | (7210,7240) | 7663 (79) | 8236 (25) | 18340 (61) |
| $AUC_{inf}$(dn)[ng•hr/mL/mg] | 69.80 | (144,145) | 102.2 (79) | 82.36 (25) | 91.68 (61) |
| $AUC_{tau}$ [ng•hr/mL] | 488.2 (21) | (3310, 3880) | 3990 (55) | 5110 (28) | 11410 (43) |
| $AUC_{tau}$(dn)[ng•hr/mL/mg] | 48.82 (21) | (66.1, 77.7) | 53.14 (54) | 51.10 (28) | 57.13 (43) |
| CL/F [L/hr] | 14.30 | (6.91, 6.94) | 9.788 (79) | 12.14 (25) | 10.90 (61) |
| $C_{max}$ [ng/mL] | 50.80 (17) | (390, 423) | 489.1 (45) | 595.5 (37) | 1201 (19) |
| $C_{max}$(dn) [ng/mL/mg] | 5.080 (17) | (7.80, 8.46) | 6.523 (45) | 5.955 (37) | 6.003 (19) |
| MRT [hr] | 23.7 | (27.7, 43.1) | 36.0 ± 11.7 | 27.0 ± 7.04 | 25.8 ± 6.36 |
| $T_{max}$[hr] | 1.98 (1.00-2.97) | 1.25 (0.500-2.00) | 1.09 (0.500-4.03) | 1.96 (0.517- 4.33) | 2.00 (1.18- 3.00) |
| Vz/F [L] | 373.0 | (166, 307) | 367.9 (54) | 356.3 (39) | 307.8 (41) |
| t½ [hr] | 18.0 | (16.6, 30.8) | 27.2 ± 8.30 | 20.9 ± 5.03 | 19.8 ± 3.30 |
| **Day -7 Lead In:** ***BID Doses*** | *35 mg BID* | *75 mg BID* | *100 mg BID* | | |
| N, n | 3,2 | 3,1 | 4,4 | | |
| $AUC_{inf}$ [ng.hr/mL] | (2630, 3690) | 6860 | 6318 (56) | | |
| $AUC_{inf}$(dn)[ng.hr/mL/mg] | (75.1, 105) | 91.40 | 63.18 (56) | | |
| $AUC_{tau}$ [ng.hr/mL] | 982.4 (9) | 2996 (20) | 2925 (47) | | |
| $AUC_{tau}$(dn)[ng.hr/mL/mg] | 28.03 (9) | 40.00 (20) | 29.25 (47) | | |
| CL/F [L/hr] | (9.48, 13.3) | 10.9 | 15.83 (56) | | |
| $C_{max}$ [ng/mL] | 202.2 (57) | 594.9 (27) | 507.2 (51) | | |
| $C_{max}$(dn) [ng/mL/mg] | 5.776 (57) | 7.933 (27) | 5.072 (51) | | |
| MRT [hr] | (30.8, 37.7) | 33.0 | 22.1 ± 6.76 | | |
| $T_{max}$[hr] | 1.20 (0.500- 1.97) | 1.23 (1.00- 2.00) | 2.00 (1.10-3.07) | | |
| Vz/F [L] | (362, 472) | 410.0 | 378.3 (54) | | |
| t½ [hr] | (24.6, 26.5) | 26.00 | 17.18 ± 5.19 | | |
| **Cycle 1 Day 1:** ***QD Doses*** | *25 mg QD* | *150 mg QD* | | | |
| N, n | 3,3 | 3,3 | | | |
| $AUC_{tau}$[ng.hr/mL] | 1387 (35) | 7474 (73) | | | |
| $AUC_{tau}$(dn) [ng.hr/mL/mg] | 55.49 (35) | 49.80 (73) | | | |
| $C_{max}$ [ng/mL] | 149.2 (71) | 760.0 (58) | | | |
| $T_{max}$ [hr] | 2.00 (0.500- 2.05) | 1.05 (1.00-3.00) | | | |

a. Geometric mean (geometric %CV) for all except: median (range) for $T_{max}$; arithmetic mean ± Std Dev for t½ and MRT. The single observation was reported when n=1 and the range was reported when n=2.
N = Number of patients in the treatment group; n= number of patients where $t_{½}$, MRT, $AUC_{inf}$, CL/F and Vz/F were determined.
Parameters are defined in Table 4.
Source: Table 14.4.4.1.1.1

Source: 2.7.2 Summary of Clinical Pharmacology Studies; Table 25; Pages 91 and 92



Reference ID: 4344794

**Table 97 Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following Multiple Oral Doses of Lorlatinib**

| | Parameter Summary Statistics[a] by Treatment | | | | | | |
|---|---|---|---|---|---|---|---|
| Parameter, units | | | | | | | |
| **Cycle 1 Day 15: *QD Doses*** | *10 mg QD* | *25 mg QD* | *50 mg QD* | *75 mg QD* | *100 mg QD* | *150 mg QD* | *200 mg QD* |
| N,n[b], n[c] | 3,3,1 | 3,3,0 | 3,2,2 | 12,12,11 | 16,15,14 | 3,3,0 | 2,2,2 |
| $AUC_{tau}$ [ng.hr/mL] | 752.1 (26) | 1701 (29) | 3367 (39) | 4107 (53) | 5121 (30) | 6157 (9) | (4480, 12900) |
| $AUC_{tau}$(dn)[ng.hr/mL/mg] | 75.21 (26) | 68.12 (29) | 67.50 (39) | 56.62 (48) | 51.21 (30) | 41.02 (9) | (22.4, 64.7) |
| CL/F [L/hr] | 13.27 (26) | 14.72 (29) | 14.84 (39) | 176.66 (48) | 19.52 (30) | 24.37 (9) | (15.5, 44.6) |
| $C_{max}$ [ng/mL] | 67.29 (18) | 138.1 (35) | 359.7 (27) | 429.6 (48) | 550.2 (32) | 541.0 (42) | (760, 1430) |
| $C_{max}$(dn) [ng/mL/mg] | 6.729 (18) | 5.522 (35) | 7.193 (27) | 5.925 (44) | 5.502 (32) | 3.604 (42) | (3.80, 7.15) |
| $R_{ac}$ | 1.54 ± 0.075 | 1.24 ± 0.210 | (0.879, 1.33) | 1.12 ± 0.446 | 1.07 ± 0.311 | 1.00 ±0.791 | (0.571, 0.729) |
| $R_{ss}$ | 0.993 | ND | (0.401, 0.719) | 0.613 ± 0.290 | 0.660 ± 0.186 | ND | (0.384, 0.403) |
| $T_{max}$ [hr] | 1.00 (1.00-1.08) | 1.00 (1.00-2.00) | 2.00 (1.92-2.75) | 1.03 (0.500-2.00) | 1.13 (1.00-4.00) | 1.30 (1.00-24.0) | 1.61 (1.22-2.00) |
| **Cycle 1 Day 15: *BID Doses*** | *35 mg BID* | *75 mg BID* | *100 mg BID* | | | | |
| N,n[b], n[c] | 1,1,1 | 3,3,1 | 3,3,3 | | | | |
| $AUC_{tau}$ [ng.hr/mL] | 2140 | 3574 (35) | 4058(33) | | | | |
| $AUC_{tau}$(dn)[ng.hr/mL/mg] | 61.30 | 47.67 (35) | 44.66 (47) | | | | |
| CL/F [L/hr] | 16.30 | 20.99 (35) | 22.37 (47) | | | | |
| $C_{max}$ [ng/mL] | 370.0 | 550.0 (23) | 600.5 (27) | | | | |
| $C_{max}$(dn) [ng/mL/mg] | 10.60 | 7.333 (23) | 6.609 (37) | | | | |
| $R_{ac}$ | 2.090 | 1.23± 0.352 | 1.52 ±0.296 | | | | |
| $R_{ss}$ | 0.8150 | 0.5420 | 0.769 ± 0.136 | | | | |
| $T_{max}$ [hr] | 0.500 | 0.550 (0.500-2.05) | 2.00 (1.00-2.00) | | | | |

Source: Table 14.4.4.1.1.1
N = Number of patients in the treatment group;;n[b]=number of patients where $R_{ac}$ were determined; n[c]=number of patients where $R_{ss}$ were determined.
Parameters are defined in Table 4.
a. Geometric mean (geometric %CV) for all except: median (range) for $T_{max}$; arithmetic mean± Std Dev for t½ ,MRT $R_{ac}$ and $R_{ss}$. Single observation was reported when n=1 and range when n=2.

Source: 2.7.2 Summary of Clinical Pharmacology Studies; Table 26; Page 97

## OFFICE OF CLINICAL PHARMACOLOGY:

## PHYSIOLOGICALLY BASED PHARMACOKINETIC REVIEW

| | |
|---|---|
| NDA Number | 210868 |
| Drug Name | LORBRENA (Lorlatinib) |
| Dose Regimen | Oral 100 mg administered daily with or without food |
| Indication | Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on alectinib as first-line therapy or on crizotinib and at least one other ALK kinase inhibitors |
| Primary Reviewer | Edwin C. Y. Chow, Ph.D. |
| Secondary Reviewer | Manuela Grimstein, Ph.D.<br>Yuching Yang, Ph.D. (Team Lead) |
| Applicant | Pfizer Inc. |



Reference ID: 4344794

## Study objectives

The main objective of this review is to evaluate the adequacy of FDA's physiologically-based pharmacokinetic (PBPK) model 1) to predict the effect of a strong CYP3A inhibitor on the steady state exposure of lorlatinib; and 2) to provide a dosing recommendation based on the predicted DDI potential.

The FDA-developed PBPK model for lorlatinib will be used to support the proposed US prescription information [USPI] in sections 2.4, 7.1 and 12.3.

## Executive Summary

The PBPK model of lorlatinib was developed by FDA to evaluate the effect of a strong CYP3A inhibitor on the steady state exposure of lorlatinib and guide dosing recommendations.

The model could adequately predict the PK and auto-induction characteristic of lorlatinib over the dose range from 10 to 200 mg administered QD under fasted conditions. The model could also adequately predict the observed increased exposure of lorlatinib when a single 100 mg dose of lorlatinib was administered concomitantly following multiple dosing of 200 mg QD itraconazole (strong CYP3A inhibitor). Based on these validation results, the model was considered adequate to predict the effect of itraconazole dosed to steady state, on the PK of lorlatinib at steady state. The simulation results showed that the steady state exposure of lorlatinib at 75 mg QD dosing with concomitant 200 mg QD itraconazole dosing to steady state is comparable to the steady state exposure of lorlatinib at 100 mg QD dosing alone. This supports the recommendation to reduce the starting dose of lorlatinib to 75 mg QD when concomitant strong CYP3A inducers must be administered.

## Background

Lorlatinib (also known as PF-06463922) is a small molecule inhibitor of the Anaplastic Lymphoma Kinase (ALK) ($IC_{50}$ values ranging from 0.65 to 65 nM for wild-type and mutated ALK) and c-ROS oncogene 1 (ROS1) ($IC_{50}$ values ranging from 0.23 to 1.3 nM) kinase activities. The recommended dosage is lorlatinib is 100 mg orally QD.

In vitro, lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3 to form lorlatinib metabolites, M6, M1a, and M2a. CYP3A4 is the only enzyme responsible for the formation of M6 (preclinical report 123802). CYP3A4, CYP3A5, CYP2C8, CYP2C19, and CYP1A2 are responsible for the formation of M2a (preclinical report 123802). UGT1A4 and UGT1A3 are responsible for the formation of M1a (preclinical report 060322). In vivo (mass balance study B7461004), M6, M1a, and M2a are



Reference ID: 4344794

considered minor lorlatinib metabolites representing 4.5%, 8.0%, and 2.3% of the lorlatinib dose, respectively, in plasma. The metabolite M8, resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib, was the most abundant human circulating metabolite (21% of radioactivity in plasma). The M8 metabolite is pharmacologically inactive. M8 formation was not observed in vitro, likely due to low metabolic turnover of lorlatinib, and the formation of this metabolite involved multiple biotransformation steps. Radioactivity recovery in feces and urine were 41% (9% unchanged lorlatinib) and 48% (<1% unchanged lorlatinib), respectively.

In vitro, lorlatinib activates PXR ($EC_{50}$ value of 2.85 µM and $E_{max}$ value of 13.8) and induces CYP3A4 mRNA (>40-fold), which is in within the range observed for the positive control rifampin (45-fold) (Preclinical Study Report 125344). Lorlatinib induces CYP3A4 activity, but it is not comparable to rifampicin (Table 30). In human hepatocytes, lorlatinib demonstrates time-dependent inhibition characteristics ($K_I$ value of 7.92 µM and $k_{inact}$ value of 0.081 $min^{-1}$, at higher lorlatinib concentrations (Preclinical Study Report 145029).

In Phase 1 of Study B7461001, the steady-state lorlatinib maximum plasma concentration ($C_{max}$) and area under the curve (AUC) appeared to increase proportionally over the dose range from 10 mg to 200 mg orally once daily, and there was no accumulation at the recommended dosing regimen (100 mg QD). The mean oral clearance (CL/F) was 11 L/h (35% CV) following a single oral 100 mg dose and increased to 18 L/h (39% CV) at steady state, possibly due to an autoinduction effect on CYP3A4. The mean plasma half-life ($t_{1/2}$) of lorlatinib was 24 hours (40% CV) after a single oral 100 mg dose of lorlatinib.

In drug-drug interaction studies, administration of repeated 150 mg QD doses of lorlatinib resulted in significant decrease in the AUC (63%) and $C_{max}$ (40%) of the CYP3A index substrate midazolam. Administration of repeated 200 mg QD doses of itraconazole, a strong CYP3A inhibitor, resulted in a significant increase in the AUC (1.42-fold) and $C_{max}$ (1.24-fold) of lorlatinib. Administration of repeated 600 mg QD doses of rifampicin, a strong CYP3A inducer, resulted in a significant decrease in the AUC (85%) and $C_{max}$ (75%) of lorlatinib. Based on the observed data from the clinical DDI studies, Pfizerproposed the following dosing recommendations in the USPI:

- Avoid concomitant use of CYP3A substrates
- Avoid concomitant use of strong CYP3A inhibitors. If concomitant use cannot be avoided, reduce the dose of lorlatinib
- Do not use strong CYP3A inducers

The dosing recommendation for concomitant use of strong CYP3A inhibitors was based on the exposure increase of a single dose of lorlatinib, and not based on steady state lorlatinib exposure changes. Thus, a PBPK model was developed to simulate DDI trials to assess the effect of multiple dose itraconazole on the steady state PK of lorlatinib at the recommended dosage in healthy subjects.



Reference ID: 4344794

## Methods

A population-based PBPK software (Simcyp® V16, release 1, Sheffield, UK) was used by FDA to develop a PBPK model for lorlatinib. Parameters and their sources for lorlatinib are summarized in Appendix Tables 1 -3.

The lorlatinib PBPK model was developed and verified using the physiochemical properties of lorlatinib (in Module 3.2.S.1), in vitro data (in Module 4.2.2), including metabolic data using human microsomes and hepatocytes, and clinical PK data (B7461001, B7461004, and B7461007). A brief description of the workflow of model development follows below:

A full PBPK model was selected for lorlatinib based on the optimal comparison between observed and predicted plasma concentration-time profiles following IV dose (absolute bioavailability study B7461007).

The advanced dissolution, absorption, and metabolism (ADAM) model (SimCYP v16) was used to describe lorlatinib absorption incorporating in vitro apparent permeability ($P_{app}$) and dissolution data (Table 103).

In vitro, lorlatinib is metabolized to three main metabolites, M6, M1a, and M2a. The kinetic parameters for formation of the metabolites M6, M2a, and M1a were incorporated into the PBPK model (Table 103). Refer to the Supplemental Material for detailed information on the in vitro the re-optimized kinetic parameters for M6 formation and the rational for assignment of the apparent intrinsic clearances for M2a and M1a formation. M8 was not included in the model due to the fact that M8 formation may involve multiple biotransformation steps, which are not evaluated.

Regarding the interaction parameters of lorlatinib towards CYP3A, the induction kinetics obtained in vitro (preclinical report 125344) were incorporated in the PBPK model; whereas the time-dependent inhibition kinetics ($K_I$ value of 7.92 µM and $k_{inact}$ value of 0.081 $min^{-1}$ reported in the preclinical report 145029) was not incorporated because it is unlike that $C_{max}$ (0.46 µM unbound at 100 mg QD) would reach the $K_I$ value.

The Lorlatinib PBPK model was verified against the PK data following a single dose and multiple doses of lorlatinib in Study B7461001 and from the drug interaction studies (B7461001, B7461011, and B7461012).

Simulations were conducted for the following clinical trials:

- Study B7461001: Phase 1/2 study conducted in patients with ALK-positive or ROS1-positive NSCLC.
- Study B7461011: Phase 1, open-label, 2-period, 2-treatment, fixed-sequence, crossover study to estimate the effect of multiple dose rifampin on the single dose PK of lorlatinib in healthy volunteers (HV).

- Study B7461012: Phase 1, open-label, fixed sequence, 2-period study to investigate the effect of multiple doses of itraconazole on the PK of single dose lorlatinib.

Unless otherwise stated, all simulations were conducted in Software's built-in "Sim-Healthy volunteer" population and ten trials of 10 subjects were simulated for each dosing regimen (age range 20-50 years, female ratio 0.5).

Perpetrator models for itraconazole "SV-Itraconazole_fed capusle.cmpz", and rifampicin "SV-Rifampicin-MD.cmpz", and victim model for midazolam "Sim-Midazolam.cmpz" from the software's drug model library (v16) were directly used.

## Results

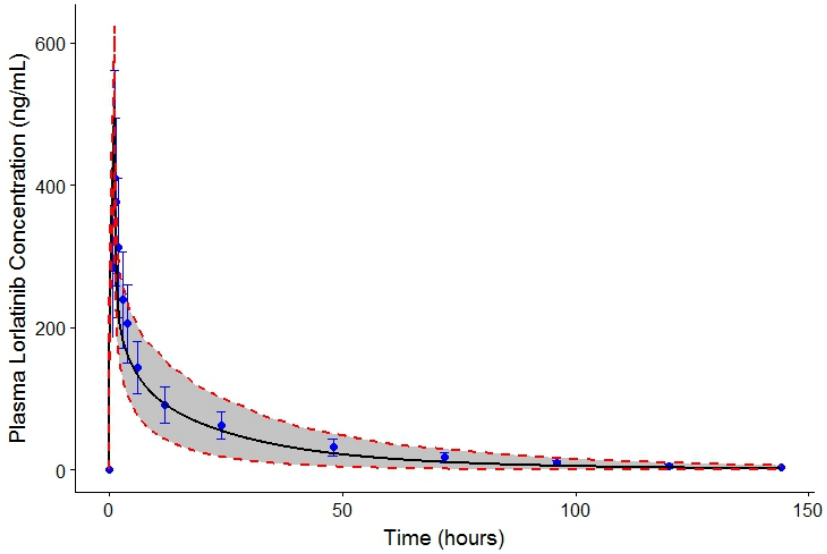
**Does FDA's PBPK model adequately describe the PK profiles of lorlatinib after single and multiple dose scenarios?**
Yes. The predictive performance of lorlatinib PBPK model was assessed by 1) the ability to predict pharmacokinetic parameters estimated from intravenous and oral administration; and dose proportionality following 2) a single oral dose and 3) multiple dosing. The simulations of the PBPK model were verified using clinical PK data following intravenous and oral dosing of lorlatinib from the absolute bioavailability study (B7461007) in healthy subjects, and phase 1/2 study in cancer patients (B741001).

As shown in Figure 11, the model could predict lorlatinib PK following a single dose of 50 mg IV (A) and 100 mg oral administration of lorlatinib (B). Similarly, the model could predict lorlatinib PK following multiple 100 mg QD doses of lorlatinib (Figure 12).The estimated PK parameters predicted by the model were comparable to the observed values (Table 98) .

**Figure 11 The observed and simulated concentration-time profiles of a single (A) 50 mg IV and (B) 100 mg oral administration of lorlatinib in healthy subjects. Blue circles with standard derivation denoted the observed mean values obtained from Study B7461007; Black solid line denoted the simulated concentrations from PBPK model with 95$^{th}$ percentile highlighted by gray shadow and red dash lines.**
**(A)**



Reference ID: 4344794


Plasma Lorlatinib Concentration (ng/mL)
600
400
200
0
0
50
100
150
Time (hours)

**(B)**

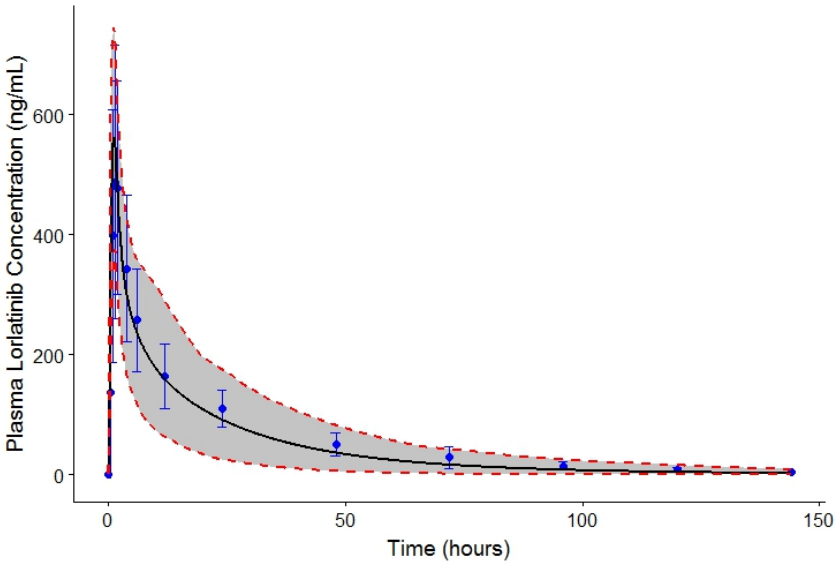
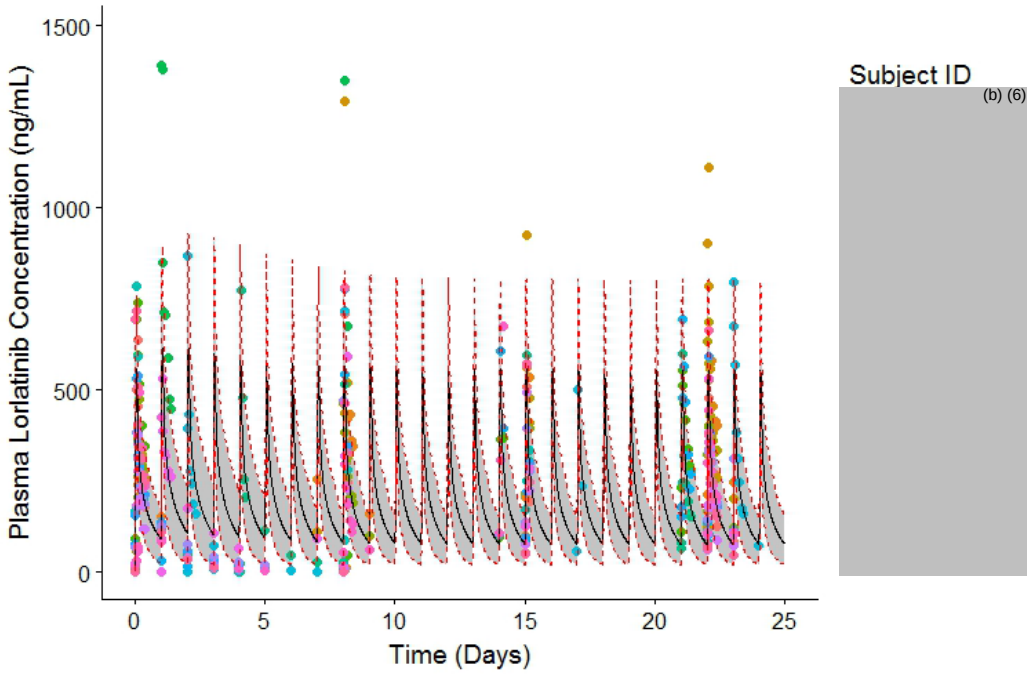

Plasma Lorlatinib Concentration (ng/mL)
600
400
200
0
0
50
100
150
Time (hours)

**Table 98 Comparison of lorlatinib pharmacokinetic parameters between observed values[a] and predicted values from PBPK model following a single 50 mg IV or 100 mg SD or MD oral administration**

| PK parameters | Observed Value | Predicted Value |
|---|---|---|
| **$V_{ss}$ (L/kg)** | 3.89 | 3.96 |
| **$t_{1/2}$ (hr)** | 18-27 | 21.1 |
| **$CL_{iv}$ (L/hr)** | 9.713 | 10.51 |
| **$CL_{po}$ or CL/F (L/hr)** | 12.05 | 12.87 |
| **$E_H$** | 0.118 | 0.14 |
| **F** | 0.808 | 0.81 |
| **Single Dose $C_{max}$[b] (ng/mL)** | 595.5 (37% CV) | 558.3 |
| **Single Dose $AUC_{inf}$[b] (ng·hr/mL)** | 8236 (25% CV) | 6541 |
| **Steady State $C_{max}$[c]** | 550.2 (32% CV) | 560.3 |
| **Steady State $AUC_{ss}$[c]** | 5121 (30% CV) | 4266 |

[a] Source: B7461007 Final Study Report; Table 13, Page 48
[b] PK parameter in Table 96 following lorlatinib 100 mg single oral dose
[c] PK parameter in Table 97 following lorlatinib 100 mg multiple oral doses

**Figure 12 The observed and simulated concentration-time profiles of 100 mg QD doses of lorlatinib in NSCLC patients. Color circles denoted the individual observed values obtained from Study B7461001; Black solid line denoted the simulated concentrations from PBPK model with 95th percentile highlighted by gray shadow and red dash lines.**



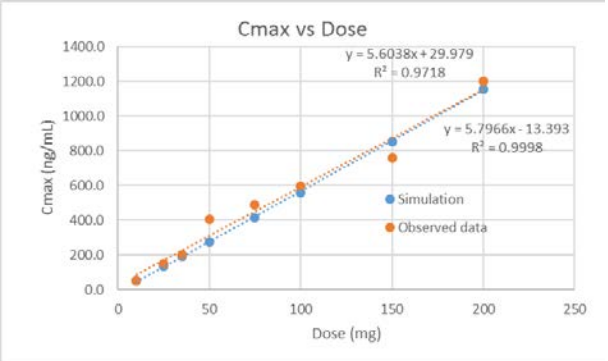

Dose proportionality was assessed between single doses ranging from 10 to 200 mg and exposure of lorlatinib ($C_{max}$ and AUC). As shown in the Figure 13, the calculated R ratio



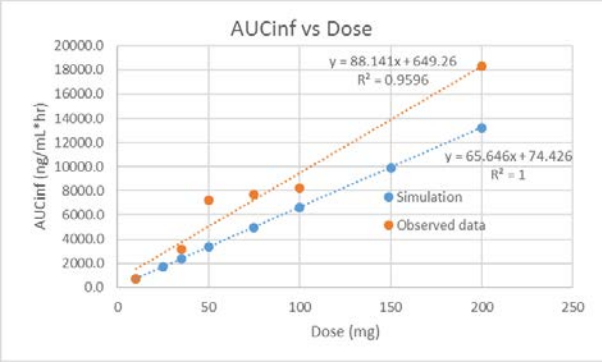
Reference ID: 4344794

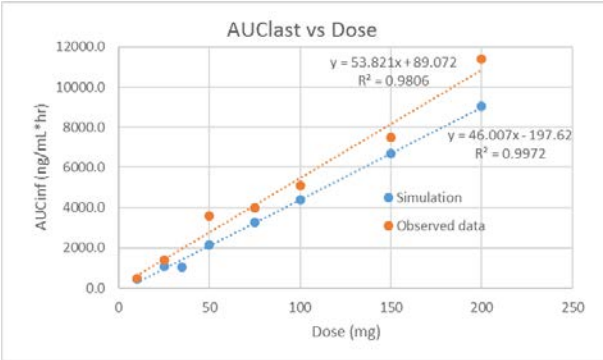
(predicted/observed) demonstrated the model could predict the lorlatinib across different doses.

**Figure 13 Dose proportionality between dose and exposure ($C_{max}$ and AUC) and the calculated R ratio.**




| | Predicted/Observed Data | | |
|---|---|---|---|
| Dose (mg) | $R_{Cmax}$ | $R_{AUCinf}$ | $R_{AUCtau}$ |
| 10 | 1.04 | 1.02 | 0.89 |
| 25 | 0.90 | NA | 0.78 |
| 35 | 0.93 | 0.76 | NA |
| 50 | 0.67 | 0.47 | 0.60 |
| 75 | 0.85 | 0.65 | 0.82 |
| 100 | 0.93 | 0.80 | 0.86 |
| 150 | 1.12 | NA | 0.89 |
| 200 | 0.96 | 0.72 | 0.79 |




The half-life of lorlatinib is about 24 hours and the anticipated accumulation ratio is about 2. However, at 100 mg QD dose, the observed mean accumulation ratio ($R_{ac}$ or $AUC_{tau,ss}/AUC_{inf,first\ dose}$) is about 1.1 , and the steady state accumulation ratio ($R_{ss}$ or $AUC_{tau,ss}/AUC_{tau,first\ dose}$) is 0.66 (Table 97), suggesting a net auto induction effect. The kinetic parameters for CYP3A induction is incorporated in lorlatinib PBPK model (Table 103). To evaluate the model's predictability on net auto-induction, the mean accumulation ratio and steady state accumulation ratio were compared between observed (study B7461001) and PBPK predicted values following multiple oral doses (day 15). As shown in Table 99, accumulation ratios estimated by the model were comparable to those observed.



Reference ID: 4344794

**Table 99 Comparison of mean accumulation ratio ($R_{ac}$) and steady state accumulation ratio ($R_{ss}$) between observed and predicted values**

| | $R_{ac}$ | | | $R_{ss}$ | | |
|---|---|---|---|---|---|---|
| **Dosing** | **Observed[a]** | **Predicted** | **Pred/Obs Ratio** | **Observed[a]** | **Predicted** | **Pred/Obs Ratio** |
| **10 mg QD** | 1.54 | 1.36 | 0.88 | 0.99 | 0.85 | 0.86 |
| **25 mg QD** | 1.24 | 1.18 | 0.95 | ND | 0.76 | ND |
| **50 mg QD** | 1.10 | 1.05 | 0.95 | 0.56 | 0.69 | 1.23 |
| **75 mg QD** | 1.12 | 0.98 | 0.88 | 0.61 | 0.66 | 1.08 |
| **100 mg QD** | 1.07 | 0.94 | 0.88 | 0.66 | 0.64 | 0.97 |
| **150 mg QD** | 1.00 | 0.88 | 0.88 | ND | 0.61 | ND |
| **200 mg QD** | 0.65 | 0.85 | 1.30 | 0.39 | 0.59 | 1.51 |
| **35 mg BID** | 2.09 | 1.36 | 0.65 | 0.82 | 0.71 | 0.87 |
| **75 mg BID** | 1.23 | 1.17 | 0.95 | 0.54 | 0.63 | 1.17 |
| **100 mg BID** | 1.52 | 1.12 | 0.74 | 0.77 | 0.61 | 0.79 |

ND denoted as not determined
[a]Source: B7461001 Final Study Report

**Can FDA's PBPK model predict the PK profiles of lorlatinib when co-administrated with various CYP3A modulators?**

Yes. To quantitative determine the contribution of the CYP3A pathway that is modulated by the comedication (e.g., assumption of fm, CYP3A for lorlatinib), the ratios of lorlatinib exposure with or without CYP3A modulators were estimated by the model and compared to the observation clinical data (studies B7461011 and B7461012).

As shown in Table 100, the FDA's lorlatinib PBPK model reasonably describe lorlatinib PK with the strong CYP3A inhibitor itraconazole.

However, the model slightly under predicts the induction effect of the strong CYP3A inducer rifampicin on the exposure of lorlatinib. One possible explanation for the PBPK underprediction may be related to the current rifampicin PBPK model (default library compound). Rifampicin induction kinetics towards CYP3A4, an enzyme that has a major contribution to lorlatinib metabolism, may be under estimated. Recent research proposed that rifampicin models have a more potent induction potential (Fahmi et al., 2016; Yamashita et al., 2013) than the default values. Also, rifampicin is a strong inducer of CYP2C8, and CYP2D8 has a minor contribution to lorlatinib metabolism. The default rifampicin model does not incorporate this mechanism of induction.



Reference ID: 4344794

**Table 100 Observed and simulated lorlatinib exposure following a single dose of lorlatinib with multiple daily doses of itraconazole, a strong CYP3A inhibitor, or rifampicin, a strong CYP3A inducer**

| | $R_{Cmax}$ | | | $R_{AUClast}$ | | |
|---|---|---|---|---|---|---|
| | **Observed** | **Predicted** | **Observed/Predicted** | **Observed** | **Predicted** | **Observed/Predicted** |
| 200 mg QD Itraconazole, 100 mg single lorlatinib dose on day 6 | | | | | | |
| | 1.24[a] | 1.16 | **0.94** | 1.43[a] | 1.60 | **1.12** |
| 200 mg QD Itraconazole, 75 mg single lorlatinib dose on day 6 | | | | | | |
| | 1.57[a] | 1.17 | **0.75** | 1.57[a] | 1.64 | **1.04** |
| 200 mg QD Itraconazole, 25 mg single lorlatinib dose on day 6 | | | | | | |
| | 1.30[a] | 1.18 | **0.91** | 1.68[a] | 1.70 | **1.01** |
| 600 mg QD rifampicin, 100 mg single lorlatinib dose on day 9 | | | | | | |
| | 0.24[b] | 0.63 | **2.63** | 0.14[b] | 0.30 | **2.14** |

[a]Source: B7461012 study report
[b]Source: B7461011 study report

To verify the lorlatinib net CYP3A interaction effect (i.e., auto-induction effect on lorlatinib exposure and competitive inhibition), PBPK simulations were conducted with the CYP3A index substrate midazolam. The ratios of midazolam exposure with or without lorlatinib at various doses were estimated by the model and compared to the observed data (studies B7461011 and B7461012). As shown in Table 101, the FDA lorlatinib PBPK model reasonably described midazolam PK in the presence of lorlatinib.

**Table 101 Observed and simulated midazolam exposure following a single dose of midazolam, a CYP3A index substrate, with multiple daily doses of lorlatinib**

| | $R_{Cmax}$ | | | $R_{AUClast}$ | | |
|---|---|---|---|---|---|---|
| | **Observed** | **Predicted** | **Predicted/Observed** | **Observed** | **Predicted** | **Predicted/Observed** |
| 150 mg QD lorlatinib, 2 mg single lorlatinib dose on day 15 | | | | | | |
| | 0.50[a] | 0.47 | **0.94** | 0.36[a] | 0.35 | **0.97** |
| 25 mg QD lorlatinib, 2 mg single lorlatinib dose on day 15 | | | | | | |
| | 0.60[a] | 0.69 | **1.15** | 0.40[a] | 0.57 | **1.43** |

[a]Source: B7461001 study report

Subsequently, the FDA PBPK model was used to simulate the steady state exposure of lorlatinib with a strong CYP3A inhibitor (itraconazole) to guide DDI-based dosing recommendations. The simulation was performed for 15 days daily dosing of lorlatinib with or without itraconazole (200 mg QD). The steady state ratio of lorlatinib exposure in the presence or absence of the CYP3A inhibitor, and lorlatinib exposure with lorlatinib alone were calculated and compared. As show in Table 102, the steady state exposure of lorlatinib with concurrent use of 75 mg QD lorlatinib and 200 mg itraconazole would be equivalent to that of 100 mg QD lorlatinib alone (Figure 14). The simulation supports that a lorlatinib dose reduction is necessary with concurrent use of a strong CYP3A inhibitor.

**Figure 14 Simulated lorlatinib concentration-time profiles with (multiple doses of lorlatinib and itraconazole) or without itraconazole under steady state condition using PBPK modeling**

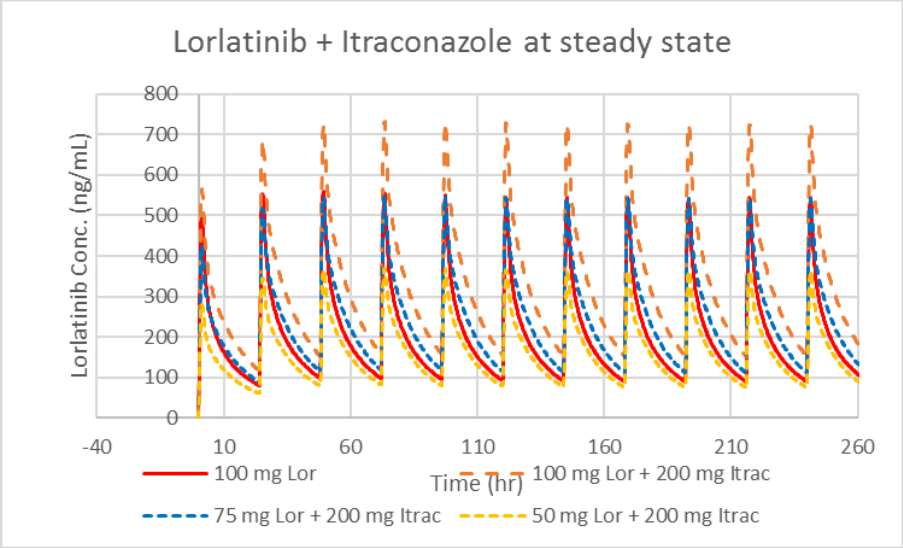



**Table 102 Steady state exposure of lorlatinib with (+) or without (-) CYP3A inhibitor itraconazole (200 mg QD) and relative exposure ratios**

| CYP3A Inhibitor | Lorlatinib dose (mg) | Steady state exposure of lorlatinib | | | |
|---|---|---|---|---|---|
| | | $C_{max,ss}$ | $AUC_{tau,ss}$ | $C_{max,ss}(+)/C_{max,ss}(-)$ | $AUC_{tau,ss}(-)/AUC_{tau,ss}(+)$ |
| | 100 | 560.26[a] | 4266.28[a] | | |
| Itraconazole | 50 | 362.06 | 3171.82 | 0.65 | 0.74 |
| Itraconazole | 75 | 525.02 | 4384.95 | 0.94 | 1.03 |
| Itraconazole | 100 | 684.83 | 5541.46 | 1.22 | 1.30 |

## Conclusions

The FDA lorlatinib PBPK model was considered adequate to predict the lorlatinib steady-state exposure in patients when a strong CYP3A inhibitor is co-administered. The model predicted a 30% increase in steady state lorlatinib AUC after multiple doses of 100 mg QD lorlatinib and 200 mg QD itraconazole but predicted comparable steady state lorlatinib AUC with the reduced 75 mg QD lorlatinib dose. These analyses are adequate to support Pfizer's statement in the proposed package insert as follows: "avoid concomitant use of strong CYP3A inhibitors. If cannot be avoided, reduce the dose of lorlatinib".



Reference ID: 4344794

# Supplemental Material

**Table 103 Lorlatinib PBPK model input parameters (Simcyp, v16, release 1)**



Reference ID: 4344794

| Property | Value | Source |
|---|---|---|
| Name | Lorlatinib | |
| Molecular weight (g/mol) | 406.41 | Module 3.2.S.1.2 |
| Compound Type | Monoprotic base | Module 3.2.S.1.2 |
| LogP | 2.47 (from LogD at pH 9 estimated in SimCyp v16) | Module 3.2.S.1.3 |
| pKa | 4.92 (base) | Module 3.2.S.1.3 |
| $f_{u,p}$ | 0.34 | Study ADME-2012-001-0027 |
| B/P | 0.99 | Study YDP_067_087 |
| Absorption | Advanced Dissolution, Absorption, and metabolism (ADAM) model | |
| $f_u$(gut) | 1 | Assumed |
| $P_{app}$ ($10^{-6}$ cm/s) | 28.1 (transfected MDCKII cell lines) | Preclinical Study Report 135242 |
| Dissolution profile | Immediate release with dissolution profile<br>Time (hr) / % Release<br>0.083 / 40<br>0.25 / 70<br>0.5 / 82<br>0.75 / 90<br>1 / 93<br>1.25 / 97 | Module 3.2.P.2.2 |
| $V_{ss}$ (L/kg) | 3.95 | (Predicted by Full PBPK model, method 2) |
| $CL_{renal}$ (L/h) | 0.0942 | 1.57 mL/min from 78.3 kg BW obtained from mass balance study (B7461004) |



Reference ID: 4344794

| | | |
|---|---|---|
| Metabolism<br>M6<br><br><br><br><br>M2a<br><br><br><br><br><br><br><br>M1a | HLM (average of 3 lots)<br>CYP3A4 (100%)<br>$V_{max}$ = 14.588 pmol/min/mg<br>$K_m$ = 2.1165 µM<br>$f_{umic}$ = 0.83<br><br>$CL_{int,app}$ (µL/min/mg)<br>CYP3A4 (12.8%)=0.196<br>CYP3A5 (62.1%)=0.952<br>CYP1A2 (2.9%)=0.044<br>CYP2C8(8.9%)=0.137<br>CYP2C19(13.3%)=0.204<br>$f_{umic}$ = 0.83<br><br>$CL_{int,app,u}$ (µL/min/mg)<br>UGT1A4 (90%)=1.311<br>UGT1A3 (10%)=0.146 | <br><br>Re-optimized from Preclinical Study Report 123802 (See Table 104)<br><br><br>Used 1.532 µL/min/mg from Study 123802<br>Estimate $f_m$ from rhCYP metabolite formation rate data<br><br><br>Used 1.46 µL/min/mg from Study 060322<br>Estimate $f_m$ from metabolite formation rate data ($f_{umic}$ = 0.78) |
| Interaction (CYP3A4/5)<br>Induction<br><br><br>Competitive inhibition | Hepatocytes (avg 3 lots)<br>$IndC_{50}$ = 0.288 µM<br>$Ind_{max}$ = 5.99<br><br>$K_I$ = 328.23 µM | <br>Preclinical Study Report 125344<br><br><br>Re-optimized from Preclinical Study Report 123802 (See Table 104) |
| Population | Sim-Healthy volunteer | |

**Assignment of in vitro kinetic parameters for lorlatinib metabolites**

Based on in vitro metabolic data (Preclinical Study Report 123802 and 060322) of lorlatinib using human microsomes, the kinetic parameters for formation of the metabolites M6, M2a, and M1 suggest that the enzyme responsible for M6 formation has low affinity and low capacity for lorlatinib; whereas, the enzymes responsible for M2a and M1a formation have high affinity and high capacity for lorlatinib. As such, $K_m$, $V_{max}$, and $K_I$ values were included in the PBPK model to describe the potential non-linear metabolic characteristic for the M6 formation; whereas, apparent clearance values were included to describe the M2a and M1a formation.



Reference ID: 4344794

**Table 104 Enzyme Kinetic Parameters for the metabolism of lorlatinib in pooled liver microsomes[a]**

| Parameters | M2a (CYPs) | M6 (CYP3A4) | M1a (UGTs) |
|---|---|---|---|
| $V_{max}$ (pmol/min/mg protein) | 40.6 | 12.9 | 153 |
| $K_m$ (µM) | 26.5 | 1.52 | 134 |
| $K_I$ (µM) | NA | 440 | NA |
| $CL_{int,app}$ (µl/min/mg) | 1.53[b] | 8.487[b] | 1.46[c] |

[a] values obtained from Preclinical Study Report 123802; Table 6.1 on Page 13, and Preclinical Study Report 060322; Table 6.4 on Page 13
[b] Need to correct for unbound fraction (0.83)
[c] scaled to unbound apparent intrinsic clearance

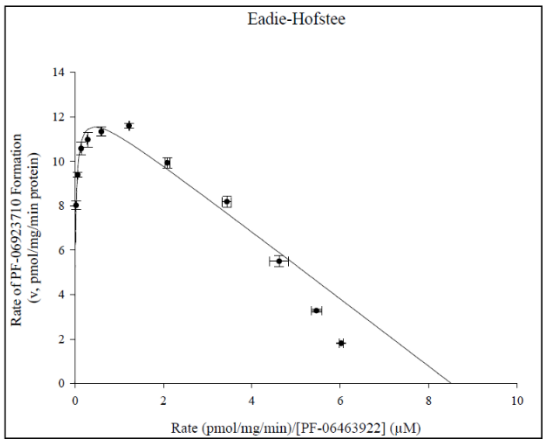
Based on in vitro metabolic data (Preclinical Study Report 123802), a substrate self-inhibition model [ $V = \frac{V_{max} \times S}{K_m + S \times (1 + S / Ki)}$ ] best described the formation of M6 (Table 104). However, based on the Eadie Hofstee plot and Michalis-Menten plots in Figure 15 provided by Pfizer, the model fitting was not optimized to predict the lorlatinib metabolism at low concentrations (right side of the Eadie-Hofstee plot). Lorlatinib steady state $C_{max}$ is about 550.2 ng/mL (Table 97), equivalent to 0.46 µM unbound (considering $f_u$~0.34 and MW = 406.41 g/mol). Thus, the model was re-optimized with higher weights ($1/y^2$) in data with lower lorlatinib concentrations. The new estimated kinetic parameters for M6 formation are $K_m$ = 2.1165 µM, $V_{max}$ = 14.588 pmol/min/mg, and $K_I$ = 328.23 µM with better predictions at lower lorlatinib concentrations as shown in Figure 15.

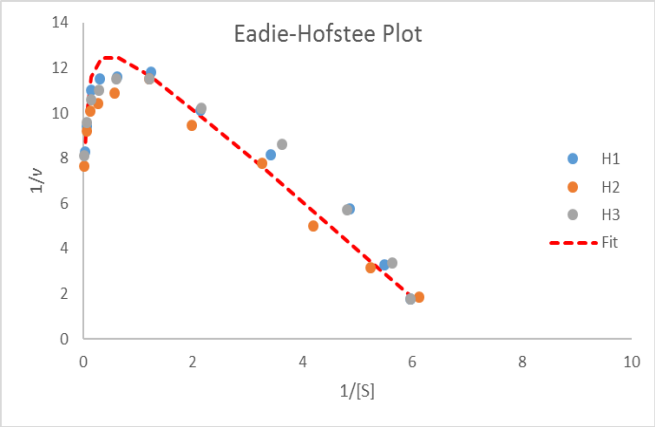


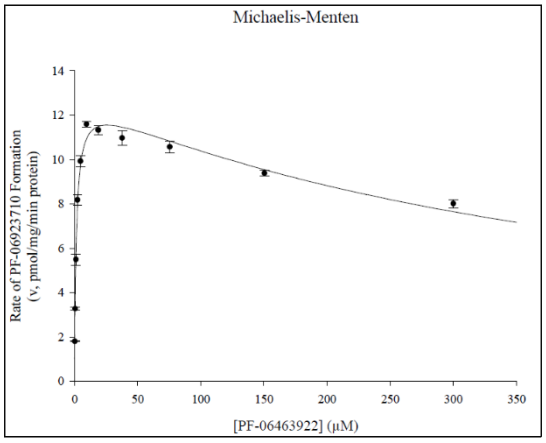
Reference ID: 4344794

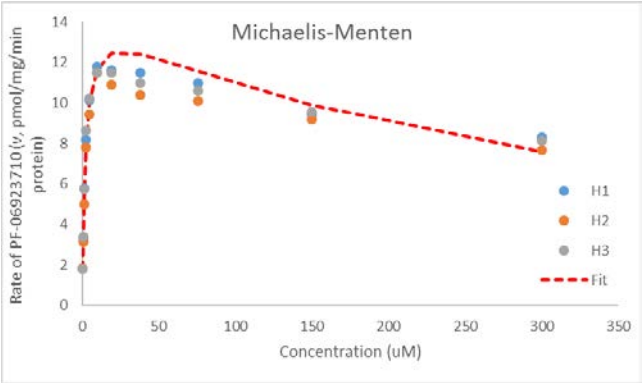
**Figure 15 Eadie-Hofstee, Michaelis-Menten, and Lineweaver-Burk plots for M6 formation from lorlatinib (Source: Preclinical Report 123802; Figures 8.2 and 6.1 on Page 22)**

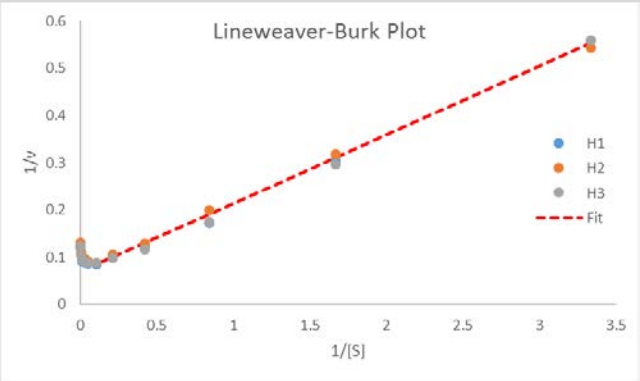
**Applicant's plots** | **FDA assessments**




Since M2a was formed from multiple CYP isozymes, the predicted fraction metabolic contribution of each enzyme for M2a formation was calculated based on M2a formation rates of each enzyme as shown in Table 105. The apparent clearance for M2a formation was then divided to individual enzyme contributions.



Reference ID: 4344794

**Table 105 M2a formation rates and prediction of fraction metabolic contribution determined from lorlatinib metabolism in rhCYPs**

| rhCYP Isoform | $v$[a] (pmol/min/pmol enzyme) | ISEF[a] | CYP abundance[a] | $v_{sc}$[c] | % contribution[d] |
|---|---|---|---|---|---|
| **CYP1A2** | 0.000399 | 0.31 | 52 | 0.006432 | 3.9% |
| **CYP2C8** | 0.000363 | 2.3 | 24 | 0.020038 | 8.9% |
| **CYP2C19** | 0.00889 | 0.24 | 14 | 0.02987 | 13.3% |
| **CYP3A4** | 0.00175 | 0.12 | 137 | 0.02877 | 12.8% |
| **CYP3A5** | 0.0113 | 0.12[b] | 103 | 0.139668 | 62.1% |

[a] values obtained from Preclinical Study Report 123802; Tables 6.6 and 7.1 on Pages 18 and 20.
[b] value assumed to be the same as CYP3A4
[c] scaled velocity = $v$ × ISEF× abundance
d estimated by $v_{sc}$/total $v_{sc}$

Since M1a was formed from multiple UGT isozymes, the predicted fraction metabolic contribution of each enzyme for M1a formation was calculated based on M1a formation rates. Based on the data in Table 106, the fraction metabolic contribution of UGT1A3 for M1a formation was estimated to be 10% whereas for UGT1A4 about 90% at lower lorlatinib concentration (40 µM). The apparent clearance for M1a formation was then divided to individual enzyme contributions (Table 106).

**Table 106 Metabolite formation rates of M1a from lorlatinib metabolism in rhUGTs[a]**

| rhUGT Isoform | M1a formulation rate (pmol/min/mg) | | |
|---|---|---|---|
| | **40 µM** | **200 µM** | **1000 µM** |
| **UGT1A3** | 4.62 | 12.4 | 11 |
| **UGT1A4** | 41.7 | 112 | 146 |

[a] values obtained from Preclinical Study Report 060322; Table 6.5 on Page 13

**Reference**

Yamashita F, Sasa Y, Yoshida S, Hisaka A, Asai Y, Kitano H, et al. (2013) Modeling of rifampicin-induced CYP3A4 activation dynamics for the prediction of clinical drug-drug interactions from in vitro data. PLoS One 8(9): e70330.

Fahmi OA, Shebley M, Palamanda J, Sinz MW, Ramsden D, Einolf HJ, et al. (2016) Evaluation of CYP2B6 Induction and Prediction of Clinical Drug-Drug Interactions: Considerations from the IQ Consortium Induction Working Group-An Industry Perspective. Drug Metab Dispos 44(10): 1720-1730.



Reference ID: 4344794

# OFFICE OF CLINICAL PHARMACOLOGY:

# PHARMACOMETRIC REVIEW

| | |
|---|---|
| NDA Number | 210868 |
| Drug Name | LORBRENA (Lorlatinib) |
| Dose Regimen | Oral 100 mg administered daily with or without food |
| Indication | Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on alectinib as first-line therapy or on crizotinib and at least one other ALK kinase inhibitors |
| Pharmacometrics Reviewer | Xiaofeng Wang, Ph.D. |
| Pharmacometrics Team Lead | Jiang Liu, Ph.D. |
| Applicant | Pfizer Inc. |

### 19.4.2. Applicant's population pharmacokinetic analysis

**Objective:**

- To develop a pharmacokinetic (PK) model that describes lorlatinib plasma PK following administration of the drug to subjects in various Phase 1 and 2 studies in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) and healthy volunteers.
- To identify potential covariates that may be important predictors of variability in lorlatinib absorption, distribution, and elimination.
- To provide individual predictions of lorlatinib exposure from the PK model that will be used in a sequential pharmacokinetic-pharmacodynamic (PKPD) analyses described in separate population modeling analysis plans (PMAPs).

**Data:**

The present population PK analysis was based on pooled data from studies B7461001, B7461004, B7461005, B7461007, B7461008, B7461011, and B7461016. A brief description for these studies is provided in Table 107.



Reference ID: 4344794

## Table 107 Clinical Studies Included in Population PK Analysis

| Protocol Number | Study Design/Objective(s) | Study Drug, Dose, Route, Duration | Number of Subjects | Study Population | Day(s) of Lorlatinib PK sampling | Time point(s) of sampling (hours) |
|---|---|---|---|---|---|---|
| B7461001 | Ph 1/2, open label, multicenter, multiple dose, dose escalation, safety, PK, PD and anti-cancer efficacy exploration study of lorlatinib as a single agent.<br><br>The Ph 1 portion estimated the maximum tolerated dose and RP2D for single agent lorlatinib. Additionally, a food effect substudy and a MDZ DDI substudy was conducted in Ph 1.<br><br>The Ph 2 portion evaluated overall (intra- and extra-cranial) and intracranial anti-tumor activity of single agent lorlatinib at RP2D in patients | In Ph 1, lorlatinib: 10, 25, 50, 75, 100, 150, 200 mg orally QD or 35 75 or 100 mg orally BID, continuously in 21 day cycles. Phase 2 was 100 mg daily. The Ph 1 portion used the **acetic acid solvate** formulation (as 5 mg and 25 mg tablets) and the Ph 2 portion used the **free base** formulation (as 25 mg strength tablets). | Ph 1: 54 (Including food-effect substudy: 6; MDZ DDI: 25 and 150 mg dose level)<br><br>Ph 2: 277 total (EXP-1: 30, EXP-2: 28, EXP-3: 61,EXP-4: 64, EXP-5: 46, EXP-6: 47) | Patients with advanced ALK+ or ROS1+ NSCLC | All patients in Ph 1 and 10 non-Japanese and 3 Japanese (non-LIC) patients in Ph 2: Day -7, C1D1, C1D8, and C1D15 and D1 of C2-C5. Additionally, in Ph 2 only, for D1 of C6 and D1 of every other cycle.<br><br>Ph 2 sparse plasma PK: pre-dose on D1 of C1-C5 and pre-dose on D1 of every other cycle beginning with C6.<br><br>Patients in MDZ substudy: C1D1, C1D8, and C1D15. For C2-C5, PK samples were also collected on D1.<br><br>Patients in food effect substudy: Day -7, C1D1, C1D8, and C1D15. For C2-C5, PK samples were also collected on D1. | Ph 1 full PK: Day -7: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96 and 120 hrs post dose. C1D1 and C1D8: pre-dose, 1, 4 hrs post dose. C1D15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs. For patients on BID dosing, the 24-hr time point sample need not be collected. D1 of C2-C5: Pre-dose and 1 hr post dose .<br><br>Ph 1 MDZ DDI substudy: C1D1 and C1D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs post dose. C1D8: Pre-dose, 1, 4 hrs post-dose. C2-C5: Pre-dose and 1 hr post dose.<br><br>Ph 1 food effect substudy: Day -7: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96, and 120 hrs post dose. C1D1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hrs post-dose. For patients on BID dosing, the 24 hr time point sample need not be collected.<br><br>Ph 2 full PK: D-7: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96 and 120 hrs post dose. C1D1 and C1D8: pre-dose, 1 , 2, and 4 hr post dose. C1D15: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hrs. D1 of C2-C5: Pre-dose 1 hr and 2 hrs post-dose. D1 of C6 and D1 of every other Cycle thereafter: Pre-dose.<br><br>Ph 2 sparse PK: pre-dose on Day 1 of C1-C5 and pre- dose on C7D1, C8D1 and C10D1. |

| Protocol Number | Study Design/Objective(s) | Study Drug, Dose, Route, Duration | Number of Subjects | Study Population | Day(s) of Lorlatinib PK sampling | Time point(s) of sampling (hours) |
|---|---|---|---|---|---|---|
| B7461004 | Open label, single dose, single center mass balance study | Single oral 100 mg dose (free base formulation) of lorlatinib containing approximately 100 $\mu$Ci of [14C]PF-06463922. | 6 | Healthy male volunteers | D1-D4 and until amount of radioactivity recovered in excreta is at least 90% of administered radioactivity or less than 1% has been recovered from excreta from two consecutive days (ie, the total for urine + feces is less than 1% on 2 consecutive days), up to 14 days post-dose. | Pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and beyond that, every 24 hours post-dose until amount of radioactivity recovered in excreta is at least 90% of administered radioactivity or less than 1% has been recovered from excreta from two consecutive days (ie, the total for urine + feces is less than 1% on 2 consecutive days). |
| B7461005 | Ph 1, crossover rBA study | Lorlatinib 100 mg tablets: **acetate solvate, anhydrous free base.**[a] | 18 | Healthy volunteers | D1 | Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 10 hrs post-dose |
| B7461007 | Ph 1, Single Dose, Randomized, Open-Label, Two-Period, Two-Treatment, Two-Sequence, Crossover Absolute BA Study of Lorlatinib In Healthy Volunteers | Treatment A:50 mg intravenous Treatment B: 100 mg oral tablet | 12 | Healthy volunteers | Treatments A and B: D1-D7 of each period. | Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72, 96, 120, and 144 hrs post-dose |
| B7461008 | Ph 1, antacid effect, food effect, and rBA study.<br>Ph 1, randomized, open label, 4 period, 4 treatment, 4 sequence, crossover study. | Single dose oral Tablets of PF 06463922 (free base formulation) without food, with food, with Pariet (rabeprazole) (without food).[b] Treatment A<br><br>(Reference): a 100 mg single dose administered in a fasted state as 4x25 mg Tablets. Treatment B (Test 1): a 100 mg single dose administered with high fat meal as 4x25 mg tablets.[c] | 24 | Healthy volunteers | Treatments A, B, D: D1-D5<br><br>Treatment C: D6-D10 | Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 48, 72 and 96 hrs post- dose |

| Protocol Number | Study Design/Objective(s) | Study Drug, Dose, Route, Duration | Number of Subjects | Study Population | Day(s) of Lorlatinib PK sampling | Time point(s) of sampling (hours) |
|---|---|---|---|---|---|---|
| B7461011 | Ph 1, Open Label, Two-Period, Two-Treatment, Fixed Sequence, Cross-Over Study To Estimate The Effect of Multiple Dose Rifampin on The Single Dose Pharmacokinetics of Lorlatinib in Healthy Volunteers | Treatment A (Reference): a 100 mg single dose of lorlatinib administered in a fasted state as 4x25 mg tablets on the morning of Day 1 of Period 1.[d] | 12 | Healthy volunteers | Period 1, D1 | Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, 120 hrs post-dose. |
| B7461016 | Ph 1, Single Dose BE Study To Compare The Proposed Commercial Image Tablets of Lorlatinib To The Ph 2 Clinical Tablet in HV Under Fasted Conditions | 4-period, 4-treatment, 4-sequence, crossover study with the reference Ph 2 clinical lorlatinib tablet (Treatment A, Reference, 4x25 mg tablets) under fasted state in adult healthy volunteers.[e] | 20 | Healthy volunteers | D1-D6 of each Period (1-4). | Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, and 120 hrs post-dose. |

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Table 1 on page 23*

**Results:**

The observed data are summarized for each continuous covariate in Table 108. The number of individuals in each categorical covariate level are summarized in Table 109.

**Table 108 Summary of Continuous Covariates**

| Variable | Study | N | Nm | Mean (Stdev) | Median (Max-Min) |
|---|---|---|---|---|---|
| Age (years) | B7461001 | 330 | 0 | 53.22 (12.11) | 53.00 (19.00-85.00) |
| | B7461004 | 6 | 0 | 33.00 (6.16) | 32.00 (27.00-44.00) |
| | B7461005 | 20 | 0 | 39.35 (8.95) | 40.50 (25.00-55.00) |
| | B7461007 | 11 | 0 | 37.64 (10.27) | 40.00 (24.00-52.00) |
| | B7461008 | 26 | 0 | 36.46 (10.15) | 34.50 (20.00-55.00) |
| | B7461011 | 12 | 0 | 36.50 (11.13) | 34.00 (21.00-55.00) |
| | B7461016 | 20 | 0 | 42.15 (9.46) | 43.50 (25.00-54.00) |
| | Overall | 425 | 0 | 49.86 (13.20) | 50.00 (19.00-85.00) |
| Baseline Albumin (g/dL) | B7461001 | 330 | 0 | 3.75 (0.55) | 3.80 (1.80-5.20) |
| | B7461004 | 6 | 0 | 4.57 (0.12) | 4.55 (4.40-4.70) |
| | B7461005 | 20 | 0 | 4.49 (0.23) | 4.55 (4.00-4.80) |
| | B7461007 | 11 | 0 | 4.45 (0.32) | 4.50 (3.90-4.80) |
| | B7461008 | 26 | 0 | 4.52 (0.21) | 4.50 (4.00-4.90) |
| | B7461011 | 12 | 0 | 4.48 (0.20) | 4.50 (4.00-4.70) |
| | B7461016 | 20 | 0 | 4.47 (0.25) | 4.50 (3.90-4.90) |
| | Overall | 425 | 0 | 3.92 (0.58) | 4.00 (1.80-5.20) |
| Baseline ALK (U/L) | B7461001 | 330 | 0 | 136.48 (119.39) | 98.00 (13.00-1552.00) |
| | B7461004 | 6 | 0 | 66.33 (10.35) | 70.50 (49.00-75.00) |
| | B7461005 | 20 | 0 | 69.80 (16.98) | 68.00 (46.00-111.00) |
| | B7461007 | 11 | 0 | 78.27 (21.12) | 69.00 (54.00-118.00) |
| | B7461008 | 26 | 0 | 72.58 (14.81) | 71.50 (38.00-100.00) |
| | B7461011 | 12 | 0 | 70.75 (15.31) | 67.50 (47.00-102.00) |
| | B7461016 | 20 | 0 | 71.20 (13.63) | 71.50 (47.00-102.00) |
| | Overall | 425 | 0 | 122.00 (108.83) | 88.00 (13.00-1552.00) |
| Baseline ALT (U/L) | B7461001 | 330 | 0 | 29.61 (27.08) | 21.00 (3.00-252.00) |
| | B7461004 | 6 | 0 | 19.50 (7.71) | 20.50 (10.00-29.00) |
| | B7461005 | 20 | 0 | 19.60 (8.60) | 17.50 (10.00-40.00) |
| | B7461007 | 11 | 0 | 17.73 (4.05) | 18.00 (9.00-24.00) |



Reference ID: 4344794

| Variable | Study | N | Nm | Mean (Stdev) | Median (Max-Min) |
|---|---|---|---|---|---|
| | B7461008 | 26 | 0 | 25.77 (10.29) | 24.50 (10.00-50.00) |
| | B7461011 | 12 | 0 | 17.42 (5.43) | 16.00 (11.00-27.00) |
| | B7461016 | 20 | 0 | 29.65 (10.15) | 25.50 (18.00-51.00) |
| | Overall | 425 | 0 | 28.11 (24.45) | 21.00 (3.00-252.00) |
| Baseline AST (U/L) | B7461001 | 330 | 0 | 26.22 (14.80) | 22.00 (10.00-141.00) |
| | B7461004 | 6 | 0 | 21.00 (5.14) | 21.50 (13.00-28.00) |
| | B7461005 | 20 | 0 | 22.30 (7.21) | 21.00 (15.00-45.00) |
| | B7461007 | 11 | 0 | 20.64 (2.46) | 21.00 (17.00-25.00) |
| | B7461008 | 26 | 0 | 25.58 (5.10) | 25.00 (15.00-36.00) |
| | B7461011 | 12 | 0 | 21.00 (4.24) | 20.50 (15.00-31.00) |
| | B7461016 | 20 | 0 | 28.30 (8.20) | 27.50 (21.00-58.00) |
| | Overall | 425 | 0 | 25.73 (13.43) | 22.00 (10.00-141.00) |
| Baseline Bilirubin (mg/dL) | B7461001 | 330 | 0 | 0.54 (0.27) | 0.50 (0.10-1.81) |
| | B7461004 | 6 | 0 | 0.72 (0.59) | 0.50 (0.30-1.90) |
| | B7461005 | 20 | 0 | 0.48 (0.18) | 0.50 (0.20-0.80) |
| | B7461007 | 11 | 0 | 0.80 (0.40) | 0.90 (0.20-1.30) |
| | B7461008 | 26 | 0 | 0.71 (0.22) | 0.70 (0.40-1.20) |
| | B7461011 | 12 | 0 | 0.57 (0.48) | 0.40 (0.20-1.90) |
| | B7461016 | 20 | 0 | 0.58 (0.15) | 0.60 (0.30-0.80) |
| | Overall | 425 | 0 | 0.56 (0.28) | 0.50 (0.10-1.90) |
| Baseline BMI ($kg/m^2$) | B7461001 | 330 | 0 | 24.35 (5.12) | 23.75 (13.11-65.85) |
| | B7461004 | 6 | 0 | 25.48 (1.68) | 25.70 (23.10-27.40) |
| | B7461005 | 20 | 0 | 26.45 (3.11) | 27.05 (19.10-30.10) |
| | B7461007 | 11 | 0 | 27.23 (3.14) | 27.60 (19.80-30.50) |
| | B7461008 | 26 | 0 | 25.10 (3.34) | 25.30 (18.70-30.00) |
| | B7461011 | 12 | 0 | 25.39 (2.68) | 25.40 (21.60-29.50) |
| | B7461016 | 20 | 0 | 24.57 (3.37) | 25.10 (18.40-30.00) |
| | Overall | 425 | 0 | 24.62 (4.77) | 24.28 (13.11-65.85) |
| Baseline Creatinine Clearance (mL/min) | B7461001 | 330 | 0 | 93.45 (33.27) | 88.79 (24.54-235.39) |
| | B7461004 | 6 | 0 | 114.48 (32.45) | 103.71 (92.00-178.72) |
| | B7461005 | 20 | 0 | 116.35 (17.34) | 118.61 (77.94-146.53) |
| | B7461007 | 11 | 0 | 121.43 (25.96) | 122.00 (85.29-160.57) |
| | B7461008 | 26 | 0 | 118.67 (17.96) | 120.29 (71.91-142.07) |

| Variable | Study | N | Nm | Mean (Stdev) | Median (Max-Min) |
|---|---|---|---|---|---|
| | B7461011 | 12 | 0 | 110.75 (18.78) | 107.47 (86.33-149.11) |
| | B7461016 | 20 | 0 | 109.01 (19.63) | 105.16 (75.34-149.17) |
| | Overall | 425 | 0 | 98.31 (32.13) | 96.56 (24.54-235.39) |
| Baseline Height (cm) | B7461001 | 330 | 0 | 166.52 (10.75) | 166.00 (141.00-198.00) |
| | B7461004 | 6 | 0 | 175.18 (9.72) | 175.10 (159.50-187.70) |
| | B7461005 | 20 | 0 | 176.70 (7.00) | 176.50 (162.00-190.00) |
| | B7461007 | 11 | 0 | 176.64 (9.05) | 174.00 (165.00-191.00) |
| | B7461008 | 26 | 0 | 176.54 (6.94) | 176.50 (159.00-190.00) |
| | B7461011 | 12 | 0 | 173.25 (6.03) | 175.00 (164.00-183.00) |
| | B7461016 | 20 | 0 | 175.80 (7.77) | 176.50 (161.00-193.00) |
| | Overall | 425 | 0 | 168.62 (10.82) | 169.00 (141.00-198.00) |
| Baseline Triglycerides (mg/dL)[a] | B7461001 | 330 | 30 | 123.22 (66.47) | 106.60 (28.00-451.40) |
| | B7461004 | 6 | 6 | ND | ND |
| | B7461005 | 20 | 20 | ND | ND |
| | B7461007 | 11 | 11 | ND | ND |
| | B7461008 | 26 | 26 | ND | ND |
| | B7461011 | 12 | 12 | ND | ND |
| | B7461016 | 20 | 20 | ND | ND |
| | Overall | 425 | 125 | 123.22 (66.47) | 106.60 (28.00-451.40) |
| Baseline Weight (kg) | B7461001 | 330 | 0 | 68.02 (17.28) | 66.46 (31.80-155.50) |
| | B7461004 | 6 | 0 | 78.28 (9.05) | 78.75 (64.50-91.10) |
| | B7461005 | 20 | 0 | 82.61 (10.68) | 83.95 (58.30-101.70) |
| | B7461007 | 11 | 0 | 85.02 (13.66) | 88.70 (60.00-110.40) |
| | B7461008 | 26 | 0 | 78.37 (12.64) | 76.58 (57.40-101.50) |
| | B7461011 | 12 | 0 | 76.19 (8.93) | 74.95 (64.10-91.30) |
| Variable | Study | N | Nm | Mean (Stdev) | Median (Max-Min) |
| | B7461016 | 20 | 0 | 76.06 (12.88) | 73.72 (57.30-104.20) |
| | Overall | 425 | 0 | 70.53 (16.89) | 70.22 (31.80-155.50) |

ePharmacology artifact ID RA13305069.
ALK=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; cm=centimeter; dL=deciliter; g=gram; kg=kilogram; L=liter; m=meter; mg=milligram; ND=not determined due to all values missing; Nm=number of missing values; Stdev=standard deviation; U=units.
[a]The high number of missing baseline triglyceride values are because collection of baseline triglycerides was not implemented in the healthy volunteer studies. Furthermore, it was implemented in Study B7461001 study after the start of the study, in the third protocol amendment.

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Table 7 on page 40*

**Table 109 Summary of Categorical Covariates**

| Variable | Category | Total | B7461001 | B7461004 | B7461005 | B7461007 | B7461008 | B7461011 | B7461016 |
|---|---|---|---|---|---|---|---|---|---|
| N | | 425 | 330 | 6 | 20 | 11 | 26 | 12 | 20 |
| Formulation | Free Base | 350 (82%) | 276 (84%) | 0 (0%) | 10 (50%) | 6 (55%) | 26 (100%) | 12 (100%) | 20 (100%) |
| | Acetic Acid Solvate | 70 (16%) | 54 (16%) | 6 (100%) | 10 (50%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | IV Solution | 5 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 5 (45%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Fed/Fasted Status[a] | Fasted | 334 (79%) | 262 (79%) | 6 (100%) | 20 (100%) | 11 (100%) | 3 (12%) | 12 (100%) | 20 (100%) |
| | Fed | 74 (17%) | 51 (15%) | 0 (0%) | 0 (0%) | 0 (0%) | 23 (88%) | 0 (0%) | 0 (0%) |
| | Missing | 17 (4%) | 17 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| PPI[b] | No PPI use | 402 (95%) | 330 (100%) | 6 (100%) | 20 (100%) | 11 (100%) | 3 (12%) | 12 (100%) | 20 (100%) |
| | PPI use | 23 (5%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 23 (88%) | 0 (0%) | 0 (0%) |
| Sex | Male | 234 (55%) | 141 (43%) | 6 (100%) | 20 (100%) | 11 (100%) | 25 (96%) | 11 (92%) | 20 (100%) |
| | Female | 191 (45%) | 189 (57%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (4%) | 1 (8%) | 0 (0%) |
| Race | White | 220 (52%) | 168 (51%) | 6 (100%) | 4 (20%) | 1 (9%) | 20 (77%) | 2 (17%) | 19 (95%) |
| | Black | 32 (8%) | 6 (2%) | 0 (0%) | 9 (45%) | 4 (36%) | 6 (23%) | 6 (50%) | 1 (5%) |
| | Asian | 113 (27%) | 112 (34%) | 0 (0%) | 0 (0%) | 1 (9%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Other | 29 (7%) | 13 (4%) | 0 (0%) | 7 (35%) | 5 (45%) | 0 (0%) | 4 (33%) | 0 (0%) |
| | Missing | 31 (7%) | 31 (9%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Patient Status | Healthy Volunteer | 95 (22%) | 0 (0%) | 6 (100%) | 20 (100%) | 11 (100%) | 26 (100%) | 12 (100%) | 20 (100%) |
| | Patient | 330 (78%) | 330 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Baseline Renal Impairment Grade | A (Normal) | 243 (57%) | 158 (48%) | 6 (100%) | 18 (90%) | 10 (91%) | 25 (96%) | 10 (83%) | 16 (80%) |
| | B (Mild) | 130 (31%) | 120 (36%) | 0 (0%) | 2 (10%) | 1 (9%) | 1 (4%) | 2 (17%) | 4 (20%) |
| | C (Moderate) | 51 (12%) | 51 (15%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Variable | Category | Total | B7461001 | B7461004 | B7461005 | B7461007 | B7461008 | B7461011 | B7461016 |
| | D (Severe) | 1 (0%) | 1 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Baseline Hepatic Impairment Grade | A (Normal) | 365 (86%) | 273 (83%) | 5 (83%) | 20 (100%) | 11 (100%) | 26 (100%) | 11 (92%) | 19 (95%) |
| | B1 (Mild) | 50 (12%) | 49 (15%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) |
| | B2 (Mild) | 10 (2%) | 8 (2%) | 1 (17%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (8%) | 0 (0%) |
| | C (Moderate) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | D (Severe) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| CYP2C19 Phenotype | Poor | 18 (4%) | 16 (5%) | 0 (0%) | 0 (0%) | 1 (9%) | 0 (0%) | 0 (0%) | 1 (5%) |
| | Intermediate | 100 (24%) | 76 (23%) | 2 (33%) | 0 (0%) | 4 (36%) | 8 (31%) | 4 (33%) | 6 (30%) |
| | Extensive | 153 (36%) | 108 (33%) | 4 (67%) | 0 (0%) | 6 (55%) | 15 (58%) | 8 (67%) | 12 (60%) |
| | Ultra-rapid | 7 (2%) | 3 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 (12%) | 0 (0%) | 1 (5%) |
| | Missing | 147 (35%) | 127 (38%) | 0 (0%) | 20 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| CYP2C9 Phenotype | Poor | 5 (1%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (4%) | 1 (8%) | 1 (5%) |
| | Intermediate | 62 (15%) | 50 (15%) | 3 (50%) | 0 (0%) | 0 (0%) | 3 (12%) | 1 (8%) | 5 (25%) |
| | Extensive | 211 (50%) | 151 (46%) | 3 (50%) | 0 (0%) | 11 (100%) | 22 (85%) | 10 (83%) | 14 (70%) |
| | Ultra-rapid | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Missing | 147 (35%) | 127 (38%) | 0 (0%) | 20 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| CYP3A5 Phenotype | Poor | 195 (46%) | 151 (46%) | 6 (100%) | 0 (0%) | 4 (36%) | 15 (58%) | 4 (33%) | 15 (75%) |
| | Intermediate | 66 (16%) | 42 (13%) | 0 (0%) | 0 (0%) | 7 (64%) | 7 (27%) | 6 (50%) | 4 (20%) |
| | Extensive | 17 (4%) | 10 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (15%) | 2 (17%) | 1 (5%) |
| | Ultra-rapid | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Missing | 147 (35%) | 127 (38%) | 0 (0%) | 20 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Table 8 on page 44*

Lorlatinib PK was well characterized by a 2-compartment model, with mixed first order and zero order absorption. The clearance was estimated using an initial clearance, CLI, and a time-dependent induced clearance after multiple dose. The time-dependent, induced clearance increases with time, approaching its maximum value at steady-state, CLMX.

In the final model, BALB (Baseline albumin), WNCL (Baseline standardized creatinine clearance), and TDOSE (Total daily dose) were found to be statistically significant and retained as covariates on CL. The effect of PPI (Proton pump inhibitor) use was found to be statistically significant and retained as a covariate on ka.

The final model parameter estimates are presented in Table 110.

**Table 110 Final PK Model Parameter Estimates**

| | Model Results | | | Bootstrap Results | |
|---|---|---|---|---|---|
| Parameter | Value | RSE(%) | Shrinkage(%) | Mean | 95% Confidence Interval |
| $\theta_{CLI\ (L/h)}$ | 9.035 | 6.860 | - | 9.088 | ( 8.0115 - 10.0609 ) |
| $\theta_{V_2\ (L)}$ | 120.511 | 10.764 | - | 120.618 | ( 103.3633 - 137.6947 ) |
| $\theta_{ka\ (h^{-1})}$ | 3.113 | 12.063 | - | 3.128 | ( 2.3125 - 3.9145 ) |
| $\theta_{Q\ (L/h)}$ | 22.002 | 8.515 | - | 22.491 | ( 17.6495 - 26.3563 ) |
| $\theta_{V_3\ (L)}$ | 154.905 | 5.314 | - | 156.640 | ( 134.2215 - 175.6205 ) |
| $\theta_{IND}$ | 0.020 | 10.787 | - | 0.027 | ( -0.2136 - 0.2535 ) |
| $\theta_{D1\ (h)}$ | 1.148 | 5.200 | - | 1.149 | ( 1.0344 - 1.2611 ) |
| $\theta_F$ | 0.759 | 7.169 | - | 0.764 | ( 0.6728 - 0.8462 ) |
| $\theta_{CLMX\ (L/h)}$ | 14.472 | 6.860 | - | 14.584 | ( 12.7286 - 16.2186 ) |
| $\theta_{Res.\ Error\ for\ IV}$ | 0.115 | 14.929 | - | 0.110 | ( 0.0811 - 0.1487 ) |
| $\theta_{Res.\ Error\ for\ PO}$ | 0.438 | 3.485 | - | 0.437 | ( 0.4090 - 0.4670 ) |
| $\theta_{BALB\ on\ CL}$ | 0.067 | 37.112 | - | 0.069 | ( 0.0214 - 0.1122 ) |
| $\theta_{TDOSE\ on\ CL}$ | 0.001 | 55.719 | - | 0.001 | ( 0.0004 - 0.0023 ) |
| $\theta_{WNCL\ on\ CL}$ | 0.235 | 20.164 | - | 0.240 | ( 0.1457 - 0.3238 ) |
| $\theta_{PPI\ on\ k_a}$ | -0.675 | -11.020 | - | -0.664 | ( -0.8508 - -0.4986 ) |
| IIV | Value | CV(%) | Shrinkage(%) | Mean | CI |
| $\omega^2_{CL}$ | 0.030 | 17.201 | 23.212 | 0.030 | ( 0.0159 - 0.0433 ) |
| $\omega_F\omega_{CLMX\ (L/h)}$ | -0.006 | 7.460 | - | -0.005 | ( -0.0173 - 0.0061 ) |
| $\omega^2_F$ | 0.022 | 14.964 | 40.174 | 0.023 | ( 0.0027 - 0.0420 ) |
| $\omega^2_{V_2}$ | 0.086 | 29.268 | 52.835 | 0.085 | ( 0.0430 - 0.1284 ) |
| $\omega_{V_2}\omega_{V_3}$ | -0.017 | 12.881 | - | -0.017 | ( -0.0492 - 0.0160 ) |
| $\omega^2_{V_3}$ | 0.101 | 31.742 | 53.123 | 0.099 | ( 0.0513 - 0.1502 ) |
| $\omega^2_{ka}$ | 2.329 | 152.626 | 45.113 | 2.345 | ( 1.5982 - 3.0608 ) |
| OFV | -2588.508 | - | - | -2640.454 | ( -3277.2723 - -1899.7429 ) |

ePharmacology artifact ID RA13523032. Line 1 substituted.
The mean and 95% Confidence Intervals are generated from a bootsrap run of 1000 resampled datasets
BALB=baseline albumin; CV= Coefficient of Variation; CI=Confidence Interval; Res Err= Residual Error; CLI=initial clearance; D1=zero order duration of absorption; F=bioavailability; h=hour; IIV=inter-individual variability; IND=rate constant of induction; ka=rate constant of absorption; L=liter; OFV=objective function value; PO=oral; PPI=proton pump inhibitor use; RSE=Relative Standard Error; TDOSE=total daily dose (mg); $V_2$=central volume of distribution; $V_3$=peripheral volume of distribution; WNCL=baseline standardized creatinine clearance.

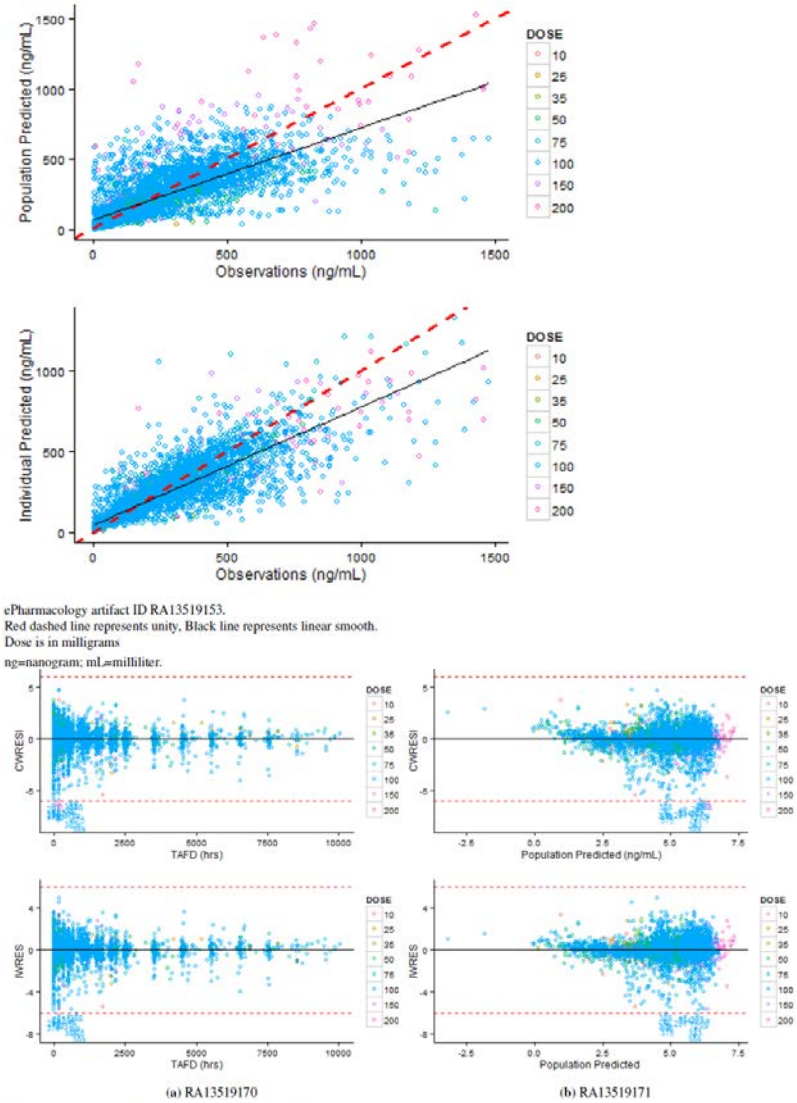
*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Table 12 on page 58*

Goodness-of-fit plots of the final model are shown in Figure 16.



Reference ID: 4344794

**Figure 16 Goodness-of-fit Plots of the Final Model**



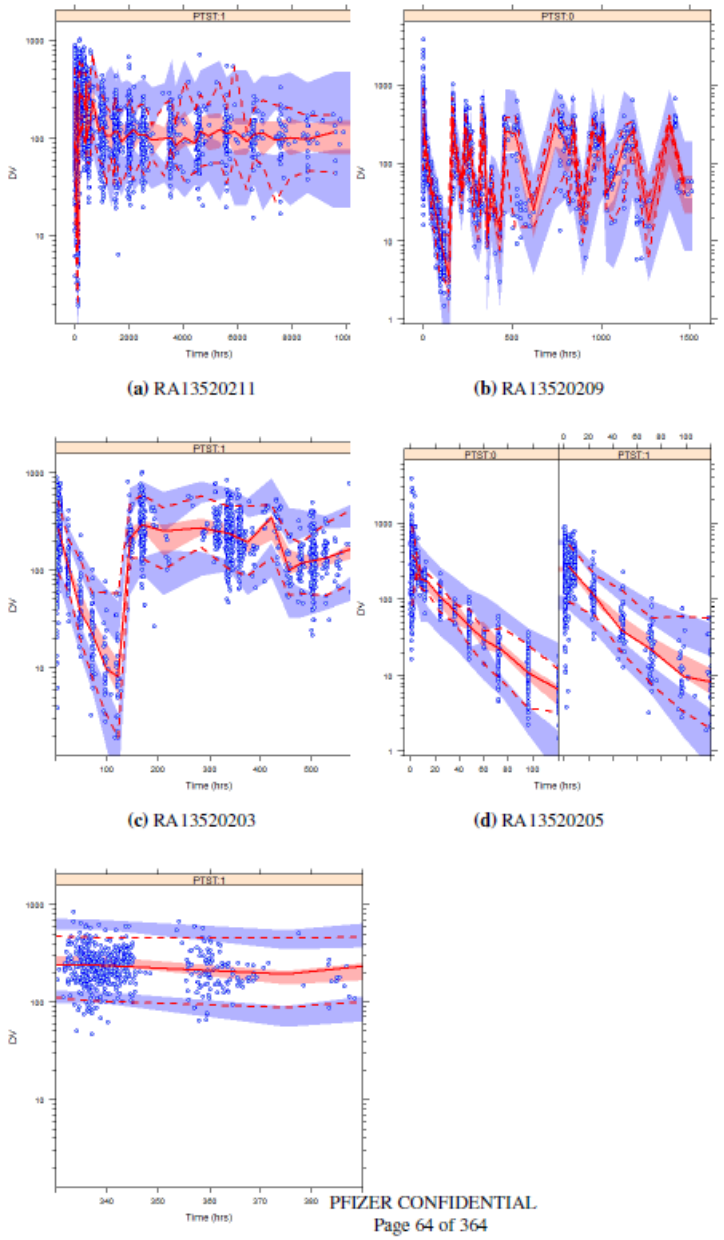

ePharmacology artifact ID RA13519153.
Red dashed line represents unity, Black line represents linear smooth.
Dose is in milligrams
ng=nanogram; mL=milliliter.

ePharmacology artifact IDs are shown in subfigure labels.
CWRES and IWRES versus TAFD Figure 7a, and PRED Figure 7b.
Dose is in milligrams.
CWRES=conditional weighted residuals; IWRES=individual weighted residuals; TAFD=time after first dose.

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Figure 6-7 on page 60-61*

The predictive performance of the final model was evaluated using prediction- and variability-corrected Visual Predictive Check (pvcVPC) and the results are shown in Figure 17.

**Figure 17 Prediction- and Variability- Corrected Visual Predictive Check**




(a) RA13520211

(b) RA13520209

(c) RA13520203

(d) RA13520205

(e) RA13520207

PFIZER CONFIDENTIAL
Page 64 of 364

ePharmacology artifact IDs are shown in subfigure labels.
TAFD was reset on Period 1 Day 1 and thus the first 120 hours represents a pooling of Day -7 and Period 1 Day 1. Shaded areas represent a simulation based 90% prediction interval of the 5th, 50th, and 95th percentile of the simulated data. Red lines represent the 5th, 50th, and 95th percentile of the observed data. Figure 9a All Patient Data, Figure 9b All healthy volunteer data, Figure 9c First 600 hours (patients only), Figure 9d First 120 hours (both patients and healthy volunteers), and Figure 9e Day 15 of Cycle 1 (patients only).

DV=dependent variable or observed concentrations; hr=hour; PTST=patient status, 0 for healthy volunteer, 1 for patients; TAFD=time after first dose.

*Source: Applicant's popPK study report PMAR-EQDD-B746-DP4-681, Figure 9 on page 64*

**Covariate Modeling:**

Various covariates were tested on the lorlatinib POPPK model, and the statistically significant covariates that improved model fit were retained in the final model. Interindividual variability



Reference ID: 4344794

(IIV) was only estimated for the overall CL. Thus, covariate assessments could only be done for overall CL and not the separate components, CLI and CLMX.

In order to remove the confounding effect of BWT on sex, BWT was included a priori in the base model, using allometric scaling exponents of 0.75 and 1 on CL and V2, respectively. Individuals who had a BWT of 50 kg (10th percentile BWT of this analysis population) had a decrease in CL of 22.3% and a decrease in V2 of 28.6% compared to the typical individual with BWT of 70 kg. Individuals who had a BWT of 91.3 kg (90th percentile BWT of this analysis population) had an increase in CL of 22.0% and an increase in V2 of 30.4% compared to the typical individual with BWT of 70 kg. A sensitivity analysis was conducted comparing a simulated typical individual with BWT of 50 kg and 91.3 kg, dosed at 100 mg QD compared to a simulated typical 70 kg patient, dosed at 100 mg QD. The exposure for patients at 50 kg and 91.3 kg were within the 95% PI of the exposure of the typical 70 kg individual.

Lorlatinib total daily dose (TDOSE) was found to be statistically significant on CL. This was consistent with lorlatinib exposure estimated from non-compartmental analysis (NCA). In Study B7461001, the steady-state CL increased with increasing dose. In this POPPK analysis, individuals who received the 10 mg QD dose had a 12.4% lower CL (both initial and time-dependent, induced clearance) compared to individuals receiving 100 mg QD lorlatinib. Similarly, individuals receiving the 200 mg QD dose had a 13.8% higher CL compared to individuals receiving 100 mg QD lorlatinib. This dose non-linearity is likely due to an increase in potency of induction, with increasing dose, which was accounted for with TDOSE as a covariate on CL.

Baseline albumin (BALB) was found to be statistically significant on CL. With every unit of baseline albumin over 4 mg/dL, there was a 6.68% increase in CL. For individuals with a BALB value of 3.2 mg/dL (the 10$^{th}$ percentile value of the analysis population), the clearance was 5.3% lower compared to the typical patient with 4 mg/dL of BALB. At a BALB value of 4.6 mg/Dl (the 90$^{th}$ percentile value of the analysis population), the clearance was increased 4% compared to the typical patient. While the exact reason for this relationship is unknown, it is not uncommon that individuals with decreased BALB also have a decreased CL. A sensitivity analysis was conducted comparing simulated typical individuals with BALB at 3.2 and 4.6 mg/dL, with a typical simulated individual with BALB of 4 mg/dL, each dosed at 100 mg QD. The simulated exposure for individuals at 3.2 and 4.6 mg/dL were within the 95% PI of the exposure of the typical 4 mg/dL individual, suggesting that BALB does not have a meaningful impact on lorlatinib PK that would warrant dose adjustment.

PPI use was found to be statistically significant on ka with a 67.5% decrease in ka. The absorption of lorlatinib was characterized with mixed zero order and first order absorption. Therefore, the impact of PPI was modeled only on the first order component of the absorption. The effect of PPI use on absorption was consistent with the results of the B7461008 study. In B7461008, PPI use decreased the Cmax by 30% without change in AUCinf. A sensitivity analysis was conducted comparing simulated typical individuals with PPI use, with a typical individual without PPI use, each dosed at 100 mg once daily (QD). Although, the median simulated exposure was decreased with PPI use, it was still within the 95% PI of the exposure of the



Reference ID: 4344794

typical individual without PPI use, suggesting that PPI use does not have a meaningful impact on lorlatinib PK that would warrant dose adjustment.

The effect of hepatic and renal impairment on lorlatinib PK was also assessed. For the assessment of hepatic impairment, neither of the baseline associated safety laboratory measurements (BAST nor BBIL), were found to be statistically significant covariates in the final model. For the assessment of renal impairment, baseline creatinine clearance was found to be statistically significant on CL in the final model. The impact of renal and hepatic impairment on lorlatinib PK was tabulated by summarizing the individual estimates of CL for each hepatic and renal impairment grade. For hepatic impairment, there was no trend in the median and mean individual estimates of lorlatinib clearance with worsening hepatic impairment. For renal impairment, there was a trend of decrease in the median and mean individual estimates of lorlatinib clearance with worsening renal impairment. However, there was only 1 patient in the most severe renal impairment group at baseline. Furthermore, the range of post-hoc estimates of lorlatinib clearance for patients with mild and moderate renal impairment, were largely within the range of the patients with normal renal function.

*Reviewer's comments:*
*Pfizer's population PK analysis is reasonable. The reviewer agrees with the Pfizer's conclusion that no dose adjustment is warranted for age, sex, race/ethnicity, body weight, mild to moderate renal impairment, and mild hepatic impairment.*

### 19.4.3. Applicant's Exposure-Response Analysis for Efficacy

**Objectives:**

The primary objectives of this population modeling analysis were:

- To assess the potential relationship between lorlatinib pharmacokinetic (PK) exposure (such as but not limited to, cumulative area under the concentration-time curve (cAUC)) and the efficacy endpoints objective response (OR) and intracranial objective response (IC-OR). For simplification, the endpoints will be referred to as objective response rate (ORR) and intracranial objective response rate (IC-ORR), respectively, since this was the measurement of the endpoints in the analysis dataset.
- To evaluate the effect of moderators (i.e., covariates) in the E-R relationship for the efficacy endpoints ORR and IC-ORR as assessed by independent central review (ICR).

**Data:**
The E-R analysis for efficacy was based on data for Study B7461001.

This was a Phase 1/2, open label, multicenter, multiple dose, dose escalation, safety, PK, pharmacodynamic (PD) and anti-cancer efficacy exploration study of lorlatinib as a single agent in patients with advanced ALK-positive or ROS1-positive NSCLC.

The Phase 1 portion included evaluations to assess the safety and tolerability of lorlatinib as a single agent at increasing dose levels in patients with advanced ALK-positive or ROS1-positive NSCLC in order to estimate the maximum tolerated dose (MTD), select the recommended



Reference ID: 4344794

Phase 2 dose (RP2D), examine lorlatinib single- and multiple-dose PK after once daily (QD) and twice daily (BID) dosing, the effect of lorlatinib on midazolam PK (as a probe for cytochrome P450 (CYP)3A4), and the effect of food on lorlatinib PK.

The Phase 2 portion evaluated overall (intra- and extra-cranial) and intracranial anti-tumor activity of lorlatinib at the RP2D, which was 100 mg QD based on Phase 1 study results, as well as single- and multiple-dose PK of lorlatinib at the RP2D, in patients with advanced ALK-positive or ROS1-positive NSCLC. In total, 276 patients were enrolled from the following 6 sub-populations for the Phase 2 portion of Study B7461001. The number of patients enrolled in each cohort of Study B7461001 are summarized in Table 111.

**Table 111 Summary of Patients with Advanced NSCLC Enrolled in Study B7461001**

| Phase (Treatment) | NSCLC Population | Mutation | Number of Patients (Treated) |
|---|---|---|---|
| Phase 1 (Lorlatinib 10 mg to 200 mg daily) | Treatment naive in the advanced setting or patients that had disease progression after at least 1 previous ALK or ROS inhibitor therapy(ies) | ALK+<br>ROS1+<br>Missing<br>Total | 42 (41)<br>12 (12)<br>1 (1)<br>55 (54) |
| Phase 2 (Lorlatinib 100 mg daily) | Cohort 1: Treatment naive | ALK+<br>Missing | 30 (30)<br>0 (0) |
| | Cohort 2: Disease progression after crizotinib | ALK+<br>Missing | 27 (27)<br>0 (0) |
| | Cohort 3: Disease progression after crizotinib and 1 to 2 prior chemotherapy regimens or after 1 prior ALK inhibitor | ALK+<br>Missing | 59 (59)<br>1 (1) |
| | Cohort 4: ALK+ and 2 prior ALK inhibitor therapies | ALK+<br>Missing | 66 (65)<br>0 (0) |
| | Cohort 5: ALK+ and 3 prior ALK inhibitor therapies | ALK+ | 46 (46) |
| | Cohort 6: ROS1+ and any line therapy | ROS1+<br>Total | 47 (47)<br>276 (275) |

Source: ePharmacology ID RA13493685
Last patient last visit first dose was on 06 October 2016. However, Study B7461001 is still ongoing.
NSCLC=Non-small cell lung cancer; ALK+=anaplastic lymphoma kinase-positive; ROS1+=ROS proto-oncogene 1-positive.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 1 on page 33*

**Method:**

The modeling analyses for ORR and IC-ORR were performed using generalized binomial logistic regression, as implemented with the glm (family="binomial") function using R software. The models developed for this analysis consisted of the following three components:

1. The base model component
2. The full model component, which included all tested fixed effects (covariates) that may influence response
3. The final model component, which included all retained fixed effects (covariates) that influence response

The covariates considered as potential predictors for the efficacy endpoints ORR and IC-ORR are listed in Table 112.

**Table 112 Potential Predictors of Response (i.e. Covariates)**

| Category | Variable. |
|---|---|
| Demographic Information | Race, sex, age, and baseline body weight |
| Prior Treatment | Crizotinib (Y/N), ALK inhibitors[a] (Y/N), chemotherapy[b] (Y/N), CNS radiation (Y/N), statin therapy (Y/N) number of prior systemic treatments (0, 1, 2 or greater) |
| Baseline safety laboratory information | Alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, amylase, bilirubin, hemoglobin, lipase, and creatinine clearance |
| Baseline disease status | ECOG (score of 0 or 1)<br>Sum of diameters for target lesions (mm),<br>Presence of CNS metastatis (Y/N) |
| Lorlatinib exposure | AUC24, $C_{avg,P1}$, $C_{trough,P1}$, $C_{max,P1}$, $cAUC_{P1}$, most frequent total daily dose |

ALK=anaplastic lymphoma kinase; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; mm=millimeter; N=No; Yes=Yes; AUC24=area under the time-concentration curve up to 24 hours after lorlatinib dose on Cycle 1 Day 1; $cAUC_{P1}$=predicted cumulative area under the concentration-time curve up to Cycle 2 Day 1; $C_{avg,P1}$=predicted average concentration calculated as the ratio of $cAUC_{P1}$ over the time frame for the cumulative exposure; $C_{trough,P1}$=predicted concentration prior to Cycle 2 Day 1 lorlatinib dose; $C_{max,P1}$=predicted maximum concentration up to Cycle 2 Day 1.

*a*. Prior ALK inhibitor refers to patients that were taking the following therapy prior to study therapy: alectinib, brigatinib, ceritinib, crizotinib, entrecitinib, or investigational drug X-396.

*b*. Prior chemotherapy refers to patients that were taking the following therapy prior to study therapy: bleomycin, carboplatin, cisplatin, docetaxel, etoposide, gemcitabine, paclitaxel, premetrexed, temozolomide, vinorelbine

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 4 on page 36*

**Results:**

**In total, 331 patients were enrolled in Study B7461001. Out of the 55 patients enrolled in the Phase 1 portion, 54 patients received at least 1 dose of lorlatinib and, of these, 41 patients were confirmed ALK-positive. Out of the 276 patients enrolled in the Phase 2 portion, 275 patients received at least 1 dose of lorlatinib and, of these, 227 patients were confirmed ALK-positive. The observed baseline characteristics for the total analysis populations (N=268) are summarized in Table 113 and**

Table 114.

**Table 113 Summary of Patient Categorical Covariate Characteristics**

| Variable | Category | Phase 1 | Phase 2 | Total |
|---|---|---|---|---|
| N | | 41 | 227 | 268 |
| Sex | Male | 17 (41%) | 97 (43%) | 114 (43%) |
| | Female | 24 (59%) | 130 (57%) | 154 (57%) |
| Race | White | 32 (78%) | 107 (47%) | 139 (52%) |
| | Black | 2 (5%) | 2 (1%) | 4 (1%) |
| | Asian | 5 (12%) | 87 (38%) | 92 (34%) |
| | Other | 0 (0%) | 8 (4%) | 8 (3%) |
| | Missing | 2 (5%) | 23 (10%) | 25 (9%) |
| Baseline ECOG | 0 | 15 (37%) | 101 (44%) | 116 (43%) |
| | 1 | 24 (59%) | 118 (52%) | 142 (53%) |
| | 2 | 1 (2%) | 8 (4%) | 9 (3%) |
| | 3 | 1 (2%) | 0 (0%) | 1 (0%) |
| Prior systemic therapy | 0 | 1 (2%) | 29 (13%) | 30 (11%) |
| | 1 | 6 (15%) | 38 (17%) | 44 (16%) |
| | 2(+) | 34 (83%) | 160 (70%) | 194 (72%) |
| Prior ALK inhibitor[a] | No | 4 (10%) | 34 (15%) | 38 (14%) |
| | Yes | 37 (90%) | 193 (85%) | 230 (86%) |
| Prior chemotherapy[b] | No | 17 (41%) | 103 (45%) | 120 (45%) |
| | Yes | 24 (59%) | 124 (55%) | 148 (55%) |
| Prior crizotinib | No | 6 (15%) | 62 (27%) | 68 (25%) |
| | Yes | 35 (85%) | 165 (73%) | 200 (75%) |
| Prior CNS radiation | No | 19 (46%) | 142 (63%) | 161 (60%) |
| | Yes | 22 (54%) | 85 (37%) | 107 (40%) |
| Baseline CNS met by ICR | No | 7 (17%) | 87 (38%) | 94 (35%) |
| | Yes | 34 (83%) | 140 (62%) | 174 (65%) |
| Total randomized daily dose (mg) | 10 | 2 (5%) | 0 (0%) | 2 (1%) |
| | 25 | 2 (5%) | 0 (0%) | 2 (1%) |
| | 50 | 3 (7%) | 0 (0%) | 3 (1%) |
| | 70 | 1 (2%) | 0 (0%) | 1 (0%) |
| | 75 | 10 (24%) | 0 (0%) | 10 (4%) |
| | 100 | 15 (37%) | 227 (100%) | 242 (90%) |
| | 150 | 4 (10%) | 0 (0%) | 4 (1%) |
| | 200 | 4 (10%) | 0 (0%) | 4 (1%) |
| Statin therapy | No | 10 (24%) | 37 (16%) | 47 (18%) |
| | Yes | 31 (76%) | 190 (84%) | 221 (82%) |
| Prior statin therapy | No | 40 (98%) | 208 (92%) | 248 (93%) |
| Variable | Category | Phase 1 | Phase 2 | Total |
| | Yes | 1 (2%) | 19 (8%) | 20 (7%) |

ePharmacology artifact ID RA13722428.
ALK=anaplastic lymphoma kinase; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; N=number of patients; ICR=independent central review; mg=milligram.
*a*. Prior ALK inhibitor refers to patients that were taking the following therapy prior to study therapy: alectinib, brigatinib, ceritinib, crizotinib, entrecitinib, or investigational drug X-396.
*b*. Prior chemotherapy refers to patients that were taking the following therapy prior to study therapy: bleomycin, carboplatin, cisplatin, docetaxel, etoposide, gemcitabine, paclitaxel, premetrexed, temozolomide, vinorelbine.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 5 on page 40*

**Table 114 Summary of Patient Continuous Covariate Characteristics**

| Variable | Group | N | Nm | Mean (StdDev) | Median (Range) |
|---|---|---|---|---|---|
| Age (years) | Phase 1 | 41 | 0 | 50.95 ( 11.18 ) | 50.00 (27.00-77.00) |
| | Phase 2 | 227 | 0 | 53.80 ( 11.98 ) | 54.00 (27.00-85.00) |
| | Total | 268 | 0 | 53.36 ( 11.89 ) | 53.00 (27.00-85.00) |
| Baseline weight (kg) | Phase 1 | 41 | 0 | 72.10 ( 19.65 ) | 69.85 (42.00-155.50) |
| | Phase 2 | 227 | 0 | 67.33 ( 16.86 ) | 64.00 (31.80-124.70) |
| | Total | 268 | 0 | 68.06 ( 17.37 ) | 66.64 (31.80-155.50) |
| Baseline creatinine clearance (mL/min) | Phase 1 | 41 | 0 | 93.50 ( 34.91 ) | 85.70 (44.52-180.31) |
| | Phase 2 | 227 | 0 | 92.53 ( 31.45 ) | 87.80 (24.54-195.18) |
| | Total | 268 | 0 | 92.68 ( 31.94 ) | 87.45 (24.54-195.18) |
| Baseline albumin (g/dL) | Phase 1 | 41 | 0 | 3.85 ( 0.63 ) | 3.90 (2.10-5.20) |
| | Phase 2 | 227 | 0 | 3.77 ( 0.51 ) | 3.80 (1.80-4.80) |
| | Total | 268 | 0 | 3.78 ( 0.53 ) | 3.85 (1.80-5.20) |
| Baseline alkaline phosphatase (IU/L) | Phase 1 | 41 | 0 | 122.29 ( 65.20 ) | 103.00 (34.00-404.00) |
| | Phase 2 | 227 | 0 | 138.92 ( 129.78 ) | 98.00 (13.00-1552.00) |
| | Total | 268 | 0 | 136.37 ( 122.19 ) | 98.00 (13.00-1552.00) |
| Baseline ALT (IU/L) | Phase 1 | 41 | 0 | 32.56 ( 30.09 ) | 22.00 (5.00-158.00) |
| | Phase 2 | 227 | 0 | 27.67 ( 22.04 ) | 21.00 (3.00-172.00) |
| | Total | 268 | 0 | 28.41 ( 23.45 ) | 21.00 (3.00-172.00) |
| Baseline AST (IU/L) | Phase 1 | 41 | 0 | 27.20 ( 11.93 ) | 22.00 (13.00-61.00) |
| | Phase 2 | 227 | 0 | 25.44 ( 13.09 ) | 22.00 (10.00-141.00) |
| | Total | 268 | 0 | 25.71 ( 12.92 ) | 22.00 (10.00-141.00) |
| Baseline bilirubin (mg/dL) | Phase 1 | 41 | 0 | 0.51 ( 0.28 ) | 0.48 (0.17-1.60) |
| | Phase 2 | 227 | 0 | 0.56 ( 0.27 ) | 0.50 (0.19-1.81) |
| | Total | 268 | 0 | 0.56 ( 0.27 ) | 0.50 (0.17-1.81) |
| Baseline amylase (IU/L) | Phase 1 | 41 | 9 | 59.12 ( 24.76 ) | 60.50 (11.00-118.00) |
| | Phase 2 | 227 | 5 | 71.65 ( 34.60 ) | 64.00 (13.00-218.00) |
| | Total | 268 | 14 | 70.07 ( 33.74 ) | 63.00 (11.00-218.00) |
| Baseline serum lipase (IU/L) | Phase 1 | 41 | 0 | 35.17 ( 39.30 ) | 24.00 (4.00-237.00) |
| | Phase 2 | 227 | 0 | 44.02 ( 51.74 ) | 29.00 (3.00-450.00) |
| | Total | 268 | 0 | 42.66 ( 50.07 ) | 29.00 (3.00-450.00) |
| Baseline gamma-glutamyl transferase (IU/L) | Phase 1 | 41 | 40 | 44.00 ( NaN ) | 44.00 (44.00-44.00) |

| Variable | Group | N | Nm | Mean (StdDev) | Median (Range) |
|---|---|---|---|---|---|
| | Phase 2 | 227 | 225 | 67.00 ( 21.21 ) | 67.00 (52.00-82.00) |
| | Total | 268 | 265 | 59.33 ( 20.03 ) | 52.00 (44.00-82.00) |
| Baseline hemoglobin (g/dL) | Phase 1 | 41 | 0 | 12.37 ( 1.52 ) | 12.60 (9.70-15.80) |
| | Phase 2 | 227 | 0 | 12.66 ( 1.69 ) | 12.60 (8.90-16.90) |
| | Total | 6 | 0 | 12.62 ( 1.67 ) | 12.60 (8.90-16.90) |
| Baseline tumor size by ICR (mm) | Phase 1 | 41 | 3 | 89.42 ( 68.26 ) | 75.00 (18.00-358.60) |
| | Phase 2 | 227 | 12 | 75.16 ( 51.34 ) | 64.80 (10.00-348.00) |
| | Total | 268 | 15 | 77.30 ( 54.30 ) | 67.10 (10.00-358.60) |
| Baseline IC tumor size by ICR (mm) | Phase 1 | 41 | 21 | 38.69 ( 23.74 ) | 39.05 (5.20-81.60) |
| | Phase 2 | 227 | 144 | 40.35 ( 26.77 ) | 32.40 (5.50-129.00) |
| | Total | 268 | 165 | 40.02 ( 26.11 ) | 33.90 (5.20-129.00) |

ePharmacology artifact ID RA13610731. Line 1 substituted.
ALK=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; dL=deciliter; g=gram; IC=intracranial; ICR=independent central review; IU=international units; kg=kilogram; L=liter; mg=milligram; min=minute; mL=milliliter; mm=millimeter; N=number of patients; Nm=number of patients with missing observations; StdDev=standard deviation.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 6 on page 42*

**<u>Logistic regression modeling for efficacy endpoint ORR in patients that received ≥1 prior ALK-inhibitors</u>**

**For the E-R analysis, each lorlatinib exposure metric (e.g., Cmax, P1, Ctrough, P1, Cavg, P1), as such or as its logarithmic value, was incorporated into the base model.**

Table 115 lists the AIC, ΔD and the z for each exposure metric tested. The best exposure predictor based on the lowest ΔD value was the logarithmic value of Cmax,P1, which was included in the full model.

In the final model, none of the tested predictors, including lorlatinib exposure metric Cmax,P1, were statistically significant predictors of achieving ORR.



Reference ID: 4344794

**Table 115 Univariate Analysis Results for Lorlatinib Exposure Metrics: ORR ≥1 Prior ALK-Inhibitors**

| Parameter | AIC | ΔD | Pr(>\|z\|) |
|---|---|---|---|
| AUC24 | 243.8498 | 239.8498 | 0.111 |
| $Ctrough_{P1}$ | 245.3568 | 241.3568 | 0.2968 |
| $Cavg_{P1}$ | 244.3525 | 240.3525 | 0.1506 |
| $Cmax_{P1}$ | 243.6939 | 239.6939 | 0.1008 |
| $cAUC_{P1}$ | 244.3473 | 240.3473 | 0.1502 |
| Mode dose (mg) | 246.306 | 242.306 | 0.6986 |
| Log of AUC24 | 244.2534 | 240.2534 | 0.143 |
| Log $Ctrough_{P1}$ | 246.3547 | 242.3547 | 0.7482 |
| Log $Cavg_{P1}$ | 244.6737 | 240.6737 | 0.1849 |
| Log $Cmax_{P1}$ | 243.6609 | 239.6609 | 0.0991 |
| Log $cAUC_{P1}$ | 244.6684 | 240.6684 | 0.1843 |

ePharmacology artifact ID RA13719080.
ALK=anaplastic lymphoma kinase; AIC=Akaike information criterion; AUC24=area under the time-concentration curve up to 24 hours after lorlatinib dose on C1D1; C1D1=Cycle 1 Day 1; $cAUC_{P1}$=predicted cumulative area under the concentration-time curve up to Cycle 2 Day 1; $C_{avg,P1}$=predicted average concentration calculated as the ratio of $C_{AUC,P1}$ over the time frame for the cumulative exposure; $C_{trough,P1}$=predicted concentration prior to Cycle 2 Day 1 lorlatinib dose; $C_{max,P1}$=predicted maximum concentration up to Cycle 2 Day 1ΔD=deviance difference between null and residual; mg=milligram;

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 14 on page 57*

**<u>Logistic regression modeling for efficacy endpoint IC-ORR in patients that received ≥1 prior ALK-inhibitors</u>**

**For the E-R analysis, each lorlatinib exposure metric, (e.g., Cmax, P1, Ctrough,P1, Cavg,P1), as such or as its logarithmic value, was tested alone in the base model using a univariate approach.**

Table 116 lists the AIC, ΔD and the z for each exposure metric tested. The best exposure predictor was the logarithmic value of Ctrough,P1, based on the lowest ΔD value, and was included in the full model.

**Table 116 Univariate Analysis Results for Lorlatinib Exposure Metrics: IC-ORR ≥1 Prior ALK-Inhibitors**

| Parameter | AIC | ΔD | Pr(>\|z\|) |
|---|---|---|---|
| AUC24 | 105.2939 | 101.2939 | 0.4613 |
| $Ctrough_{P1}$ | 105.7256 | 101.7256 | 0.7347 |
| $Cavg_{P1}$ | 105.84 | 101.84 | 0.9773 |
| $Cmax_{P1}$ | 105.4755 | 101.4755 | 0.5465 |
| $cAUC_{P1}$ | 105.8401 | 101.8401 | 0.9782 |
| Mode dose (mg) | 104.9442 | 100.9442 | 0.9918 |
| Log of AUC24 | 105.2198 | 101.2198 | 0.4341 |
| Log $Ctrough_{P1}$ | 104.6219 | 100.6219 | 0.3052 |
| Log $Cavg_{P1}$ | 105.8394 | 101.8394 | 0.9699 |
| Log $Cmax_{P1}$ | 105.3236 | 101.3236 | 0.4754 |
| Log $cAUC_{P1}$ | 105.8395 | 101.8395 | 0.9705 |

ePharmacology artifact ID RA13719189.

ALK=anaplastic lymphoma kinase; AIC=Akaike information criterion; AUC24=area under the time-concentration curve up to 24 hours after lorlatinib dose on Cycle 1 Day 1; $cAUC_{P1}$=predicted cumulative area under the concentration-time curve up to Cycle 2 Day 1; $C_{avg,P1}$=predicted average concentration calculated as the ratio of $C_{AUC,P1}$ over the time frame for the cumulative exposure; $C_{trough,P1}$=predicted concentration prior to Cycle 2 Day 1 lorlatinib dose; $C_{max,P1}$=predicted maximum concentration up to Cycle 2 Day 1 ΔD=deviance difference between null and residual; IC-ORR=intracranial objective response rate; mg=milligram; Pr(>|z|)=it represents the tail area in a 2-tail test.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 21 on page 73*

In the final model, LBAP (log of baseline alkaline phosphatase) and BAMY (baseline amylase) were statistically significant predictors of achieving IC-ORR. Table 117 tabulates parameter estimates or coefficients and the odds ratio. The odds ratio is calculated by exponentiating the parameter estimates. The odds of success were defined as the ratio of the probability of success over the probability of failure. Based on the odds ratio estimated in the final model, the odds of achieving IC-ORR were 1.015 times higher for every 1 unit increase in value of BAMY and 0.363 times lower for every 1 unit increase in value of LBAP. To better understand the obtained logistic regression parameters, Figure 18 illustrates the differences in predicted probabilities for increasing values of BAMY and LBAP.



Reference ID: 4344794

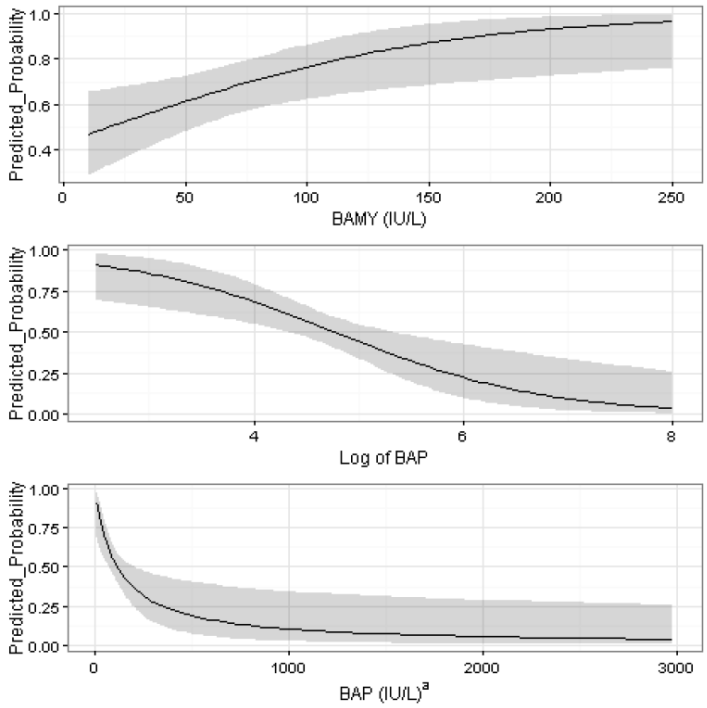
**Table 117 Final Model for Exposure Response Analysis: IC-ORR ≥1 Prior ALK-Inhibitors**

| Variables | Estimate | 95% CI | z-Value | Probability >\|z\| |
|---|---|---|---|---|
| Intercept | 3.929 | (1.0210 - 7.0845) | 2.553 | 0.0107 |
| LBAP (IU/L) | -1.015 | (-1.7145 –0.3889) | -3.015 | 0.0026 |
| BAMY (IU/L) | 0.015 | (0.0037 - 0.0268) | 2.506 | 0.0122 |
| | Odds ratio | | | |
| Intercept | 50.863 | (2.7759 - 1193.3282) | NA | NA |
| LBAP (IU/L) | 0.363 | (0.1801 - 0.6778) | NA | NA |
| BAMY (IU/L) | 1.015 | (1.0037 - 1.0272) | NA | NA |
| ΔD | 15.15341 | NA | NA | NA |
| AIC | 167.510 | NA | NA | NA |
| df | 2 | NA | NA | NA |
| 1-p-Value | 0.0005122 | NA | NA | NA |
| Log-likelihood | -80.75511 | NA | NA | NA |

ePharmacology artifact ID RA13719183. Line 1 substituted.
If the 95% CI did not cross 0, the parameter estimate was statistically significant.
ALK=anaplastic lymphoma kinase; AIC=Akaike information criterion; LBAP=log of baseline alkaline phosphatase; BAMY=baseline amylase; CI=confidence interval; CNS=central nervous system; df=degrees of freedom; ΔD=deviance difference between null and residual; NA=not applicable; IC-ORR=intracranial objective response rate; IU=international unit; L=liter; p-Value=level of marginal significance within a statistical hypothesis test; |z|=represents the tail area in a 2-tail test.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Table 22 on page 74*

**Figure 18 Predicted Probability of Achieving IC-ORR Stratified by Significant Predictor Variable: IC-ORR ≥1 Prior ALK-Inhibitors**




ePharmacology artifact ID RA13719188.
ALK=anaplastic lymphoma kinase; BAMY=baseline amylase; LBAP=log of baseline alkaline phosphatse; IC-ORR=intracranial objective response rate; IU=international unit; L=liter.
*a*.The exponentiated value of BAP is plotted for better visualization.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-682, Figure 24 on page 75*

*Reviewer's comments:*
*No significant E-R relationship between lorlatinib exposure and efficacy endpoints of ORR and IC-ORR was identified using multivariate logistic regression analysis in patients that received ≥1 prior ALK-inhibitors.*

*In addition, E-R analyses were also conducted in two different patient population, i.e. patients that received any number of prior ALK-inhibitors and patients that received ≥2 prior ALK-inhibitors. Since the proposed indication for this submission is for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK TKIs, the E-R analyses for ORR in patients that received any number of prior ALK-inhibitors or ≥2 prior ALK-inhibitors are not appropriate for this indication. Therefore, analysis details for these two populations are not included in this review. However, one problem with the E-R analysis for ORR in patients that received any number of prior ALK-inhibitors needs to be noted. The post-treatment safety event, maximum hypercholesterolemia adverse event Grade, was tested and included in the ER for efficacy model. Since the post-treatment safety event is correlated with lorlatinib exposure, the exposure-response relationship based the ER analysis is highly likely to be confounded by the post-treatment safety event. Including the post-treatment safety events which are correlated with drug exposure in the E-R analysis for efficacy should be avoided.*

### 19.4.4. Applicant's Exposure-Response Analysis for Safety

**Objective:**

The objectives of this population modeling analysis were:

- To use data from patients with advanced ALK-positive or ROS1-positive NSCLC, to perform a population modeling analysis to assess the relationship between lorlatinib PK exposure values (maximum concentration (Cmax), minimum concentration (Cmin), average or time-normalized drug concentration (Cave), and/or area under the curve (AUC)) and, if the data allows, the following safety endpoints:
    - Central nervous system (CNS) effects, as measured by the incidence of:
        - Mood effects;
        - Speech effects;
        - Cognitive effects;
        - Peripheral neuropathy;
        - Seizure.
    - Hepatotoxicity, as measured by the incidence of elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
    - Pancreatic toxicity as measured by the incidence of elevated serum lipase and amylase.
    - Lipid abnormalities, as measured by the incidence of:
        - Hypercholesterolemia (elevated serum low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol);
        - Hypertriglyceridemia;



Reference ID: 4344794

        - Weight gain.
    - Other adverse events (AEs), as measured by the incidence of:
        - Atrioventricular (AV) block;
        - Peripheral edema;
        - Treatment emergent AEs Grade ≥ 3.

If the data did not allow for a full analysis due to low incidence of the safety endpoint (incidence <10%), the exposure-response (E-R) analysis for these endpoints would be exploratory.

- To evaluate the effect of moderators (covariates) in the exposure-response relationships for lorlatinib safety.

**Data:**

The E-R analysis for safety was based on data from the Phase 1/2 Study B7461001 in patients with advanced ALK-positive NSCLC and patients with advanced ROS1-positive NSCLC, with or without asymptomatic CNS metastases.

**Method:**

Prior to the modeling analysis, the data was graphically explored for trends. Box plots were generated for each of the lorlatinib exposure metrics versus the AE endpoints.
The E-R modeling analyses was performed using generalized binomial logistic regression as implemented in the glm(), glm(family="binomial") functions, respectively, in the R programming language, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).
The models developed for this analysis consisted of four components:

1. The base model component which defined the regression parameters in the absence of covariate influences, including the relevant baseline laboratory parameters (e.g. baseline cholesterol for hypercholesterolemia).
2. The addition of the significant lorlatinib exposure parameter, identified by a univariate screen.
3. The full covariate model component, which describes the influence of all identified fixed effects (i.e. demographic factors) on regression parameters.
4. The final covariate model component, which describes the influence of all significant fixed effects (i.e. demographic factors) on regression parameters.

For all model evaluations, model building was conducted using standard accepted methods. An initial base model was developed to describe the response (e.g., typical change from baseline value or overall probability of an event). Metrics of drug exposure, such as but not limited to Cmax, Cmin, Cavg, and AUC, were tested as predictors of the response. Log-transformed exposure metrics were also explored.

The exposure metric and functional form (log or linear) that yielded a better fitting model and a statistically significant E-R relationship ($p<0.05$) was selected for the final model. If no lorlatinib exposure metric was significant, the modeling analysis was carried forward without an exposure metric.



Reference ID: 4344794

Potential predictors of response that were tested are shown in Table 118.

**Table 118 Potential Predictors of Covariate Analysis**

| Predictors | Description |
|---|---|
| Demographic characteristics | Race, sex, age, and baseline body weight |
| Safety laboratory information at baseline | Albumin, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, hemoglobin, serum creatinine, lipase, amylase, LDL, HDL, triglycerides, total cholesterol |
| Treatments | Concomitant hepatotoxic drugs (Y/N)[a], prior treatment with any ALK inhibitor (Y/N), prior treatment with chemotherapy (Y/N), concomitant CYP inducers (Y/N)[b], concomitant steroids (Y/N), concomitant narcotics (Y/ N), prior CNS radiation treatment (Y/N) |
| Disease characteristics | CNS metastasis prior to or anytime on study (Y/N), Baseline ECOG |
| Additional events that occurred while on study | Weight gain (Y/N), peripheral neuropathy (Y/N), peripheral edema (Y/N), and arthralgia (Y/N) |

ALK=anaplastic lymphoma kinase; CNS=central nervous system; CYP=cytochrome P450; ECOG=Eastern Cooperative Oncology Group; HDL=high density lipoprotein; LDL=low density lipoprotein; GGT=gamma-glutamyl transferase; Y/ N=Yes/No.
[a]Separately examined hepatotoxic drugs that have been associated with >100 cases of drug-induced liver injury and drugs that have been associated with >30 published case reports of drug induced liver injury [8].
[b]Included only potent CYP inducers defined by University of Washington Drug-Drug Interaction Database [9].

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 3 on page 49*

**Results:**

Table 119 and Table 120 show the summaries of the continuous and categorical covariates in the analysis dataset.

**Table 119 Continuous Covariates**

| Variable | N | Nm | Mean (Stdev) | Median (Max-Min) |
|---|---|---|---|---|
| Age (years) | 328 | 0 | 53.39 (12.21) | 53.00 (19.00-85.00) |
| Baseline Weight (kg) | 328 | 0 | 68.07 (17.21) | 66.79 (31.80-155.50) |
| Baseline Creatinine Clearance (mL/min) | 328 | 0 | 93.37 (33.33) | 88.68 (24.54-235.39) |
| Baseline Gamma Glutamyl Transferase (U/L) | 328 | 323 | 51.00 (25.61) | 52.00 (13.00-82.00) |
| Baseline Albumin (g/dL) | 328 | 0 | 3.76 (0.55) | 3.80 (1.80-5.20) |
| Baseline Alkaline Phosphatase (U/L) | 328 | 0 | 135.27 (119.08) | 98.00 (13.00-1552.00) |
| Baseline Alanine Aminotransferase (U/L) | 328 | 0 | 29.56 (27.17) | 21.00 (3.00-252.00) |
| Baseline Aspartate Aminotransferase (U/L) | 328 | 0 | 26.19 (14.81) | 22.00 (10.00-141.00) |
| Baseline Bilirubin (mg/dL) | 328 | 0 | 0.55 (0.27) | 0.50 (0.10-1.81) |
| Baseline Serum Amylase (U/L) | 328 | 17 | 71.95 (35.80) | 64.00 (11.00-259.00) |
| Baseline Hemoglobin (g/dL) | 328 | 0 | 12.59 (1.66) | 12.60 (8.60-16.90) |
| Baseline HDL (mg/dL) | 328 | 36 | 55.97 (28.30) | 52.00 (0.58-361.00) |
| Baseline LDL (mg/dL) | 328 | 36 | 114.04 (35.02) | 111.50 (38.61-226.00) |
| Baseline Total Cholesterol (mg/dL) | 328 | 28 | 192.95 (44.06) | 193.00 (3.00-321.00) |
| Baseline Triglycerides (mg/dL) | 328 | 30 | 123.98 (66.59) | 107.50 (28.00-451.40) |
| Baseline Serum Lipase (U/L) | 328 | 0 | 43.20 (48.24) | 30.00 (3.00-450.00) |

dL=deciliter; g=gram; HDL=high density lipoprotein; LDL=low density lipoprotein; kg=kilogram; L=liters; N=total patient number; Nm=total missing; Max=maximum; mg=milligram; Min=minimum; Stdev=standard deviation; U=unit.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 4 on page 52*



Reference ID: 4344794

**Table 120 Categorical Covariates**

| Variable | Category | Total |
|---|---|---|
| N | | 328 |
| Sex | Male | 139 (42%) |
| | Female | 189 (58%) |
| Race | White | 168 (51%) |
| | Black | 6 (2%) |
| | Asian | 110 (34%) |
| | Other | 13 (4%) |
| | Missing | 31 (9%) |
| Asian | Non-Asian | 218 (66%) |
| | Asian | 110 (34%) |
| Baseline ECOG | 0 | 138 (42%) |
| | 1 | 178 (54%) |
| | 2 | 11 (3%) |
| | 3 | 1 (0%) |
| Prior CNS radiation therapy | No | 201 (61%) |
| | Yes | 127 (39%) |
| Concomitant Steroid Therapy | No | 189 (58%) |
| | Yes | 139 (42%) |
| Concomitant CYP Inducer | No | 327 (100%) |
| | Yes | 1 (0%) |
| Concomitant Hepatoxic Drugs[a] | No | 204 (62%) |
| | Yes | 124 (38%) |
| Prior treatment with crizotinib | No | 87 (27%) |
| | Yes | 241 (73%) |
| Prior treatment with ALK inhibitors | No | 49 (15%) |
| | Yes | 279 (85%) |
| Prior treatment with chemotherapy | No | 123 (38%) |
| | Yes | 205 (62%) |
| CNS metastasis anytime | No | 101 (31%) |
| | Yes | 227 (69%) |
| Weight gain of any Grade | No | 247 (75%) |
| | Yes | 69 (21%) |

| Variable | Category | Total |
|---|---|---|
| | Missing | 12 (4%) |
| Peripheral neuropathy of any Grade | No | 178 (54%) |
| | Yes | 150 (46%) |
| Peripheral edema of any Grade | No | 153 (47%) |
| | Yes | 175 (53%) |
| Concomitant statin therapy | No | 62 (19%) |
| | Yes | 266 (81%) |
| Arthralgia | No | 263 (80%) |
| | Yes | 65 (20%) |

ePharmacology artifact ID RA13503194.
ALK=anaplase lymphoma kinase; CNS=central nervous system; CYP=cytochrome P450; ECOG=Eastern Cooperative Oncology Group; N=total patient number.
[a]Drugs that, according to analysis of data in LiverTox, have been associated with more than 100 cases of drug-induced liver injury[8]

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 5 on page 53*

Table 121 lists the incidence of each of the safety endpoints in the analysis dataset.

**Table 121 Incidence of Safety Endpoints**

| Variable | Category | Total |
|---|---|---|
| N | | 328 |
| CNS Mood Grade ≥ 2 | Yes | 14 (4.3%) |
| | No | 314 (95.7%) |
| CNS Speech Grade ≥ 2 | Yes | 3 (0.9%) |
| | No | 325 (99.1%) |
| CNS Cognition Grade ≥ 2 | Yes | 23 (7%) |
| | No | 305 (93%) |
| Elevated AST Grade ≥ 2 | Yes | 7 (2.1%) |
| | No | 321 (97.9%) |
| Elevated ALT Grade ≥ 2 | Yes | 9 (2.7%) |
| | No | 319 (97.3%) |
| Hypercholesterolemia Grade ≥ 3 | Yes | 51 (15.5%) |
| | No | 277 (84.5%) |
| Hypertriglyceridemia Grade ≥ 3 | Yes | 49 (14.9%) |
| | No | 279 (85.1%) |
| Weight Gain Grade ≥ 2 | Yes | 39 (11.9%) |
| | No | 289 (88.1%) |
| Elevated Serum Lipase Grade ≥ 3 | Yes | 20 (6.1%) |
| Variable | Category | Total |
| | No | 308 (93.9%) |
| Elevated Serum Amylase Grade ≥ 3 | Yes | 8 (2.4%) |
| | No | 320 (97.6%) |
| AV Block Grade ≥ 1[a] | Yes | 1 (0.3%) |
| | No | 327 (99.7%) |
| Seizures Grade ≥ 1 | Yes | 9 (2.7%) |
| | No | 319 (97.3%) |
| Peripheral Neuropathy Grade ≥ 3 | Yes | 32 (9.8%) |
| | No | 296 (90.2%) |
| Peripheral Edema Grade ≥ 3 | Yes | 7 (2.1%) |
| | No | 321 (97.9%) |
| Treatment Emergent AE Grade ≥ 3 | Yes | 139 (42.4%) |
| | No | 189 (57.6%) |

ePharmacology artifact ID RA13649412.
AST=aspartate aminotransferase; ALT=alanine aminotransferase; AV=atrioventricular; CNS=central nervous system; N=total number of patients.
[a]No analysis was conducted due to only one patient experiencing AV block. An additional analysis investigating the relationship between lorlatinib exposure and PR prolongation, as well as AV block, is reported in PMAR-EQDD-B746a-DP4-684.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 6 on page 55*

Out of the safety points evaluated, significant E-R relationship was identified for Grade ≥ 3 Hypercholesterolemia and Grade ≥ 3 Treatment Emergent Adverse Events (TEAEs).

The final logistic regression model parameter estimates and odds ratio for Grade ≥ 3 Hypercholesterolemia are shown in Table 122. Figure 19 visualizes the predicted probabilities of

Grade ≥ 3 Hypercholesterolemia versus $C_{max,event}$ with time to AE event fixed at the median value of 41 days, stratified by baseline cholesterol level.

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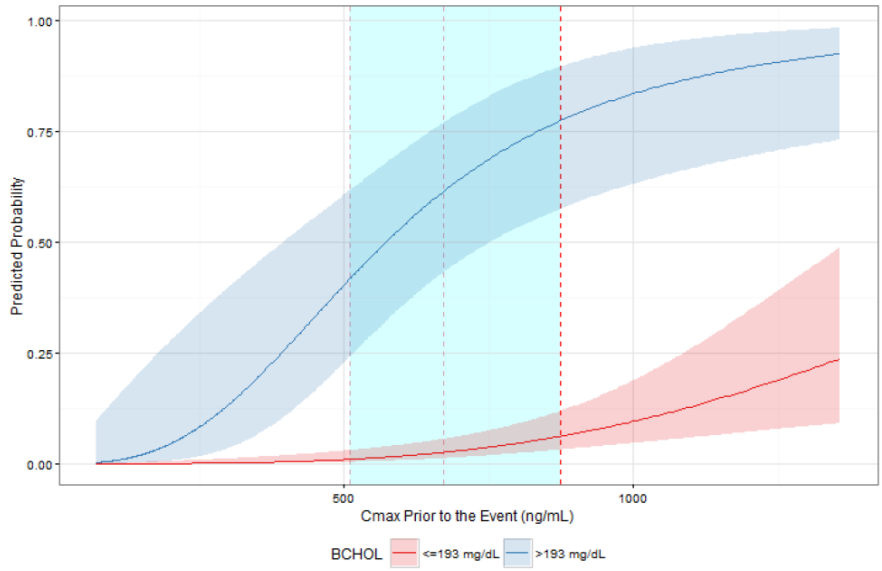
**Table 122 Logistic Regression Analysis Results for Grade ≥ 3 Hypercholesterolemia**

| Variables | Estimate | 95% CI | z-Value | Probability>\|z\| |
|---|---|---|---|---|
| Intercept | -18.829 | (-30.4373–8.1449) | -3.320 | 0.0009 |
| BCHOL | 0.029 | (0.0199-0.0386) | 6.071 | <0.0001 |
| DAY1 | 0.004 | (0.0001-0.0069) | 2.040 | 0.0413 |
| log($C_{max\ event}$) | 1.659 | (0.0762-3.3330) | 2.002 | 0.0452 |
| | Odds ratio | | | |
| Intercept | 7E-09 | (6E-14-0.0003) | NA | NA |
| BCHOL | 1.029 | (1.0201-1.0393) | NA | NA |
| DAY1 | 1.004 | (1.0001-1.0069) | NA | NA |
| log($C_{max\ event}$) | 5.256 | (1.0792-28.0220) | NA | NA |
| ΔD | 53.36145 | NA | NA | NA |
| AIC | 211.039 | NA | NA | NA |
| df | 3 | NA | NA | NA |
| 1-p-Value | <0.0001 | NA | NA | NA |
| Log-likelihood | -101.5195 | NA | NA | NA |

ePharmacology artifact ID RA13713443. Line 1 substituted.
1-p-Value=one tailed p-value; AIC=akaike information criteria; BCHOL=baseline cholesterol; CI=confidence interval; $C_{max\ event}$=maximum observed concentration prior to the adverse event; ΔD= change in deviance; DAY1=time to event; df=degrees of freedom; probability>|z|=the tail area in a 2-tail test; p-Value=level of marginal significance within a statistical hypothesis test; NA=not applicable; z-value=Wald statistic for testing the hypothesis that the corresponding parameter (regression coefficient).

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 14 on page 69*

**Figure 19 Predicted Probability of Grade ≥ 3 Hypercholesterolemia Versus Cmax Prior to the AE with Fixed Time to Event Stratified by Baseline Cholesterol Level**




ePharmacology artifact ID RA13747200.
DAY1 is fixed to the median, 41 days.
The light blue panels represent the 10th to 90th percentiles of observed log($C_{max\ event}$) for patients dosed at 100 mg QD
The blue shaded ribbon is the 95% PI for patients with baseline cholesterol >193 mg/dL. The red shaded ribbon is the 95% PI for patients with baseline cholesterol ≤ 193 mg/dL.
BCHOL=baseline cholesterol; $C_{max}$=maximum observed concentration; DAY1=time to event, starting from Cycle 1 Day 1 (day); ng=nanogram; mL=milliliter; PI=prediction interval; QD=once daily.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Figure 12 on page 71*

The Hosmer–Lemeshow goodness of fit test results for the logistic regression model for Grade ≥ 3 Hypercholesterolemia is shown in Table 123 and Figure 20.

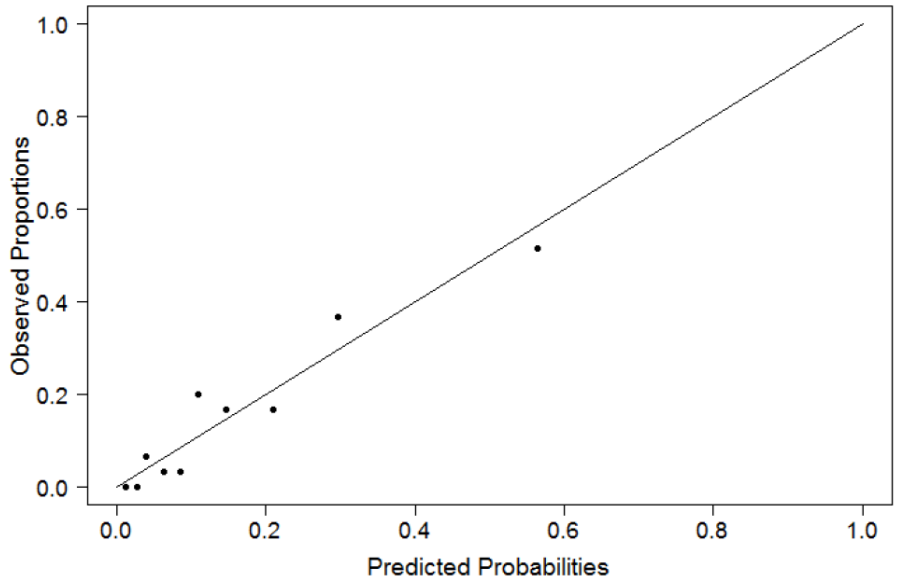
**Table 123 Hosmer-Lemeshow Goodness of Fit Test Results for Grade ≥ 3 Hypercholesterolemia**

| Predicted Groups | Total | Mean Predicted Probabilities | Mean Observed Proportions | Predicted Events | Observed Events |
|---|---|---|---|---|---|
| (0.000431-0.0209) | 30 | 0.012 | 0 | 0.36 | 0 |
| (0.020950-0.0347) | 30 | 0.027 | 0 | 0.82 | 0 |
| (0.034694-0.0526) | 30 | 0.04 | 0.067 | 1.21 | 2 |
| (0.052579-0.0754) | 30 | 0.063 | 0.033 | 1.89 | 1 |
| (0.075386-0.0957) | 29 | 0.085 | 0.034 | 2.47 | 1 |
| (0.095681-0.1295) | 30 | 0.11 | 0.2 | 3.31 | 6 |
| (0.129547-0.1703) | 30 | 0.146 | 0.167 | 4.39 | 5 |
| (0.170285-0.2390) | 30 | 0.209 | 0.167 | 6.27 | 5 |
| (0.238959-0.3980) | 30 | 0.297 | 0.367 | 8.91 | 11 |
| (0.398024-0.7744) | 29 | 0.564 | 0.517 | 16.35 | 15 |
| $\chi^2$ | 7.006 | NA | NA | NA | NA |
| df | 8 | NA | NA | NA | NA |
| p-value | 0.536 | NA | NA | NA | NA |

ePharmacology artifact ID RA13661081.
$\chi^2$=statistic parameter to assess goodness-of-fit; df=degrees of freedom; NA=not applicable; p-value=level of marginal significance within a statistical hypothesis test.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 16 on page 73*

**Figure 20 Hosmer-Lemeshow Goodness of Fit Calibration Plot for Grade ≥ 3 Hypercholesterolemia**




ePharmacology artifact ID RA13661076.
The black line represents the line of unity.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Figure 14 on page 73*

The final logistic regression model parameter estimates and odds ratio for Grade ≥ 3 TEAEs are shown in Table 124. Visualizes the predicted probabilities of Grade ≥ 3 TEAEs versus

$CAUC_{complete}$ (calculated cumulative AUC over a complete cycle) with time to AE event fixed at the median value of 55.5 days, stratified by age, concomitant narcotics, and concomitant steroids.

**Table 124 Logistic Regression Analysis Results for Grade ≥ 3 TEAEs**

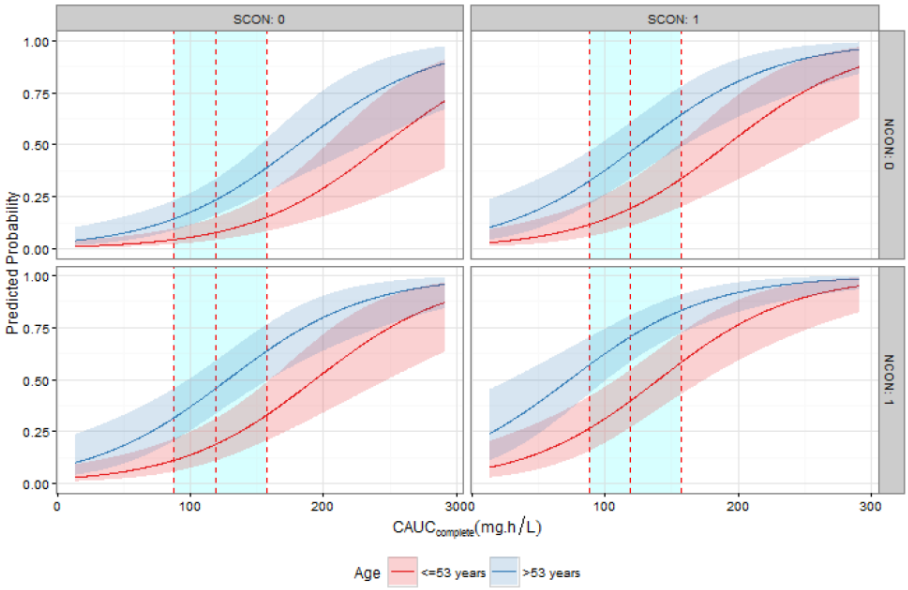
| Variables | Estimate | 95% CI | z-Value | Probability>\|z\| |
|---|---|---|---|---|
| Intercept | -5.829 | (-7.5624–4.2370) | -6.889 | <0.0001 |
| AGE | 0.038 | (0.0168-0.0604) | 3.442 | 0.0006 |
| SCON1 | 1.048 | (0.5287-1.5818) | 3.911 | 0.0001 |
| NCON1 | 1.009 | (0.4925-1.5403) | 3.785 | 0.0002 |
| DAY1 | 0.006 | (0.0041-0.0091) | 5.039 | <0.0001 |
| $CAUC_{complete}$ | 0.015 | (0.0073-0.0233) | 3.689 | 0.0002 |
| | Odds ratio | | | |
| Intercept | 0.003 | (0.0005-0.0145) | NA | NA |
| AGE | 1.039 | (1.0169-1.0622) | NA | NA |
| SCON1 | 2.853 | (1.6967-4.8638) | NA | NA |
| NCON1 | 2.744 | (1.6364-4.6660) | NA | NA |
| DAY1 | 1.006 | (1.0041-1.0091) | NA | NA |
| $CAUC_{complete}$ | 1.015 | (1.0074-1.0235) | NA | NA |
| ΔD | 92.12496 | NA | NA | NA |
| AIC | 366.928 | NA | NA | NA |
| df | 5 | NA | NA | NA |
| 1-p-Value | <0.0001 | NA | NA | NA |
| Log-likelihood | -177.4639 | NA | NA | NA |

ePharmacology artifact ID RA13713383. Line 1 substituted.

1-p-Value=one tailed p-value; AIC=akaike information criteria; AE=adverse event; AGE=age; AUC=area under the lorlatinib-time concentration curve; $CAUC_{complete}$=calculated cumulative AUC over a complete cycle; based on maximum total daily dose, individual estimate of bioavailability, and the maximum individual estimate of clearance; CI=confidence interval; ΔD= change in deviance; DAY1=time to event; df=degrees of freedom; probability>|z|=the tail area in a 2-tail test; p-Value=level of marginal significance within a statistical hypothesis test; NA=not applicable; NCON1=concomitant narcotics; SCON1=concomitant steroids; z-value=Wald statistic for testing the hypothesis that the corresponding parameter (regression coefficient).

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 17 on page 75*

**Figure 21 Predicted Probability of Grade ≥ 3 TEAEs Versus CAUCcomplete with Fixed Time to Event Stratified by Age, Concomitant Narcotics, and Concomitant Steroids**




ePharmacology artifact ID RA13747195.
DAY1 is fixed to the median, 55.5 days.
The light blue panels represent the 10th to 90th percentiles of observed $CAUC_{complete}$ for patients dosed at 100 mg QD
The shaded ribbon is the 95% PI of the predicted probability of experiencing Treatment Emergent AE Grade ≥ 3.
AE=adverse events; AGE=Age (years); AUC=area under the lorlatinib concentration-time curve; $CAUC_{complete}$=calculated cumulative AUC over a complete cycle; based on maximum total daily dose, individual estimate of bioavailability, and the maximum individual estimate of clearance; DAY1=time to event starting from Cycle 1 and Day 1 (day); h=hour; L=liter; mg=milligram; NCON=concomitant narcotics; PI=prediction interval; SCON=concomitant steroids.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Figure 17 on page 77*

The Hosmer–Lemeshow goodness of fit test results for the logistic regression model for Grade ≥ 3 TEAEs is shown in Table 125 and Figure 22.

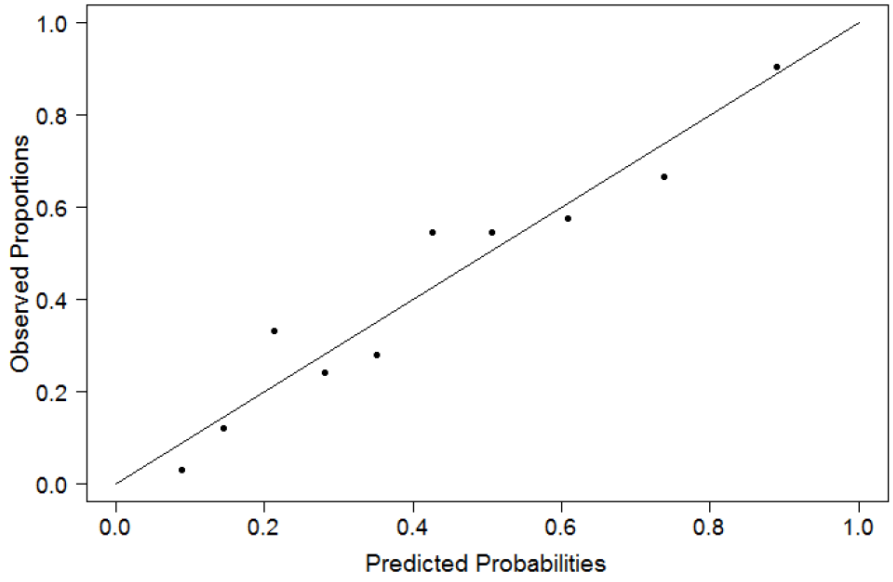
**Table 125 Hosmer-Lemeshow Goodness of Fit Test Results for Grade ≥ 3 TEAEs**

| Predicted Groups | Total | Mean Predicted Probabilities | Mean Observed Proportions | Predicted Events | Observed Events |
|---|---|---|---|---|---|
| (0.0475-0.113) | 33 | 0.089 | 0.03 | 2.94 | 1 |
| (0.1132-0.178) | 33 | 0.145 | 0.121 | 4.8 | 4 |
| (0.1777-0.254) | 33 | 0.213 | 0.333 | 7.03 | 11 |
| (0.2535-0.314) | 33 | 0.282 | 0.242 | 9.32 | 8 |
| (0.3139-0.385) | 32 | 0.351 | 0.281 | 11.22 | 9 |
| (0.3851-0.464) | 33 | 0.427 | 0.545 | 14.09 | 18 |
| (0.4638-0.541) | 33 | 0.506 | 0.545 | 16.69 | 18 |
| (0.5406-0.681) | 33 | 0.608 | 0.576 | 20.06 | 19 |
| (0.6807-0.800) | 33 | 0.738 | 0.667 | 24.37 | 22 |
| (0.8003-0.995) | 32 | 0.89 | 0.906 | 28.49 | 29 |
| $\chi^2$ | 8.557 | NA | NA | NA | NA |
| df | 8 | NA | NA | NA | NA |
| p-value | 0.3811 | NA | NA | NA | NA |

ePharmacology artifact ID RA13651084.
AE=adverse effect; $\chi^2$=; statistic parameter to assess goodness-of-fit; df=degrees of freedom; NA=not applicable; p-value=level of marginal significance within a statistical hypothesis test.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Table 19 on page 79*

**Figure 22 Hosmer-Lemeshow Goodness of Fit Calibration Plot for Grade ≥ 3 TEAEs**




ePharmacology artifact ID RA13651079.
The black line represents the line of unity.
AE=adverse event.

*Source: Applicant's ER study report PMAR-EQDD-B746A-DP4-683, Figure 19 on page 79*

*Reviewer's comments:*
*Overall, Pfizer's E-R analysis for safety is reasonable. Due to low frequency of the safety endpoints (<10%), only exploratory analysis was conducted for some endpoints. Out of safety endpoints with frequency ≥ 10%, significant E-R relationship was identified for Grade ≥ 3*

*Hypercholesterolemia and Grade ≥ 3 TEAEs using multivariate logistic regression analysis. Hosmer-Lemeshow test was used for model evaluation and showed acceptable goodness of fit.*

## 19.5. Statistical Appendices

### Patient Disposition by Pre-Specified Cohort

Table 126 shows the disposition of patients in the primary efficacy population.

**Table 126: Disposition by Pre-Specified Cohort of Patients in the Primary Efficacy Population**

| | EXP-2 | EXP-3A | EXP-3B | EXP-4 | EXP-5 |
|---|---|---|---|---|---|
| N | 28 | 36 | 28 | 75 | 48 |
| **Withdrawn (%)** | | | | | |
| Adverse Event | 2 (29) | 2 (33) | 2 (13) | 3 (7) | 5 (19) |
| Death | 1 (14) | 1 (17) | 1 (7) | 3 (7) | 2 (8) |
| Protocol Violation | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| Other | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |
| No Longer Willing To Partcipate In Study | 1 (14) | 0 (0) | 0 (0) | 2 (5) | 2 (8) |
| Objective Progression Or Relapse | 3 (43) | 2 (33) | 12 (80) | 27 (66) | 15 (58) |
| Global Deterioration Or Relapse | 0 (0) | 1 (17) | 0 (0) | 4 (10) | 2 (8) |

### Table of Demographic Characteristics

Table 127 presents demographic characteristics for patients in the primary efficacy population.

**Table 127: Demographic Characteristics by Pre-Specified Cohort of Patients in the Primary Efficacy Population**

| | EXP-2 | EXP-3A | EXP-3B | EXP-4 | EXP-5 |
|---|---|---|---|---|---|
| N | 28 | 36 | 28 | 75 | 48 |
| AGE (Mean (Sd)) | 56.8 (12.6) | 52.5 (11.9) | 55.0 (11.6) | 52.1 (11.7) | 51.5 (11.0) |
| **Age (%)** | | | | | |
| <65 | 19 (68) | 30 (83) | 22 (79) | 65 (87) | 41 (85) |
| >=65 | 9 (32) | 6 (17) | 6 (21) | 10 (13) | 7 (15) |
| **Sex (%)** | | | | | |
| Female | 17 (61) | 25 (69) | 16 (57) | 43 (57) | 26 (54) |
| Male | 11 (39) | 11 (31) | 12 (43) | 32 (43) | 22 (46) |
| **Race (%)** | | | | | |
| White | 14 (50) | 20 (56) | 7 (25) | 39 (52) | 29 (60) |
| Asian | 10 (36) | 8 (22) | 16 (57) | 26 (35) | 14 (29) |
| Missing | 2 (7) | 8 (22) | 3 (11) | 7 (9) | 3 (6) |
| Other | 2 (7) | 0 (0) | 2 (7) | 3 (4) | 2 (4) |



Reference ID: 4344794

### Other Baseline Characteristics by Pre-Specified Cohort

Table 128 shows other baseline characteristics by pre-specified cohort in the primary efficacy population.

**Table 128: Other Baseline Characteristics by Pre-Specified Cohort in the Primary Efficacy Population**

| | EXP-2 | EXP-3A | EXP-3B | EXP-4 | EXP-5 |
|---|---|---|---|---|---|
| n | 28 | 36 | 28 | 75 | 48 |
| Stage IV (%) | 28 (100) | 36 (100) | 27 (100) | 75 (100) | 48 (100) |
| **Histology (%)** | | | | | |
| ADENOCARCINOMA NOS | 25 (89) | 28 (78) | 22 (79) | 60 (80) | 41 (85) |
| OTHER | 3 (11) | 8 (22) | 6 (21) | 15 (20) | 7 (15) |
| **ECOG (%)** | | | | | |
| 0 | 16 (57) | 14 (39) | 15 (54) | 29 (39) | 21 (44) |
| 1 | 11 (39) | 22 (61) | 13 (46) | 42 (56) | 24 (50) |
| 2 | 1 (4) | 0 (0) | 0 (0) | 4 (5) | 3 (6) |
| **CNS disease (per IRC) (%)** | | | | | |
| 0 | 10 (36) | 13 (36) | 15 (54) | 20 (27) | 8 (17) |
| 1 | 18 (64) | 23 (64) | 13 (46) | 55 (73) | 40 (83) |
| **Measurable disease at baseline (per IRC) (%)** | | | | | |
| No | 3 (11) | 2 (6) | 2 (7) | 6 (8) | 1 (2) |
| Yes | 25 (89) | 34 (94) | 26 (93) | 69 (92) | 47 (98) |
| With CNS disease | 17 (61) | 22 (61) | 13 (46) | 52 (69) | 39 (81) |
| **Number of disease sites involved at baseline (%)** | | | | | |
| 1 | 2 (7) | 2 (6) | 4 (14) | 5 (7) | 2 (4) |
| 2 | 12 (43) | 7 (19) | 8 (29) | 17 (23) | 13 (27) |
| 3 | 7 (25) | 14 (39) | 10 (36) | 23 (31) | 16 (33) |
| 4+ | 7 (25) | 13 (36) | 6 (21) | 30 (40) | 17 (35) |

### Efficacy Results – Secondary and other relevant endpoints

*PFS per IRC and OS*

Table 129 presents the PFS per IRC and OS results for all patients in the primary efficacy population.

*Reviewer comment: These data are not interpretable in the context of a non-randomized, multi-cohort trial.*

**Table 129: PFS per IRC and OS for the Primary Efficacy Population**

| | N = 215 |
|---|---|
| Number of events (%) | 111 (52) |
| Progressive disease | 14 (7) |
| Death | 97 (45) |
| Median PFS in months (95% CI) | 7.3 (5.6, 11.0) |
| Median OS in months (95% CI) | 14.7 (NE, NE) |

**Additional Analyses Performed on Trial**

*Discordance in CNS Assessment*

Table 130 presents the discordance between CNS disease at baseline as assessed by IRC and CNS disease at baseline as assessed by INV for all patients who were ALK positive and received 100 mg of lorlatinib.

**Table 130: Summary of CNS Disease Discordance for Patients in the Primary Efficacy Population**

| | No CNS by IRC | CNS by IRC |
|---|---|---|
| **No CNS by INV** | 63 | 13 |
| **CNS by INV** | 3 | 136 |

The discordance rate between IRC and INV in assessing CNS disease at baseline was 9%.

*Discordance in Response Assessment*

Table 131 presents the discordance between overall response as assessed by IRC and overall response as assessed by INV for all patients in the primary efficacy population.

**Table 131: Summary of Overall Response Discordance for Patients in the Primary Efficacy Population**

| | No Response by IRC | Response by IRC |
|---|---|---|
| No Response by INV | 98 | 23 |
| Response by INV | 18 | 76 |

The discordance rate between IRC and INV in assessing response was 19%.

*Discordance in Intracranial Response Assessment*

Table 132 presents the discordance between intracranial response as assessed by IRC and intracranial response as assessed by INV for all patients in the primary efficacy population who were found to have CNS disease by either the IRC or INV.

**Table 132: Summary of Intracranial Response Discordance for Patients in the Primary Efficacy Population**

| | No Response by IRC | Response by IRC |
|---|---|---|
| No Response by INV | 71 | 38 |
| Response by INV | 2 | 41 |

The discordance rate between IRC and INV in assessing intracranial response among those patients with CNS disease was 26%.

*Reviewer's Comment: Although the discordance rates between INV and IRC are similar for ORR and IC-ORR, the source of discordance is different. For ORR, discrepancies in response assessment are similar between IRC reporting a non-responder as a responder and vice versa. For IC-ORR, all but two of the cases of discordance are caused by the IRC reporting a non-responder per INV as a responder.*

*Discordance in Intracranial Response Assessment when CNS Assessments Agree*

Because intracranial response depends on patients having been identified as having CNS disease, some discordance may be due to discordance in CNS disease assessment at baseline between the IRC and INV. To assess the impact of baseline CNS assessment discordance, the statistical reviewer repeated the intracranial response discordance analysis for patients who were found to have CNS disease at baseline based on both the IRC and INV assessment.

Table 133 presents the discordance between intracranial response as assessed by IRC and intracranial response as assessed by INV for all patients who were ALK positive and received 100 mg of lorlatinib and who were found to have CNS disease at baseline by both the IRC or INV.

**Table 133: Summary of Intracranial Response Discordance for Patients in the Primary Efficacy Population**

| | No Response by IRC | Response by IRC |
|---|---|---|
| No Response by INV | 63 | 31 |
| Response by INV | 1 | 41 |

The discordance rate between IRC and INV in assessing response was 31%.

*Reviewer's Comment: The discordance of intracranial response when patients have been identified as having CNS disease at baseline by both the IRC and INV is similar to the discordance based on patient who had CNS disease by either IRC or INV. This suggests that the source of discordance was not the IRC and INV identifying different patients as having CNS disease at baseline.*

## 19.6. Additional Clinical Outcome Assessment Analyses

Table 134 shows the completion rates for the first 24 cycles of treatment of patients who were in the primary efficacy population. No PRO data was submitted for patients in the Japanese LIC.

**Table 134: PRO Completion Rates During the First 24 Cycles of Treatments for Patients in the Primary Efficacy Population**

| VISIT | Total Number of Patients Available | Number of Patients who Answered at Least One Question |
|---|---|---|
| Cycle 1 Day 1 | 212 | 197 (93) |
| Cycle 2 Day 1 | 200 | 191 (96) |
| Cycle 3 Day 1 | 190 | 185 (97) |
| Cycle 4 Day 1 | 179 | 174 (97) |
| Cycle 5 Day 1 | 166 | 164 (99) |
| Cycle 6 Day 1 | 159 | 156 (98) |
| Cycle 7 Day 1 | 157 | 150 (96) |
| Cycle 8 Day 1 | 152 | 151 (99) |
| Cycle 9 Day 1 | 150 | 142 (95) |
| Cycle 10 Day 1 | 138 | 137 (99) |
| Cycle 11 Day 1 | 123 | 122 (99) |
| Cycle 12 Day 1 | 114 | 109 (96) |
| Cycle 13 Day 1 | 98 | 96 (98) |
| Cycle 14 Day 1 | 82 | 79 (96) |
| Cycle 15 Day 1 | 64 | 62 (97) |
| Cycle 16 Day 1 | 56 | 56 (100) |
| Cycle 17 Day 1 | 49 | 49 (100) |
| Cycle 18 Day 1 | 47 | 47 (100) |
| Cycle 19 Day 1 | 41 | 41 (100) |
| Cycle 20 Day 1 | 33 | 32 (97) |
| Cycle 21 Day 1 | 30 | 29 (97) |
| Cycle 22 Day 1 | 28 | 27 (96) |
| Cycle 23 Day 1 | 22 | 21 (95) |
| Cycle 24 Day 1 | 17 | 17 (100) |

Figure 23 shows the mean EORTC QLQ-C30 QoL score over time.



Reference ID: 4344794

**Figure 23: Mean EORTC QLQ-C30 QoL Score by Visit**

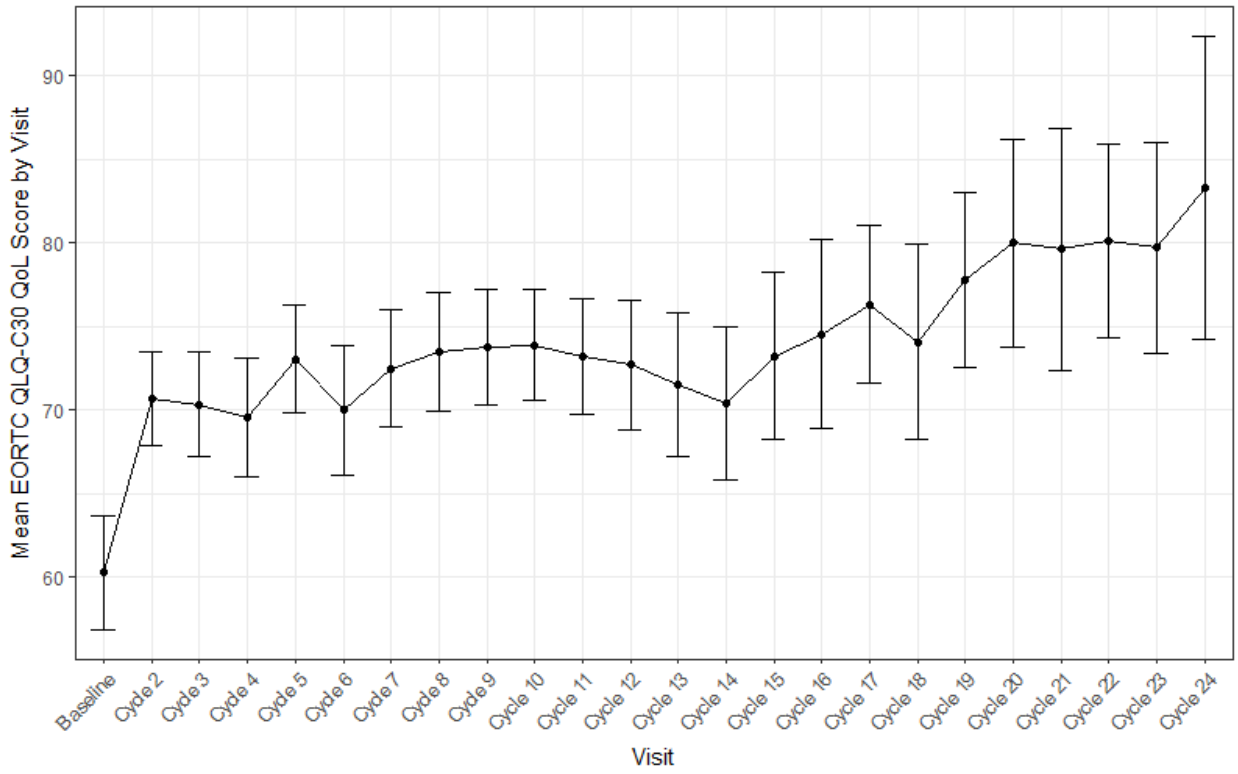



Figure 24 shows the mean change from baseline EORTC QLQ-C30 QoL score over time.

**Figure 24: Mean Change from Baseline EORTC QLQ-C30 QoL Score by Visit**

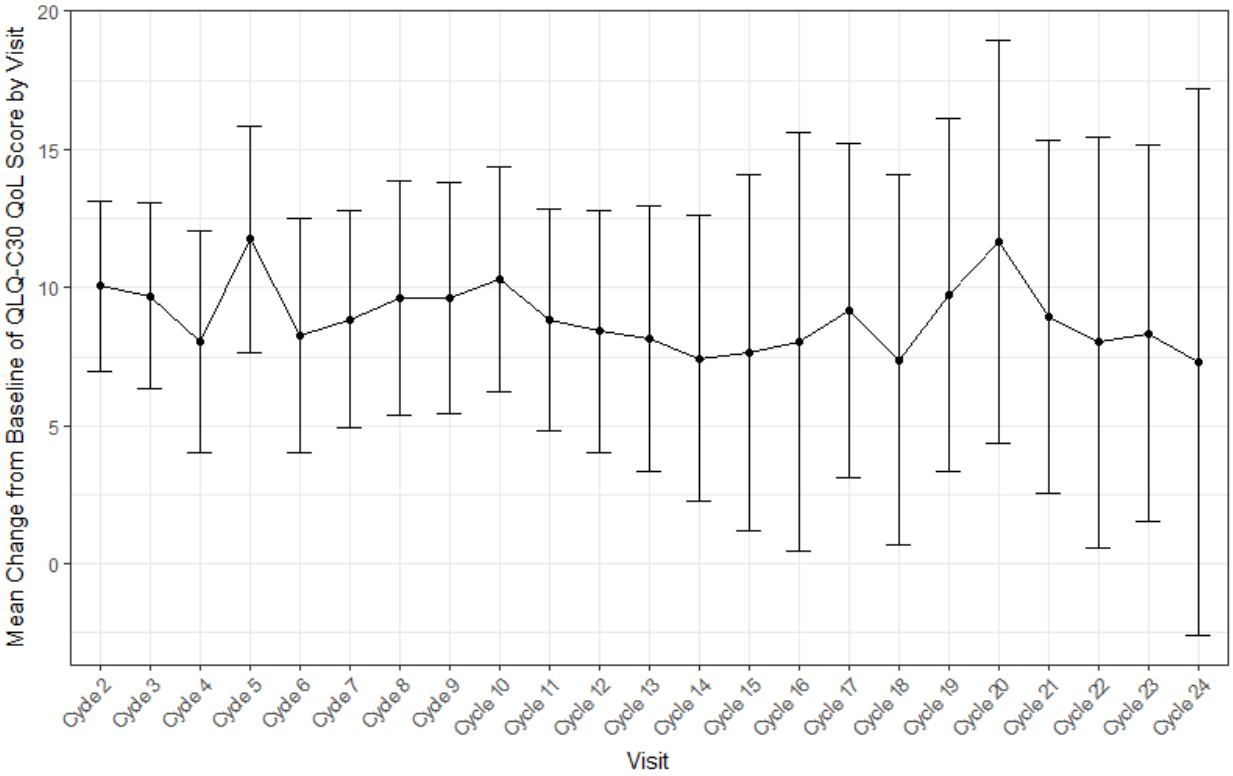



Figure 25 shows the mean EORTC QLQ-LC13 scores by category and visit.

**Figure 25: Mean EORTC QLQ-LC13 Scores by Category and Visit**

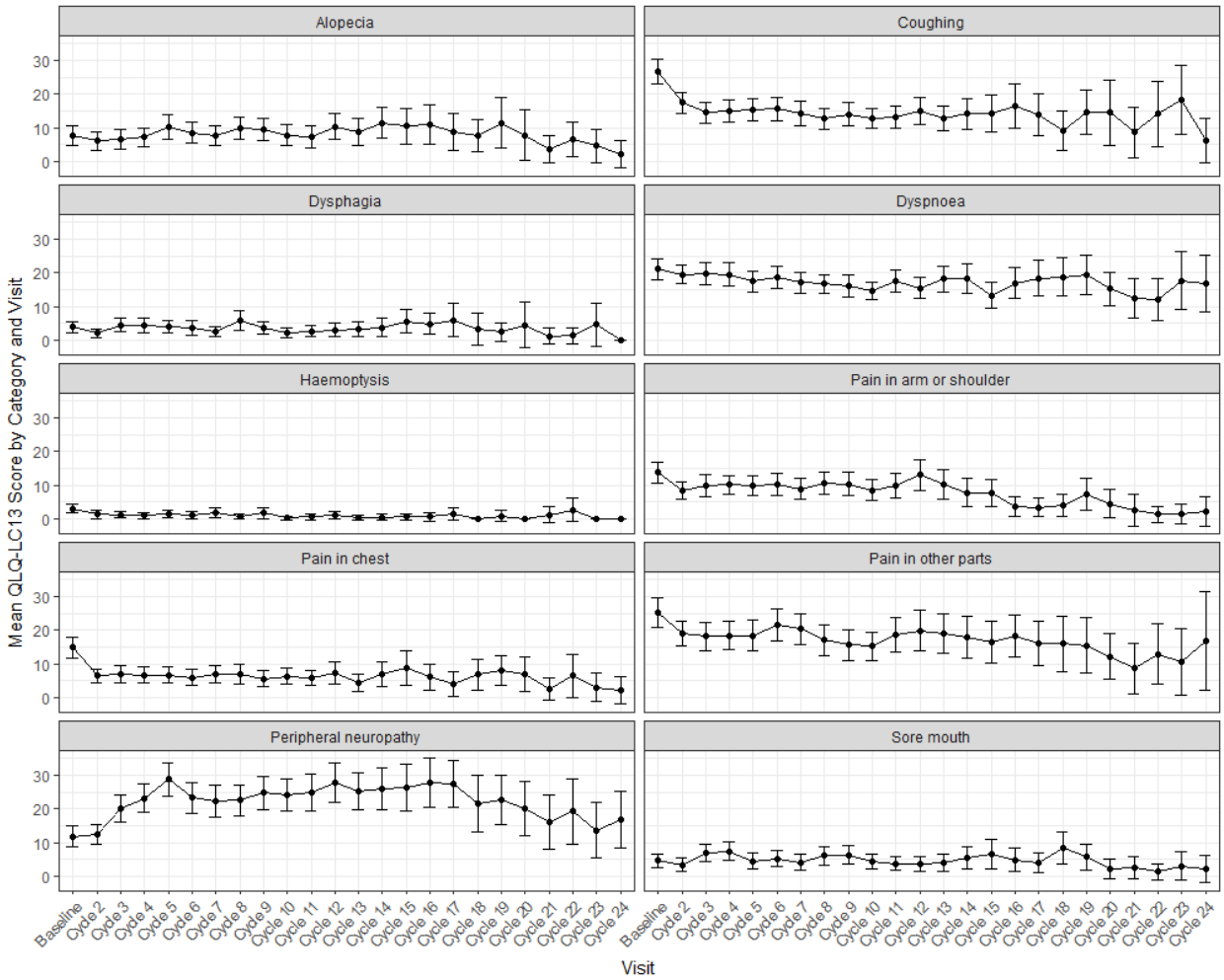
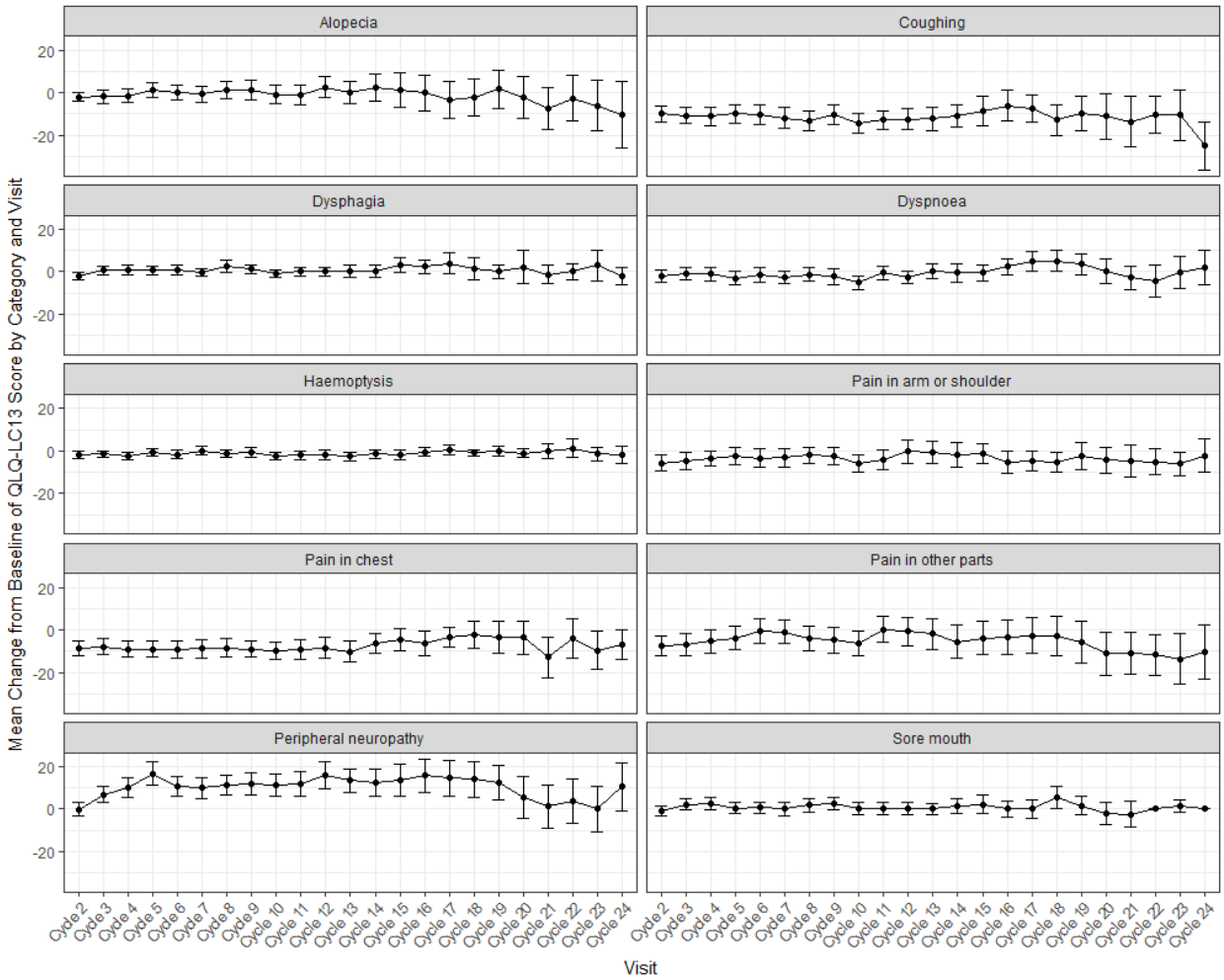



Figure 26 shows the mean change from baseline EORTC QLQ-LC13 scores by category and visit.

**Figure 26: Mean Change from Baseline EORTC QLQ-LC13 Scores by Category and Visit**



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**----------**

/s/
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SHUBHANGI H MEHTA
11/02/2018

EDWIN C CHOW
11/02/2018

JEANNE FOURIE ZIRKELBACH
11/02/2018
I concur with the conclusions from the primary clinical pharmacology and PBPK reviewer.

OLUSEYI A ADENIYI
11/02/2018

ROSANE CHARLAB ORBACH
11/02/2018

JIANG LIU
11/02/2018

NAM ATIQUR RAHMAN
11/02/2018

JONATHON J VALLEJO
11/02/2018

KUN HE
11/02/2018

RAJESHWARI SRIDHARA
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ELIZABETH I SPEHALSKI
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WHITNEY S HELMS
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HALEH SABER
11/02/2018

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11/02/2018

NICOLE L DREZNER
11/02/2018

ERIN A LARKINS
11/02/2018

PATRICIA KEEGAN
11/02/2018

GIDEON M BLUMENTHAL
11/02/2018

**MEMORANDUM**

**DATE:** May 4, 2018
**FROM:** Nicole Drezner
**THROUGH:** Erin Larkins
**TO:** File for NDA 210868 lorlatinib (LORBRENA)
**Re:** Clinical Review for NDA 210868

Pfizer, Inc. submitted NDA 210868 for lorlatinib (LORBRENA) 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 (TKIs). The clinical review of safety and efficacy is ongoing and will be added to the NDA/BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. At this time, the clinical reviewers recommend the accelerated approval (21 CFR part 601, subpart E) of lorlatinib for the treatment of patients with ALK-positive NSCLC previously treated with one or more ALK TKIs and who have received prior treatment with alectinib, however, review of the indication is ongoing and will be finalized by the time of completion of the Multi-disciplinary Review and Evaluation. Refer to the Multi-disciplinary Review and Evaluation for more details.

**----------**

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

**----------**

/s/

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NICOLE L DREZNER
05/10/2018

ERIN A LARKINS
05/10/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# Memorandum

**DATE:** February 3, 2018

**FROM:** Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

**SUBJECT:** Designation of NDA application review status
Sponsor: Pfizer, Inc.
Product: lorlatinib
Proposed Indication: For the treatment of patients with ALK-positive metastatic non-small cell lung cancer previously treated with one or more ALK tyrosine kinase inhibitors.

**TO:** NDA 210868

The review status of this file submitted as an NDA efficacy supplement is designated to be:

☐ Standard (12 Months) ☒ Priority (8 Months)

---

**BACKGROUND**
Pfizer has requested priority review for lorlatinib for the treatment of patients with ALK-positive metastatic non-small cell lung cancer previously treated with one or more ALK tyrosine kinase inhibitors:

> "Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some patients with ALK-positive NSCLC will not derive any benefit, and other patients who initially experience benefit will later develop resistance. ALK-positive NSCLC remains an incurable disease, as patients ultimately develop resistance to second-generation ALK TKIs, including but not limited to emergence of brain metastases. Thus, additional drugs are needed to overcome ALK

resistance mechanisms and to improve patient outcomes through continued disease control and activity against CNS metastases.

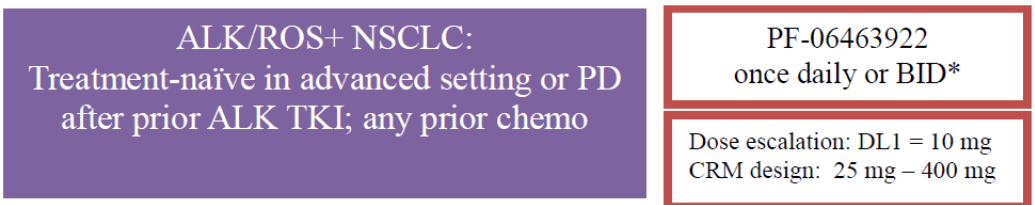
The efficacy results from Study B7461001 indicate that lorlatinib treatment provides a clinically meaningful benefit in patients with ALK-positive advanced NSCLC as evidenced by rapid, deep, and durable systemic and intracranial responses. Safety data showed that lorlatinib was generally tolerable and, when needed, adverse events were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy.

ALK-positive metastatic NSCLC is a serious disease with limited treatment options for patients who have been treated with one or more ALK TKIs. The clinical data available supports a priority review. Therefore, Pfizer requests a priority review designation for NDA 210868."

The application relies on the results of a single trial, Study B7461001, a non-randomized, multi-cohort, multi-center trial conducted in non-small cell lung cancer. In Cohorts 1-5 of the Phase 2 portion of the trial, patients were required to have a documented ALK rearrangement as determined by FDA-approved tests. All patients were required to have measurable target disease per RECIST v1.1 and patients with asymptomatic CNS metastases were eligible. Other eligibility criteria for individual cohorts are displayed in the study schema, reproduced below.

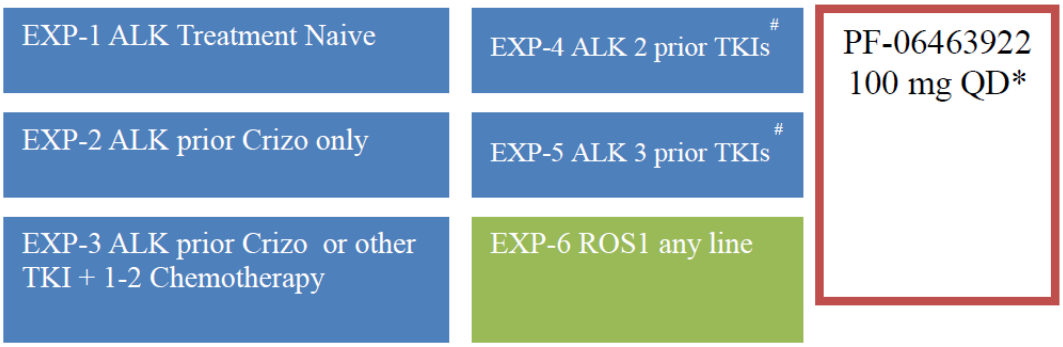
**Figure 1. Study Schema**

**Phase 1:**




* Treatment until PD or unacceptable toxicity

**Phase 2:**



Cohort 3 was further divided into subgroups (Cohorts 3A and 3B). Patients in Cohort A were required to

- have received prior crizotinib and 1 or 2 prior chemotherapy regimens administered before or after crizotinib **or**
- have received a prior ALK inhibitor other than crizotinib with or without prior chemotherapy.

The co-primary endpoints for Cohorts 1-5 were overall response rate (ORR) and intracranial ORR, as assessed by an independent central review (ICR) committee. Additional efficacy outcome measures included duration of response (DOR), intracranial DOR, and time-to-tumor response (TTR). All patients received lorlatinib 100 mg orally once daily.

The efficacy population supporting this application is derived from patients enrolled in Cohorts 2-5 who received at least one dose of lorlatinib (n=215). The demographic characteristics of the overall study population were 59% female, 51% White, 34% Asian, and the median age was 53 years (range: 29 to 85 years) with 18% of patients aged 65 years and older. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 96% patients.

Of the 215 patients, 43% received only 1 prior ALK TKI, 35% received 2 prior ALK TKIs, and 22% received ≥3 prior ALK TKIs. Brain metastases per ICR were present at baseline in 69% of patients.

Efficacy results for the pooled population are presented in the table below, abstracted from the tables provided in the study report in the NDA.

| Population | ORR per ICR (95% CI) | % Responders[1] w/DoR ≥ 6m | Population | CNS ORR per IRC (95% CI) | % Responders[2] w/DoR ≥ 6m |
|---|---|---|---|---|---|
| Cohorts 1-5 (n=215) | 46% (39, 53) | 49% (59/120) | Cohorts 1-5 (n=149) | 53% (45, 61) | 55% (42/76) |
| Cohorts 2-5 (n=197) | 47% (40, 54) | 46% (43/93) | Cohorts 2-5 (n=132) | 53% (44, 62) | 56% (39/70) |
| Cohorts 2-3A (n=59) | 69.5% (56, 81) | - | Cohorts 2-3A (n=37) | 68% (50, 82) | - |
| Cohort 3A (n=32) | 66% (47, 81) | - | Cohort 3A (n=20) | 75% (51, 91) | - |
| Cohort 3B (n=27) | 33% (16, 54) | - | Cohort 3B (n=12) | 42% (15, 72) | - |
| Cohorts 4-5 (n=111) | 39% (30, 50) | 46% (20/43) | Cohorts 4-5 (n=83) | 48% (37, 59) | 58% (23/40) |

[1] Table 14.2.2.8.1.1.3.2.1 [Summary of Duration of Objective Response Based on Independent Central Review (Phase 2) - in Patients with a Confirmed Response, by EXP-1:EXP-6; (Date of Data Cutoff: 15MAR2017 and Date of Data Snapshot: 09May2017)

[2] Table 14.2.2.8.1.2.3.2.1 [Summary of Duration of Intra-Cranial Objective Response Based on Independent Central Review (Phase 2) - in Patients with CNS Metastases and a Confirmed Response, by EXP-1:EXP-6 ((Date of Data Cutoff: 15MAR2017 and Date of Data Snapshot: 09May2017)]

## ASSESSMENT OF REQUEST

In evaluating the review designation for Pfizer's New Drug Application (NDA), I considered their rationale including the summary results of Study B7461001 and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

**Assessment***:*
This New Drug Application (NDA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition

Metastatic non-small cell lung cancer (NSCLC) is a serious and life-threatening disease, with 234,030 new cases of lung cancer and 154,050 deaths from lung cancer projected to occur in 2018 by the American Cancer Society.1 The projected 5-year survival rates of patients with Stage IVA and Stage IVB NSCLC are 10% and <1%.[2] The American Cancer Society does not provide data on expected survival for genetically defined subsets of NSCLC including ALK-positive NSCLC, which accounts for approximately 4-5% of NSCLC.[3] Available data from clinical studies reviewed by FDA in support of marketing approvals do not have mature data on survival allowing characterization of Kaplan-Meier estimated median survival or 5-year survival rates.

*I concur that the indicated population has a serious, life-threatening condition.*

Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

There are two drugs that are considered to be available therapy for the treatment of patients with ALK-positive metastatic non-small cell lung cancer previously treated with one or more ALK tyrosine kinase inhibitors: alectinib and ceritinib.

> **Alectinib** was approved on December 11, 2015 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib. Approval under the provisions of 21 CFR 314 Subpart H (accelerated approval) was based on ORR of 38% (95% CI: 28; 49) and 44% (36; 53) per ICR, with median durations of response of 7.5 and 11.2 months, respectively, in two single arm trials. The pooled (across both trials) ICR-assessed CNS ORR was 61% (46, 74) with a median duration of response of 9/1 months. In both trials, all patients received prior crizotinib and 74% and 80% had received prior chemotherapy.
>
> The indication for **alectinib** was expanded on November 6, 2017, to "the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell

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[1] https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics html
[2] https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates.html
[3] Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. Clinical Epidemiology. 2014;6:423-432. doi:10.2147/CLEP.S69718.

lung cancer (NSCLC) as detected by an FDA-approved test." This approval was based on a randomized, active controlled trial comparing alectinib with crizotinib for the first-line treatment of metastatic, ALK-positive NSCLC; this trial also verified the clinical benefit of alectinib. The randomized trial demonstrated a significant improvement in IRC-assessed progression-free survival [HR 0.53 (95% CI: 0.38, 0.73), with median PFS times of 25.7 and 10.4 months, respectively] and similar ORR (79% vs. 72%).

**Ceritinib** was approved on April 29, 2014, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Approval under the provisions of 21 CFR 314 Subpart H was based on ORR of 43.6% (36, 52) per IRC, with a median duration of response of 7.1 months in a single arm trial. Nearly all (91%) patients received prior crizotinib and 84% had received 2 or more prior lines of therapy.

The indication for **ceritinib** was expanded on May 26, 2017, to "the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test." This approval was based on a randomized, active controlled trial comparing ceritinib to platinum-based chemotherapy for the first-line treatment of metastatic, ALK-positive NSCLC; this trial also verified the clinical benefit of alectinib. The randomized trial demonstrated a significant improvement in IRC-assessed progression-free survival [HR 0.55 (95% CI: 0.42, 0.73), with median PFS times of 16.6 and 8.1 months, respectively] and a numerically higher ORR (73% vs. 27%).

The majority of patients enrolled in this clinical study supporting this application received crizotinib, an ALK tyrosine inhibitor approved for the treatment of patients with ALK-positive NSCLC in 2011, thus crizotinib would not be considered an available therapy for the proposed indicated population.

**Crizotinib** was approved on August 26, 2011 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. Approval under the provisions of 21 CFR 314 Subpart H was based ORR of 50% (42%, 59%) and 61% (52%, 70%) with median durations of response of 9.6 and 11.1 months, respectively, in two single arm trials of patients with disease progression after prior chemotherapy.

The indication for **crizotinib** was expanded (and data verifying clinical benefit) based on a randomized trial comparing crizotinib to platinum-doublet chemotherapy in the first line treatment of metastatic ALK-positive NSCLC, crizotinib demonstrated a significant improvement in progression-free survival [(HR 0.45 (95% CI: 0.35, 0.60) with median PFS times of 10.9 and 7.0 months] and a numerical increase in ORR (74% vs. 45%) as compared to chemotherapy. There was no difference in overall survival between arms, which appears to have been confounded by use of crizotinib

following disease progression in 70% of patients randomized to the chemotherapy arm.

An additional drug that is approved for the treatment of patients with metastatic, ALK-positive NSCLC who have progressed following prior crizotinib is brigatinib. Since this was approved under the provisions of accelerated approval, brigatinib is considered available therapy for the purpose of review designation.

**NCCN Practice Guidelines**: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend initial treatment of alectinib (preferred), crizotinib, or ceritinib for patients with metastatic, ALK-positive NSCLC. For patients who have progressed on or following an ALK tyrosine kinase inhibitor (the indication being sought by Pfizer in this application), the guidelines recommend continuation of crizotinib, alectinib, or ceritinib for asymptomatic or symptomatic disease progression; switching to alectinib, ceritinib, or brigatinib for symptomatic disease progression; or initiation of platinum-based chemotherapy.

*As noted in FDA's Guidance for Industry (referenced above) "Generally, if there is an available therapy (see section III.B.), sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy."*

*The proposed drug was not directly compared to alectinib or ceritinib in clinical trials and was not studied in patients who were unable to tolerate alectinib or ceritinib. Therefore, I relied primarily on the cross-study comparison between the data supporting the original approval of alectinib and those supporting the original approval of ceritinib with the results obtained in Study B7461001 Cohorts 2 and 3A as the most relevant comparator, since Cohorts 2 and 3A enrolled patients who were previously treated with crizotinib and 59% of patients received at least 1 prior line of chemotherapy. These data are summarized in the table below.*

| **Efficacy** | **Study B7461001 Cohorts 2 and 3A (N=59)** | **NP28761 (N=87)** | **NP28673 (N=138)** | **ASCEND-1 (N=163)** |
|---|---|---|---|---|
| ICR-assessed ORR (95% CI) | 69.5% (56, 81) | 38% (28; 49) | 44% (36; 53) | 44% (36, 52) |
| Median DoR | NE | 7.5 (4.9, NE) | 11.2 (9.6, NE) | 7.1 (5.6, NE) |
| % responses ≥ 6 months | 49% (20/41) | N/A | N/A | N/A |
| % responses ≥ 12 months | 4.9% (2/41) | N/A | N/A | N/A |

*Using the ICR-assessed ORR, the lower limit of the confidence interval for the pooled analysis of Cohorts 2 and 3A (56%) excludes the upper limit of the confidence intervals for the ICR-assessed ORR for the two alectinib studies and the ceritinib study.*

*Given the relatively short follow-up for the efficacy dataset from the Phase 2 portion of Study B7461001, it is unclear whether the responses achieved with lorlatinib will be as durable as those observed with alectinib or ceritinib. The longest observed response in the pooled analysis of Cohorts 2 and 3A is between 12 and 15 months and 9 of 41 (22%) patients with responses have progressed.*

*As requested by FDA, Pfizer has committed to submit additional efficacy information during review of this application to provide updated durability of responses for responding patients (but will not include new responses identified with longer follow-up).*

**Recommendation:** Priority Review

*Based on the information described above, I have concluded that lorlatinib has demonstrated a significant improvement in effectiveness over available therapy for the treatment of patients with ALK-positive metastatic non-small cell lung cancer previously treated with one or more ALK tyrosine kinase inhibitors as compared to alectinib and as compared to ceritinib.*

*{See appended electronic signature page}*

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
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Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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PATRICIA KEEGAN
02/03/2018