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SYNOPSIS

Study Title: 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

Study Number: B7461001

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT Number: 2013-002620-17

ClinicalTrials.gov Identifier: NCT01970865

Study Phase: 1/2

Name of Study Intervention: Lorlatinib (PF-06463922)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Interim CSR (Primary Completion Date [PCD]) Version 3.0	22 November 2017
Final Supplemental CSR (Last Participant Last Visit [LPLV]) Version 1.0	31 October 2023

Number of Study Center(s) and Investigator(s):

A total of 365 individual participants were enrolled at 47 centers in Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, and United States.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

A list of publications referencing data from this study is provided in Appendix 16.1.11.

Study Period:

Study Initiation Date (First Participant First Visit [FPFV]): 08 January 2014

Study Completion Date (LPLV): 24 May 2023

This study was neither discontinued nor interrupted.

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Rationale:

B7461001 interim PCD clinical study report (CSR) (version 3.0, dated 22 November 2017) presented the Phase 1, Phase 2 and Japan lead-in cohort (LIC) results with a data cut-off date of 15 Mar 2017 (PCD). Based on these results, lorlatinib received approval for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI), or after crizotinib and at least one other ALK TKI. Subsequently the results from the CROWN study expanded approval to first-line treatment in patients with metastatic NSCLC whose tumors are ALK positive.

Collection of Efficacy assessments was terminated with the implementation of Protocol Amendment 8 and a cutoff date of 15 Mar 2019 was applied to Independent Central Review (ICR) assessments.

This final supplemental CSR presents the final LPLV results from Phase 1, Phase 2, Phase 2 drug-drug interaction (DDI) substudy and Japan LIC.

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Objectives, Endpoints, and Statistical Methods:

Primary and Secondary Objectives and Endpoints - Phase 1 and Phase 2

Study Portion	Type	Objective	Endpoint
Primary Endpoint			
Phase 1	Safety	• To assess safety and tolerability of PF-06463922 as a single-agent at increasing dose levels in patients with advanced ALK+ or advanced ROS1+ NSCLC in order to estimate the MTD and select the RP2D.	• Cycle 1 DLTs.
Phase 2	Efficacy	• To evaluate overall (intra- and extracranial) and intracranial anti-tumor activity of single-agent PF-06463922 at RP2D in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC.	• Objective tumor response, as assessed by RECIST version 1.1. In patients with asymptomatic CNS metastases, up to 5 intracranial target lesions in addition to the 5 extracranial target lesions will be assessed.

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Secondary Endpoint			
Phase 1	Safety	• To evaluate the overall safety and tolerability of PF-06463922.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, and severity (as graded by NCI CTCAE v.4.03). • LVEF. • Vital Signs (heart rate, blood pressure).
Phase 2	Safety	• To confirm the safety and tolerability of single-agent PF-06463922 at the RP2D. • To evaluate the safety and efficacy of single-agent crizotinib following PF-06463922 in treatment-naïve patients with advanced ALK+ NSCLC (Phase 2 EXP-1 subgroup, if data available)	
Phase 1	PK	• To evaluate the single- and multiple-dose PK profiles of single-agent PF-06463922.	• Pharmacokinetic parameters of PF-06463922: Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and Vz/F and $t_{1/2}$, AUC_{inf} as data permit. Multiple Dose (assuming steady-state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, V_z/F, R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}/AUC_{sd,inf}$) as data permit.
Phase 2	PK	• To confirm single- and multiple-dose PK profiles of single-agent PF-06463922 at the RP2D.	
Phase 1	Safety	• To detect early signs of cognitive dysfunction.	• Total Mini Mental State Examination Score [Phase 1 only].
Phase 1	Efficacy	• To evaluate preliminary anti-tumor activity of single-agent PF-06463922 in patients with advanced ALK+ NSCLC or advanced ROS1+ NSCLC.	• DCR at 12 and 24 weeks defined as the percent of patients with a confirmed CR, PR or SD according to RECIST 1.1 at 12 and 24 weeks.

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Phase 2	Efficacy	• To assess secondary measures of clinical efficacy.	• Objective tumor response, as assessed by RECIST version 1.1 [Phase 1 only – primary endpoint in Phase 2]. In patients with asymptomatic CNS metastases, up to 5 intracranial target lesions in addition to the 5 extracranial target lesions will be assessed. • Time-to-event endpoints: PFS, OS, DoR, and TTR. • Probability of first event being a CNS progression, non-CNS progression, or death. TTP [Phase 2 only].
Phase 2	Safety	• To detect early signs of changes in mood, cognitive function, or SIB.	• Mood assessment, Cognitive Function assessment, Suicidal Ideation and Behavior assessment [Phase 2 only].
Phase 1	PRO	• To evaluate PRO of QOL functioning, and the impact of PF-06463922 on disease/treatment-related symptoms of lung cancer.	• Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL.
Phase 2	PRO	• To evaluate PRO of global QOL, functioning and the impact of PF-06463922 on disease/treatment-related symptoms of lung cancer at the RP2D.	
Phase 1	Safety/ECG	• To characterize the effects of single-agent PF-06463922 on the QTc interval.	• QTc interval.
Phase 2	Safety/ECG	• To further evaluate the effects of single-agent PF-06463922 at the RP2D on the QTc interval.	
Phase 1	Biomarker	• To evaluate tumor and blood-based molecular markers of response and resistance to single-agent PF-06463922.	• Selected molecular profiling of tumor tissue, eg, ALK kinase domain mutations, and CNA, eg, ALK kinase domain mutations.

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Phase 2	Biomarker	• To further evaluate tumor and blood-based molecular markers of response and resistance to single-agent PF-06463922 at the RP2D.	
Phase 2	Safety & Efficacy	For ALK+ NSCLC Phase 2 patients receiving single agent crizotinib following first line treatment with PF-06463922: • To evaluate the safety and efficacy of single-agent crizotinib following PF-06463922 in treatment-naïve patients with advanced ALK+ NSCLC.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, and severity (as graded by NCI CTCAE v.4.03). • Objective tumor response, as assessed by RECIST version 1.1, and time-to-event endpoints including PFS, DoR, TTR and OS.
Phase 1 & Phase 2	Efficacy	• To evaluate response to prior systemic therapies.	• Response to prior systemic therapies.

Abbreviations: ALK = anaplastic lymphoma kinase; AUC_{inf} = area under the concentration-time curve from time 0 to infinite time; AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); $AUC_{sd,inf}$ = AUC_{inf} single dose; $AUC_{sd,\tau}$ = AUC_{τ} single dose; $AUC_{ss,\tau}$ = AUC_{τ} at steady state; AUC_{τ} = area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where tau = 12 or 24 hours for twice a day (BID) or once daily (QD) dosing, respectively; CL/F = apparent oral clearance; C_{max} = maximum observed concentration; CNA = circulating nucleic acid; CNS = central nervous system; CR = complete response; $C_{ss,av}$ = average concentration (C_{av}) at steady state; $C_{ss,max}$ = C_{max} at steady state; $C_{ss,min}$ = minimum observed concentration (C_{min}) at steady state; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; EXP = expansion; LVEF = left ventricular ejection fraction; MTD = maximum tolerated dose; NCI = National Cancer Institute; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; PRO = patient reported outcome; QOL = quality of life; QTc = QT interval corrected for heart rate; R_{ac} = observed accumulation ratio; RECIST = Response Evaluation Criteria In Solid Tumors; RP2D = Recommended Phase 2 Dose; R_{ss} = steady state accumulation ratio; SD = stable disease; SIB = suicidal ideation and behavior; $t_{1/2}$ = half life; T_{max} = Time to reach C_{max}; $T_{ss,max}$ = T_{max} at steady state; TTP = time to tumor progression; TTR = time to response; Vz/F = apparent volume of distribution.

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Objectives and Endpoints - Substudies and Japanese Patient Only LIC

Study Portion	Type	Objective	Endpoint
Midazolam DDI study (Phase 1)	PK	• To evaluate the potential of single-agent PF-06463922 to cause CYP3A inhibition/induction using midazolam as a probe.	• Urine 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio • Pharmacokinetic parameters of midazolam: C_{max}, T_{max}, AUC_{last}, CL/F, and V_z/F and $t_{1/2}$, AUC_{inf} as data permitted [Phase 1 only].
Midazolam DDI study (Phase 1)	PK	• To evaluate the single- and multiple-dose PK profiles of single-agent PF-06463922.	• Pharmacokinetic parameters of PF-06463922: Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and Vz/F and $t_{1/2}$, AUC_{inf} as data permit. Multiple Dose (assuming steady-state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, V_z/F, R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}/AUC_{sd,inf}$) as data permit. Phase 1 only: urine PK parameters (Ae%, and CLR) of PF-06463922 from MDZ and food effect substudy.
Food Effect study (Phase 1)	Food effect	• To characterize the effect of food on PF-06463922.	
Japanese Patient Only LIC (Phase 2)	Safety	• To evaluate the safety and tolerability of PF-06463922 in Japanese Patients before starting enrollment of Japanese Patients in Phase 2 portion of the study.	• Cycle 1 DLTs.
DDI/Holter Monitoring Study (Phase 2)	Efficacy/DDI	• To evaluate the potential of PF-06463922 to inhibit/induce CYP2B6, CYP2C9, Pgp, and select Glucuronosyltransferases (UGT) isoforms.	• Pharmacokinetic parameters (as data permit) for probe substrate after single oral administration with or without PF-06463922: Plasma AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, CL/F, V_z/F and $t_{1/2}$. • Pharmacokinetic parameters (as data permit) for relevant probe substrate metabolite(s) and PF-06463922 metabolite(s): Plasma and AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$, MRC_{max}, $MRAUC_{inf}$, and $MRAUC_{last}$.

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Study Portion	Type	Objective	Endpoint
DDI/Holter Monitoring Study (Phase 2)	Safety	• To characterize the effects of PF-06463922 on ECG endpoints.	• PR and other ECG measurements with PF-06463922 treatment
DDI/Holter Monitoring Study (Phase 2)	Safety & Efficacy	• To characterize the safety and efficacy of PF-06463922 of patients entering the DDI/Holter monitoring study.	• Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03), seriousness and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, and severity (as graded by NCI CTCAE v.4.03). • QTc interval. • LVEF. • Vital Signs (heart rate, blood pressure). • DCR at 12 and 24 weeks defined as the percent of patients with a confirmed CR, PR or SD according to RECIST 1.1 at 12 and 24 weeks. • Objective tumor response, as assessed by RECIST version 1.1. In patients with asymptomatic CNS metastases, up to 5 intracranial target lesions in addition to the 5 extracranial target lesions will be assessed • Time to event endpoints: PFS, OS, DoR, and TTR. • Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL.

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Study Portion	Type	Objective	Endpoint
Abbreviations: Ae% = percentage of drug excreted in urine; AUC_{24} = area under the concentration-time curve from time 0 to 24 hours; AUC_{inf} = area under the concentration-time curve from time 0 to infinite time; AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}); $AUC_{sd,inf}$ = AUC_{inf} single dose; $AUC_{sd,\tau}$ = AUC_{τ} single dose; $AUC_{ss,\tau}$ = AUC_{τ} at steady state; AUC_{τ} = area under the concentration-time profile from time zero to time tau (τ), the dosing interval, where tau = 12 or 24 hours for twice a day (BID) or once daily (QD) dosing, respectively; CL/F = apparent oral clearance; CLR = clearance; C_{max} = maximum observed concentration; CNS = central nervous system; CR = complete response; $C_{ss,av}$ = average concentration (C_{av}) at steady state; $C_{ss,max}$ = C_{max} at steady state; $C_{ss,min}$ = minimum observed concentration (C_{min}) at steady state; CTCAE = Common Terminology Criteria for Adverse Events; CYP = cytochrome P450; DCR = disease control rate; DDI = drug-drug interaction; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; LIC = lead-in cohort; LVEF = left ventricular ejection fraction; MDZ = midazolam; $MRAUC_{inf}$ = metabolite-to-parent AUC_{inf} ratio; $MRAUC_{last}$ = metabolite-to-parent AUC_{last} ratio; MRC_{max} = metabolite-to-parent C_{max} ratio; NCI = National Cancer Institute; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; QOL = quality of life; QTc = QT interval corrected for heart rate; R_{ac} = observed accumulation ratio; RECIST = Response Evaluation Criteria In Solid Tumors; R_{ss} = steady state accumulation ratio; SD = stable disease; $t_{1/2}$ = half life; T_{max} = Time to reach C_{max}; $T_{ss,max}$ = T_{max} at steady state; TTR = time to response; UGT = uridine diphosphate glucuronosyltransferase; Vz/F = apparent volume of distribution.			

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Statistical Methods:

Efficacy Analysis

Primary Efficacy Parameters:

- Analysis of Objective Response Rate (ORR) and intracranial ORR were performed for the intention-to-treat (ITT) analysis set. The point estimate of the ORR was to be provided along with the corresponding 95% confidence interval (CI) using the exact method based on the binomial distribution. Intracranial ORR was also provided with the corresponding 95% CI.

Analysis of Secondary Efficacy Parameters:

- DCRs and intracranial (IC)-DCRs (IC-DCRs) are provided along with the corresponding 95% CI.

- For PFS and OS, estimates of the time-to-event curves using the Kaplan-Meier method are presented. Confidence intervals for the median and quartiles are generated by the method of Brookmeyer and Crowley.

- DoR was summarized in the populations of participants with a confirmed CR ot PR using the Kaplan−Meier method.

- TTR was only calculated for the subgroup of participants with a confirmed objective tumor response. TTR was summarized based on ICR using descriptive statistics.

- For TTP, estimates of the TTP curve using the Kaplan-Meier method are presented. Confidence intervals for the median and quartiles are generated by the method of Brookmeyer and Crowley.

- IC-TTP was calculated in a similar manner to TTP for the ITT analysis set and for subgroups of participants with and without brain metastases at baseline. For the subgroup of participants without brain metastases at baseline, only the appearance of new brain metastases were considered events.

- The probability of the first event being a CNS progression, a non-CNS progression, or death was evaluated with a competing risk approach by estimating cumulative incidence functions relative to the analysis set based on both ICR and investigator assessments. All the analyses were repeated on participants with brain lesions at study entry in the analysis set.

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Safety Analysis

All participants administered with at least 1 dose of lorlatinib in the study were included in the safety analyses. Participants were analyzed according to the product they actually received.

Safety data (AEs, vital signs, ECG, physical examinations, laboratory tests) were summarized and reported in accordance with the sponsor reporting standards.

Cluster term AEs were summarized by maximum CTCAE grade and causality (all-causality and treatment-related) together with other AEs. Clustered terms are presented using capital letters while Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) are written with only the first letter capitalized.

For participants with Multi Gated Acquisition Scan (MUGA) scans or echocardiograms, individual LVEF (%) and its changes from baseline was summarized by time point (changes from baseline should only have been calculated for the on treatment evaluation using the same method used for baseline). The number of participants and the percentage whose maximum relative decrease from baseline in LVEF was greater than 20% was calculated.

Patient Reported Outcomes

The PRO evaluable analysis set was the primary population for the analyses of PRO change from baseline based on the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.

Methodology:

This was a Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamics and anti-cancer efficacy exploration study of lorlatinib as a single agent in participants with advanced ALK+ or advanced ROS1+ NSCLC. This clinical study consisted of 2 parts, Phase 1 and Phase 2. The Phase 1 portion of the study estimated the MTD for single-agent lorlatinib in dose escalation cohorts in participants with advanced ALK+ or advanced ROS1+ NSCLC with or without asymptomatic CNS metastases. The Phase 1 portion was also the basis for selecting RP2D. The Phase 2 portion of the study employed single-agent lorlatinib at the RP2D identified in Phase 1 and was designed to evaluate the anti-cancer activity of lorlatinib in multiple subpopulations of participants with advanced ALK+ NSCLC and in participants with advanced ROS1+ NSCLC based on prior type and lines of therapy received.

Phase 1 Dose Escalation

In the Phase 1 portion, lorlatinib was planned to be evaluated at escalating doses of 10, 25, 50, 75, 100, 150, 200, 250, 300, and 400 mg QD, depending on toxicities observed.

Starting at the 25 mg dose level, a continuous reassessment method (CRM) was employed to assign participants to dose levels in order to estimate the MTD and select the RP2D. The

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goal of the Phase 1 portion was to determine the dose of lorlatinib that was the closest to but no higher than a 33% probability of a DLT (ie, a target DLT rate of 0.33). Each dose cohort was to initially include at least 3 participants evaluable for toxicity within the first cycle. The first 3 participants (ie, the first cohort) were to be treated at 10 mg QD, and the following dose level explored was to be 25 mg QD. BID dosing was not originally planned, but was also tested to support identification of the RP2D.

Based on Phase 1 safety, efficacy, and clinical pharmacology data, 100 mg QD was chosen as the RP2D.

Phase 2

The Phase 2 portion enrolled participants at the RP2D identified in Phase 1 and included participants from the following subpopulations based on mutation status and prior therapies received:

- EXP-1: Treatment-naïve patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases. No prior chemotherapy was allowed in the metastatic setting. Additionally, EXP-1 patients were eligible to receive single-agent crizotinib following treatment with lorlatinib if allowed per local guidelines and appropriate per investigator discretion.

- EXP-2: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after only crizotinib therapy. No prior chemotherapy was allowed in the metastatic setting.

- EXP-3: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after crizotinib therapy and 1 or 2 prior regimens of chemotherapy given before or after crizotinib therapy, or patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor therapy other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting.

- EXP-4: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 2 prior lines of ALK inhibitor therapies. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting.

- EXP-5: Patients with advanced ALK+ NSCLC with or without asymptomatic CNS metastases relapsing after 3 prior lines of ALK inhibitor therapies. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting.

- EXP-6: Patients with advanced ROS1+ NSCLC who were treatment naïve or have had any number of prior cancer therapies, with or without asymptomatic CNS metastases.

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Substudies in Phase 1

Midazolam Drug-Drug Interaction Study: The potential of lorlatinib to inhibit/induce CYP3A was planned to be evaluated using MDZ as a CYP3A probe substrate.

Food Effect Study: The effect of food on the PK of lorlatinib was planned to be evaluated in a food effect substudy in approximately 6 participants in Phase 1. The testing order for fed versus fasted conditions was to be as follows: the first half of the participants to participate in this substudy were tested under fed followed by fasted conditions, the next half of the participants were tested under fasted followed by fed conditions.

Substudies in Phase 2

Japanese Patient Lead-in Cohort (Japan Sites Only): To evaluate the safety and tolerability of lorlatinib in Japanese patients, a Japanese patient only LIC was enrolled to evaluate lorlatinib safety and PK in patients treated at a previously tested dose in Phase 1. This LIC was considered separate from Phase 2. Results from this cohort are presented in listings of this CSR.

Drug-Drug Interaction and Holter Monitoring: To evaluate the potential interaction effect of lorlatinib on drugs that are metabolized or transported via pathways that include CYP2B6, CYP2C9, P-gp, and select UGT isoforms, a DDI study was conducted in participants with NSCLC either ALK-positive or ROS-1 positive, met the disease status and prior treatment requirements of EXP groups 2-6, and had at least 1 measurable intracranial or extracranial lesion according to RECIST version 1.1. Additionally, an evaluation of the effects of lorlatinib on the PR interval was planned to be conducted via continuous Holter telemetry comparing the participant's pre-drug baseline values with observations of PR interval changes associated with exposure of lorlatinib following a single dose and again at steady state.

Participants in the Phase 2 DDI substudy were analyzed and summarized as a stand-alone cohort. Efficacy, safety and PRO results from the Phase 2 DDI substudy are presented in this CSR.

Number of Participants (planned and analyzed):

Number of Participants Planned

Approximately 340 participants (Phase 1, Phase 2, including DDI and Holter monitoring study) were planned to be enrolled in this study overall.

The Phase 1 portion of the study planned to enroll approximately 50 participants (depending on toxicities observed). Additionally, a food effect substudy (not reported in this CSR) was planned to be conducted in approximately 6 participants enrolled in Phase 1.

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The Phase 2 portion planned to enroll approximately 260 participants meeting the criteria for EXP-1 to EXP-6 subpopulations.

Number of Participants Analyzed

A total of 365 individual participants were enrolled, including 54 enrolled in Phase 1, 276 enrolled in Phase 2 (EXP-1 to EXP-6 cohorts), 3 in Japan LIC, and 32 in Phase 2 DDI substudy.

A total of 54 individual participants were assigned to lorlatinib treatment in Phase 1 (including 1 participant who was assigned twice to 2 different cohorts). All 54 individual participants received at least 1 dose of lorlatinib. Number of participants assigned to and treated in each cohort was 3 participants in 10 mg QD cohort, 3 participants in 25 mg QD cohort, 3 participants in 50 mg QD cohort, 12 participants in 75 mg QD cohort, 17 participants in 100 mg QD cohort, 3 participants in 150 mg QD cohort, 3 participants in 200 mg QD cohort, 3 participants in 35 mg BID cohort, 3 participants in 75 mg BID cohort, and 4 participants in 100 mg BID cohort.

Of note, 1 participant was first enrolled in the 75 mg QD cohort and assigned a first patient number, but was not treated in this cohort. The participant was re-screened and re-assigned to the 50 mg QD cohort with a second patient number. This participant was treated and contributed data to the 50 mg QD cohort.

Among 276 participants assigned to the EXP-1 to EXP-6 cohorts in Phase 2, 275 participants received lorlatinib treatment (30, 27, 60, 65, 46, 47 participants in cohorts EXP-1, EXP-2, EXP-3, EXP-4, EXP-5 and EXP-6, respectively). One participant was assigned to treatment in the EXP-4 cohort but never treated. All 275 treated participants were included in the ITT population and the safety analysis set.

All 32 participants enrolled in the Phase 2 DDI substudy received lorlatinib treatment. All participants were included in the ITT population and the safety analysis set.

Diagnosis and Main Criteria for Inclusion:

Eligible participants should have been 18 years or older and had evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC that carried an ALK rearrangement, as determined by the Food and Drug Administration (FDA) approved fluorescent in situ hybridization (FISH) assay or by Immunohistochemistry (IHC), or a ROS1 rearrangement as determined by FISH or reverse transcription polymerase chain reaction (RT-PCR) or Next Generation Sequencing (NGS) via a local diagnostic test. All participants (ALK positive or ROS1 positive) had to have archival tissue sample available and collected prior to enrollment. Participants should have had adequate bone marrow, pancreatic function, renal function and liver function. For females of childbearing potential, negative serum pregnancy test was required.

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Disease status should have met the following requirements:

- Phase 1: ALK-positive NSCLC and ROS1-positive patients must either have been treatment naïve in the advanced setting or have had disease progression after at least 1 previous ALK or ROS1 inhibitor therapy(ies), respectively.

- Phase 2:

  - ALK-positive NSCLC patients must either have been or have had:

    - Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ALK inhibitor therapy allowed). [EXP-1]

    - Disease progression after crizotinib only. No prior chemotherapy was allowed in the metastatic disease setting. [EXP-2]

    - Disease progression after crizotinib and 1 or 2 prior regimens of chemotherapy in the metastatic disease setting; or disease progression after 1 prior ALK inhibitor therapy 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 inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. [EXP-4]

    - Disease progression after 3 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting. [EXP-5]

  - ROS1-positive NSCLC patients were to have had:

    - Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ROS inhibitor therapy). [EXP-6]

    - Any number of prior therapies (ie, chemotherapy and/or ROS inhibitor therapies). [EXP-6]

- DDI and Holter Monitoring Study patients were ALK-positive or ROS1-positive NSCLC patients who had met disease status requirements for EXP groups 2-6.

Tumor Requirements:

- All Patients must have had at least 1 measurable target extracranial lesion according to RECIST version 1.1. In addition, patients with asymptomatic CNS metastases (including patients asymptomatic by means of stable or decreasing doses of steroids within the last 2 weeks prior to study entry) were eligible. Phase 1 only: patients who had leptomeningeal disease (LM) or carcinomatous meningitis (CM) and negative

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cerebrospinal fluid (CSF) were eligible. Phase 2 only: Patients who had LM or CM were eligible if the LM/CM was visualized on magnetic resonance imaging (MRI) or if documented baseline CSF positive cytology was available.

- DDI and Holter monitoring study: all patients must have had at least 1 measurable intracranial or extracranial lesion according to RECIST version 1.1 (ie, patients were eligible with only 1 CNS lesion, provided it was measurable per RECIST 1.1). Patients with CNS metastases were eligible if they were asymptomatic (including patients controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry). The brain metastases were either newly diagnosed or have been presented as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery. Patients who had LM or CM were eligible if the LM/CM was visualized on MRI or if documented baseline CSF positive cytology was available.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

In all study parts, lorlatinib was administered orally QD (or BID dosing in Phase 1) continuously in 21-day cycles. Participants self-administered lorlatinib in the outpatient setting.

Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot	Pfizer Lot	Strength	Dosage Form
PF-06463922 100 mg Oval White to Off-White Tablet	CM-07813	13-108959	100 mg	TABLET
PF-06463922 5 mg Round White to Off-White Tablet	CM-07613	13-109240	5 mg	TABLET
PF-06463922 25 mg Hexagonal White to Off-White Tablet	CM-07713	13-109241	25 mg	TABLET
Midazolam HCl syrup 2 mg/mL in a 118 mL bottle	3263523	13-110113	2 mg/ml	COMMERCIAL PRODUCT
Crizotinib 250 mg Bottle 50ct (capsule)	J28149/J21 124	14-002483	250 mg	PACKAGED BOTTLE
Crizotinib 200 mg Bottle 50ct (capsule)	J28139/J21 129	14-002484	200 mg	PACKAGED BOTTLE
PF-06463922 100 mg Oval White to Off-White Tablet	N/A	14-003016	100 mg	TABLET
PF-06463922 100 mg Oval White to Off-White Tablet	N/A	14-003438	100 mg	TABLET

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Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot	Pfizer Lot	Strength	Dosage Form
PF-06463922 25 mg Hexagonal White to Off-White Tablet	N/A	14-004521	25 mg	TABLET
PF-06463922 25 mg Hexagonal White to Off-White Tablet	N/A	14-005711	25 mg	TABLET
PF-06463922 5 mg Round White to Off-White Tablet	N/A	15-001079	5 mg	TABLET
PF-06463922 25 mg Hexagonal White to Off-White Tablet	N/A	15-001080	25 mg	TABLET
PF-06463922 100 mg Oval White to Off-White Tablet	N/A	15-001081	100 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-002606	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-004169	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-005956	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	M60859	15-007274	25 mg	TABLET
PF-02341066/Crizotinib 200 mg IR Size 1 White/Pink Capsule	N44237	16-002145	200 mg	BULK COMMERCIAL IMAGE
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	16-002268	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	16-004078	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	17-001188	25 mg	TABLET
PF-02341066/Crizotinib 250 mg IR Size 0 Pink/Pink Capsule	T79535	17-004069	250 mg	BULK COMMERCIAL IMAGE
PF-06463922 25 mg Hexagonal White to Off-White Tablet	N/A	18-001761	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	18-002755	25 mg	TABLET

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Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot	Pfizer Lot	Strength	Dosage Form
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	19-000758	25 mg	TABLET
PF-06463922 25 mg Hexagonal White to Off-White Tablet	19-DP-00043	19-002343	25 mg	TABLET
PF-06463922 25 mg Round White Film-Coated Tablet	20-DP-00118	20-000099	25 mg	TABLET
PF-06463922 25 mg Hexagonal White to Off-White Tablet	20-DP-00107	20-000140	25 mg	TABLET
PF-02341066/Crizotinib 200 mg IR Size 1 White/Pink Capsule	T79515	17-004068	200 mg	BULK COMMERCIAL IMAGE
Midazolam HCl syrup 2 mg/mL in a 118 mL bottle	4196910	15-000152	2 mg/ml	COMMERCIAL PRODUCT

Duration of Study Intervention:

In all study parts, participants were to continue with the study treatment until progression of disease as determined by the investigator, unacceptable toxicity, death or consent withdrawal. Participants were allowed to continue PF-06463922 treatment after objective progression of disease was determined if the patient was continuing to experience clinical benefit, in the opinion of the investigator, and after discussion with the sponsor.

Summary of Results:

NOTE: In this CSR, Phase 2 participants refers to participants from EXP-1 to EXP-6 cohorts pooled together. Participants in the Phase 2 DDI substudy were analyzed and summarized as a stand-alone cohort. Data from participants in the Japan LIC cohort were presented in specific listings and not discussed in the CSR.

Demographic and Other Baseline Characteristics:

Phase 1 Demographic and Other Baseline Characteristics:

Thirty-two (59.3%) female participants and 22 (40.7%) male participants were enrolled and included in the Safety Analysis Set (SAS) of Phase 1, and the mean (standard deviation [SD]) age was 51.9 (12.8) years old. Most participants (68.5%) enrolled were White.

- Of 41 ALK+ participants enrolled in Phase 1, 24 (58.5%) were female and 17 (41.5%) were male, and the mean (SD) age was 51.0 (11.2) years old. Most participants (78.0%) enrolled were White.

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- Of 12 ROS+ participants enrolled in Phase 1, 7 (58.3%) were female and 5 (41.7%) were male, and the mean (SD) age was 55.0 (18.0) years old. Five out of 12 participants (41.7%) enrolled were White.

Phase 2 Demographic and Other Baseline Characteristics:

Among 275 participants enrolled and treated in Phase 2, 157 (57.1%) were female participants and 118 (42.9%) were male participants, and the mean (SD) age was 53.6 (12.1) years. Most participants enrolled were either White (48.0%) or Asian (37.5%). The most frequently involved disease sites at the time of study entry were chest (96.4%), brain (55.6%) and other (46.2%).

Phase 2 DDI Substudy Demographic and Other Baseline Characteristics:

Among 32 participants enrolled and treated in Phase 2 DDI substudy, 15 (46.9%) were female participants and 17 (53.1%) were male participants, and the mean (SD) age was 54.9 (10.2) years. Participants were either White (65.6%) or Asian (34.4%). The most frequently involved disease sites at the time of study entry were chest (90.6%), brain (53.1%) and other (40.6%).

Exposure:

The median (range) duration of treatment was 10.18 (0.07 - 96.58) months in the Phase 1 participants and was 17.41 (0.07-96.58) months for the 100 mg QD cohort.

The median (range) duration of treatment was 16.33 (0.03 - 89.65) months in the Phase 2 participants, and was 9.15 (0.89 - 68.69) months in Phase 2 DDI substudy participants. Out of 275 participants in Phase 2, 164 were treated beyond disease progression, with a median (range) treatment duration of 7.90 (0.03 - 88.47) months beyond progression. Out of 32 participants in Phase 2 DDI substudy, 21 were treated beyond disease progression, with a median (range) treatment duration of 3.88 (0.16 - 54.66) months beyond progression.

Efficacy Results:

Phase 1 Secondary Efficacy Results:

Phase 1 ORR and DoR results with a cutoff date of 15 Mar 2019 are presented in this CSR.

Phase 1 Objective Response Rate

The confirmed ORR based on independent central review (hereafter referred to as "independent assessment") was 41.5% (95% confidence interval [CI]: 28.1, 55.9) in Phase 1 ITT population.

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Phase 1 Duration of Response

In Phase 1, The median follow-up time for ORR was 44.1 months. Out of 22 participants with a confirmed response, 8 (36.4%) were censored. The DoR was >6 months for 7/14 participants with subsequent PD or death, and was >21 months for the 8 participants censored (without subsequent PD or death). Median DoR was 23.65 months.

Phase 2 Primary Efficacy Results:

Phase 2 efficacy results with a data cutoff date of 15 May 2019 are presented in this CSR. Analysis of OS is based on LPLV.

Phase 2 Objective Response Rate

The confirmed ORR based on independent assessment was 90% (95% CI: 73.5, 97.9) for cohort EXP-1, 77.8% (95% CI: 57.7, 91.4) for cohort EXP-2, 56.7% (95% CI: 43.2, 69.4) for cohort EXP-3, 40.0% (95% CI: 28.0, 52.9) for cohort EXP-4, 37.0% (95% CI: 23.2, 52.5) for cohort EXP-5, and 38.3% (95% CI: 24.5, 53.6) for cohort EXP-6, respectively.

Phase 2 Intracranial Objective Response Rate

The confirmed IC-ORR results for participants with baseline CNS metastases in cohorts EXP-1:EXP-6, based on independent assessments in the ITT population, are summarized as follows. The analyses took into account measurable and non-measurable lesions.

- For Phase 2, the confirmed IC-ORR based on independent assessment was 75.0% (95% CI: 34.9, 96.8) for cohort EXP-1, 58.8% (95% CI: 32.9, 81.6) for cohort EXP-2, 66.7% (95% CI: 48.2, 82.0) for cohort EXP-3, 53.3% (95% CI: 37.9, 68.3) for cohort EXP-4, 43.2% (95% CI: 27.1, 60.5) for cohort EXP-5, and 56.0% (95% CI: 34.9, 75.6) for cohort EXP-6, respectively.

- For Phase 2, percentage of participants with complete intra-cranial response based on independent assessment was 50.0% (4/8) for cohort EXP-1, 35.3% (6/17) for cohort EXP-2, 24.2% (8/33) for cohort EXP-3, 33.3% (15/45) for cohort EXP-4, 24.3% (9/37) for cohort EXP-5, and 40.0% (10/25) for cohort EXP-6, respectively.

Phase 2 Secondary Efficacy Results:

Phase 2 Time to Tumor Response

For Phase 2 participants with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.2-5.4 months) for cohort EXP-1, 1.4 months (range: 1.2-18.0 months) for cohort EXP-2, 1.4 months (range: 1.1-16.6 months) for cohort EXP-3, 2.6 months (range: 1.2-16.4 months) for cohort EXP-4, 1.4 months (range: 1.2-9.3 months) for cohort EXP-5, and 1.4 months (range: 1.3-29.7 months) for cohort EXP-6.

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Phase 2 Intracranial Time to Tumor Response

For Phase 2 participants with baseline CNS metastases and a confirmed objective response by independent assessment, the median IC-TTR was 2.1 months (range: 1.2-2.8 months) for cohort EXP-1, 1.4 months (range: 1.2-1.5 months) for cohort EXP-2, 1.4 months (range: 1.1-5.7 months) for cohort EXP-3, 1.7 months (range: 1.2-17.5 months) for cohort EXP-4, 1.4 months (range: 1.2-10.6 months) for cohort EXP-5, and 1.4 months (range: 1.2-28.9 months) for cohort EXP-6.

Phase 2 Duration of Response

For Phase 2 participants with a confirmed response, the median DoR was 17.16 months (95% CI: 12.45, 35.09) for cohort EXP-1, 16.56 months (95% CI: 4.20, not reached [NR]) for cohort EXP-2, 11.10 months (95% CI: 5.55, NR) for cohort EXP-3, 15.08 months (95% CI: 5.55, 26.28) for cohort EXP-4, 7.03 months (95% CI: 4.17, 11.01) for cohort EXP-5, and 19.61 months (95% CI: 11.10, NR) for cohort EXP-6.

Phase 2 Intracranial Duration of Response

For Phase 2 participants with baseline CNS metastases and a confirmed response, the median IC-DoR was NR (95% CI: 8.28, NR) for cohort EXP-1, NR (95% CI: 20.99, NR) for cohort EXP-2, 37.12 months (95% CI: 8.38, NR) for cohort EXP-3, 14.52 months (95% CI: 11.07, NR) for cohort EXP-4, 10.32 months (95% CI: 6.90, 14.98) for cohort EXP-5, and 17.62 months (95% CI: 4.99, NR) for cohort EXP-6.

Phase 2 Disease Control Rate

For Phase 2 participants, the DCR at 24 weeks based on independent assessment was 83.3% (95 CI%: 65.3, 94.4) for cohort EXP-1, 63.0% (95 CI%: 42.4, 80.6) for cohort EXP-2, 51.7% (95 CI%: 38.4, 64.8) for cohort EXP-3, 49.2% (95 CI%: 36.6, 61.9) for cohort EXP-4, 32.6% (95 CI%: 19.5, 48.0) for cohort EXP-5, and 48.9% (95 CI%: 34.1, 63.9) for cohort EXP-6, respectively.

Phase 2 Intracranial Disease Control Rate

For Phase 2 participants, the IC-DCR at 24 weeks based on independent assessment was 75.0% (95 CI%: 34.9, 96.8) for cohort EXP-1, 70.6% (95 CI%: 44.0, 89.7) for cohort EXP-2, 60.6% (95 CI%: 42.1, 77.1) for cohort EXP-3, 62.2% (95 CI%: 46.5, 76.2) for cohort EXP-4, 48.6% (95 CI%: 31.9, 65.6) for cohort EXP-5, and 52.0% (95 CI%: 31.3, 72.2) for cohort EXP-6, respectively.

Phase 2 Time to Tumor Progression

For participants in the phase 2 ITT population, the median TTP based on independent assessment was 17.7 months (95% CI: 12.5, 40.5) for cohort EXP-1, 20.6 months (95% CI: 5.5, NR) for cohort EXP-2, 8.2 months (95% CI: 5.5, 12.5) for cohort EXP-3, 8.4 months

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(95% CI: 5.6, 13.7) for cohort EXP-4, 5.6 months (95% CI: 4.0, 8.3) for cohort EXP-5, and 12.5 months (95% CI: 8.2, 26.2) for cohort EXP-6.

Phase 2 Time to Tumor Progression on the Last Prior Treatment Regimen Before Lorlatinib

TTP in cohorts EXP-2:EXP-5, based on prior therapy, is summarized as follows:

For Phase 2 participants who had received any systemic therapy prior to lorlatinib, the median TTP was 11.5 months (95% CI: 7.2, 19.6) for cohort EXP-2, 12.8 months (95% CI: 10.9, 16.9) for cohort EXP-3, 10.2 months (95% CI: 7.6, 15.9) for cohort EXP-4, and 3.7 months (95% CI: 2.1, 6.4) for cohort EXP-5.

For Phase 2 participants who had received ALK+/ROS1+ TKI treatment prior to lorlatinib, the median TTP was 11.5 months (95% CI: 7.2, 19.6) for cohort EXP-2, 13.8 months (95% CI: 11.2, 18.1) for cohort EXP-3, 12.1 months (95% CI: 7.9, 16.4) for cohort EXP-4, and 3.7 months (95% CI: 2.1, 6.6) for cohort EXP-5.

For Phase 2 participants who had received systemic therapy other than ALK+/ROS1+ TKI treatment prior to lorlatinib, the median TTP was 19.6 months (95% CI: 16.1, NR) for cohort EXP-2, 8.5 months (95% CI: 5.0, 12.6) for cohort EXP-3, 5.0 months (95% CI: 3.1, 10.0) for cohort EXP-4, and 5.6 months (95% CI: 3.5, 11.2) for cohort EXP-5.

Phase 2 Intracranial Time to Tumor Progression

For participants in the phase 2 ITT population, the median IC-TTP based on independent assessment was NR months (95% CI: NR, NR) for cohorts EXP-1 and EXP-2, NR months (95% CI: 15.0, NR) for cohort EXP-3, 22.1 months (95% CI: 15.7, NR) for cohort EXP-4, 16.4 months (95% CI: 12.7, NR) for cohort EXP-5, and NR months (95% CI: 34.5, NR) for cohort EXP-6. Probability of being event free at Month 18 estimated from Kaplan-Meier curve was 84.5% (95% CI: 63.7%, 93.9%) for cohort EXP-1, 83.8% (95% CI: 62.1%, 93.6%) for cohort EXP-2, 59.7% (95% CI: 44.4%, 72.0%) for cohort EXP-3, 57.9% (95% CI: 39.5%, 72.6%) for cohort EXP-4, 43.4% (95% CI: 23.1%, 62.2%) for cohort EXP-5, and 85.7% (95% CI: 65.7%, 94.5%) for cohort EXP-6.

For participants with baseline CNS metastases in the phase 2 ITT population, the median IC-TTP based on independent assessment was 11.4 months (95% CI: 9.6, NR) for cohort EXP-1, NR months (95% CI: 20.6, NR) for cohort EXP-2, 16.5 months (95% CI: 6.9, NR) for cohort EXP-3, 15.7 months (95% CI: 9.9, NR) for cohort EXP-4, 16.4 months (95% CI: 8.3, NR) for cohort EXP-5, and 34.5 months (95% CI: 12.3, NR) for cohort EXP-6. Probability of being event free at Month 18 estimated from Kaplan-Meier curve was 38.1% (95% CI: 6.1%, 71.6%) for cohort EXP-1, 80.7% (95% CI: 51.1%, 93.4%) for cohort EXP-2, 47.6% (95% CI: 29.2%, 63.9%) for cohort EXP-3, 44.0% (95% CI: 23.1%, 63.0%) for cohort EXP-4, 41.1% (95% CI: 18.7%, 62.4%) for cohort EXP-5, and 71.5% (95% CI: 39.3%, 88.6%) for cohort EXP-6.

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For participants with no baseline CNS metastases in the phase 2 ITT population, the median IC-TTP based on independent assessment was NR months (95% CI: NR, NR) for cohorts EXP-1 to EXP-3 and EXP-6, NR months (95% CI: 22.0, NR) for cohort EXP-4, NR months (95% CI: 11.0, NR) for cohort EXP-5. Probability of being event free at Month 18 estimated from Kaplan-Meier curve was 100.0% (95% CI: 100.0%, 100.0%) for cohort EXP-1, 90.0% (95% CI: 47.3%, 98.5%) for cohort EXP-2, 81.5% (95% CI: 57.6%, 92.7%) for cohort EXP-3, 94.7% (95% CI: 68.1%, 99.2%) for cohort EXP-4, 53.3% (95% CI: 12.5%, 82.7%) for cohort EXP-5, and 100.0% (95% CI: 100.0%, 100.0%) for cohort EXP-6.

Phase 2 Progression-Free Survival

The median PFS based on independent assessment was 16.6 months (95% CI: 11.8, 28.3) for cohort EXP-1, 20.6 months (95% CI: 5.5, NR) for cohort EXP-2, 6.9 months (95% CI: 5.5, 11.0) for cohort EXP-3, 7.3 months (95% CI: 4.2, 11.1) for cohort EXP-4, 5.5 months (95% CI: 3.9, 8.2) for cohort EXP-5, and 9.9 months (95% CI: 5.5, 21.0) for cohort EXP-6.

Phase 2 Overall Survival

Median OS based on the Brookmeyer and Crowley Method was 52.5 months (95% CI: 24.4, NR) for cohort EXP-2, 18.7 months (95% CI: 15.1, 34.1) for cohort EXP-4, 20.4 months (95% CI: 10.5, 31.6) for cohort EXP-5 and 49.7 months (95% CI: 21.0, NR) for cohort EXP-6. Both cohort EXP-1 and EXP-3 had estimated survival probability of >50% at Month 72.

Survival probability at Month 36 estimated from the Kaplan-Meier curve was 79.7% (95% CI: 60.3%, 90.4%) for cohort EXP-1, 67.6% (95% CI: 45.4%, 82.3%) for cohort EXP-2, 64.9% (95% CI: 51.0%, 75.8%) for cohort EXP-3, 36.3% (95% CI: 24.2%, 48.5%) for cohort EXP-4, 31.5% (95% CI: 18.4%, 45.4%) for cohort EXP-5, and 62.0% (95% CI: 44.8%, 75.2%) for cohort EXP-6.

Phase 2 DDI Substudy Primary Efficacy Results:

Phase 2 DDI substudy efficacy results with a cutoff date of 15 March 2019 are presented in this CSR. Analysis of OS is based on LPLV.

Phase 2 DDI Substudy Objective Response Rate

The confirmed ORR, based on independent assessment in the ITT population, was 40.6% (95% CI: 23.7, 59.4) for the DDI substudy.

Phase 2 DDI Substudy Intracranial Objective Response Rate

For participants with baseline CNS metastases in the DDI substudy, the confirmed IC-ORR based on independent assessment was 25.0% (95% CI: 7.3, 52.4). Out of 16 participants with baseline CNS metastases in the DDI substudy, 2 participants (12.5%) had complete intracranial response.

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Phase 2 DDI Substudy Secondary Efficacy Results:

Phase 2 DDI Substudy Time to Tumor Response

For participants in the DDI substudy with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.2-11.0 months).

Phase 2 DDI Substudy Intracranial Time to Tumor Response

For participants in the DDI substudy with baseline CNS metastases and a confirmed objective response by independent assessment, the median IC-TTR was 2.0 months (range: 1.1-4.2 months).

Phase 2 DDI Substudy Duration of Response

For participants in the DDI substudy with a confirmed response, the median DoR was 5.19 months (95% CI: 4.17, NR).

Phase 2 DDI Substudy Intracranial Duration of Response

For participants with baseline CNS metastases and a confirmed response in the DDI substudy, the median IC-DoR was NR months (95% CI: 2.76, NR).

Phase 2 DDI Substudy Disease Control Rate

For participants in the DDI substudy, the DCR at 24 weeks based on independent assessment was 34.4% (95 CI%: 18.6, 53.2).

Phase 2 DDI Substudy Intracranial Disease Control Rate

For participants in the ITT population of the DDI substudy with baseline CNS metastases, the IC-DCR at 24 weeks based on independent assessment was 43.8% (95 CI%: 19.8, 70.1).

Phase 2 DDI Substudy Time to Tumor Progression

For participants in the phase 2 DDI substudy, the median TTP based on independent assessment was 5.7 months (95% CI: 4.1, 8.3).

Phase 2 DDI Substudy Intracranial Time to Tumor Progression

For participants in the phase 2 DDI substudy, the median IC-TTP based on independent assessment was NR months (95% CI: 6.9, NR). Probability of being event free at Month 18 estimated from Kaplan-Meier curve was 66.6% (95% CI: 42.5%, 82.4%).

For participants with baseline CNS metastases in the phase 2 DDI substudy, the median IC-TTP based on independent assessment was 6.9 months (95% CI: 2.5, NR). Probability of

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being event free at Month 18 estimated from Kaplan-Meier curve was 40.4% (95% CI: 14.1%, 65.8%).

For participants with no baseline CNS metastases in the phase 2 DDI substudy, the median IC-TTP based on independent assessment was NR months (95% CI: NR, NR). Probability of being event free at Month 18 estimated from Kaplan-Meier curve was 100.0% (95% CI: 100.0%, 100.0%).

Phase 2 DDI Substudy Progression-Free Survival

Median PFS based on independent review in the ITT population of the DDI substudy was 5.7 months (95% CI: 4.0, 7.1).

Phase 2 DDI Substudy Overall Survival

For participants in the DDI substudy, the median OS was 19.8 months (95% CI: 11.1, NR). A total of 17 participants (53.1%) died during the DDI substudy. The survival probability at 24 months, for participants in the DDI substudy, was 49.6% (95% CI: 30.1%, 66.4%).

Safety Results:

AE Overview

Phase 1 AE Overview:

Phase 1 All-Causality AEs

Overall in Phase 1 SAS, 54 (100%) participants had 1040 all-causality AEs; 33 (61.1%) participants had serious adverse events (SAEs); 36 (66.7%) participants had Grade 3 or 4 AEs and 10 (18.5%) participants had Grade 5 AEs; 29 (53.7%) participants and 14 (25.9%) participants had a dosing interruption (temporary discontinuation of lorlatinib) and a dose reduction in association with AEs, respectively; 6 (11.1%) participants permanently discontinued treatment due to AEs.

In the 100 mg QD cohort, 17 (100%) participants had 316 all-causality AEs; 10 (58.8%) participants had SAEs; 12 (70.6%) participants and 4 (23.5%) participants had Grade 3 or 4 AEs and Grade 5 AEs, respectively; 8 (47.1%) participants had a dosing interruption (temporary discontinuation of lorlatinib) in association with AEs; no participants had a dose reduction or permanently discontinued treatment due to AEs.

Phase 1 Treatment-Related AEs

Overall, among 54 participants in Phase 1 SAS, 50 (92.6%) participants had 398 treatment-related AEs; 8 (14.8%) participants had treatment-related SAEs; 19 (35.2%) participants had Grade 3 or 4 treatment-related AEs; no participants had Grade 5 treatment-related AEs; 20 (37.0%) participants and 14 (25.9%) participants had a dosing

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interruption (temporary discontinuation of lorlatinib) and a dose reduction in association with treatment-related AEs, respectively; 2 (3.7%) participants permanently discontinued treatment due to treatment-related AEs.

Among 17 participants of the 100 mg QD cohort, 16 (94.1%) participants had 114 treatment-related AEs; 1 (5.9%) participant had treatment-related SAE(s); 6 (35.3%) participants had Grade 3 or 4 treatment-related AEs; no participants had Grade 5 treatment-related AEs; 5 (29.4%) participants had a dosing interruption (temporary discontinuation of lorlatinib) in association with treatment-related AEs; no participants had a dose reduction or permanently discontinued treatment due to treatment-related AEs.

Phase 2 AE Overview:

Phase 2 All-Causality AEs

Among 275 participants in Phase 2 SAS, 274 (99.6%) participants had 4631 all-causality AEs; 135 (49.1%) participants had SAEs; 209 (76.0%) participants had Grade 3 or 4 AEs and 43 (15.6%) participants had Grade 5 AEs; 158 (57.5%) participants had a dosing interruption (temporary discontinuation of lorlatinib) and 77 (28.0%) participants had a dose reduction in association with AEs, respectively; 35 (12.7%) participants permanently discontinued treatment due to AEs.

Phase 2 Treatment-Related AEs

Among 275 participants in Phase 2 SAS, 262 (275%) participants had 2128 treatment-related AEs; 27 (9.8%) participants had treatment-related SAEs; 137 (49.8%) participants had Grade 3 or 4 treatment-related AEs; no participants had Grade 5 treatment-related AEs; 100 (36.4 %) participants had a dosing interruption (temporary discontinuation of lorlatinib) and 72 (26.2%) participants had a dose reduction in association with treatment-related AEs, respectively; 13 (4.7 %) participants permanently discontinued treatment due to treatment-related AEs.

Phase 2 DDI Substudy AE Overview:

Phase 2 DDI Substudy All-Causality AEs

All 32 participants enrolled in the DDI substudy had at least 1 all-causality AE, with a total of 495 all-causality AEs reported; 13 (40.6%) participants had SAEs; 24 (75.0%) participants had Grade 3 or 4 AEs and 5 (15.6%) participants had Grade 5 AEs, respectively; 14 (43.8%) participants had a dosing interruption (temporary discontinuation of lorlatinib) and 11 (34.4%) participants had a dose reduction in association with AEs, respectively; 4 (12.5%) participants permanently discontinued treatment due to AEs.

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Phase 2 DDI Substudy Treatment-Related AEs

In 32 participants enrolled in the DDI substudy, 31 (96.9%) participants had 194 treatment-related AEs; 1 (3.1%) participant had treatment-related SAE(s); 16 (50.0%) participants had Grade 3 or 4 treatment-related AEs; no participants had Grade 5 treatment-related AEs; 10 (31.3%) participants had a dosing interruption (temporary discontinuation of lorlatinib) and 7 (21.9%) participants had a dose reduction in association with treatment-related AEs, respectively; 3 (9.4%) participants permanently discontinued treatment due to treatment-related AEs.

Incidence of AEs

Phase 1 Incidence of AEs:

Phase 1 Incidence of All-Causality AEs

In 54 participants of Phase 1 SAS, the most frequently reported all-causality AEs with clustering (reported in ≥30% participants) in decreasing frequency were HYPERCHOLESTEROLEMIA (75.9%), EDEMA (64.8%), PERIPHERAL NEUROPATHY (61.1%), FATIGUE (55.6%), HYPERTRIGLYCERIDEMIA (46.3%), COGNITIVE EFFECTS (40.7%), Anaemia (35.2%), and Dyspnoea (31.5%).

Phase 1 Incidence of Treatment-Related AEs

In 54 participants of Phase 1 SAS, the most frequently reported treatment-related AEs (reported in ≥30% participants) in decreasing frequency were Hypercholesterolaemia (55.6%), Oedema peripheral (40.7%) and Hypertriglyceridaemia (35.2%).

Phase 2 Incidence of AEs:

Phase 2 Incidence of All-Causality AEs

In 275 participants of Phase 2 SAS, 274 (99.6%) participants had all-causality AEs. The most frequently reported all-causality AEs with clustering (reported in ≥30% participants) in decreasing frequency were HYPERCHOLESTEROLEMIA (84.4%), HYPERTRIGLYCERIDEMIA (68.7%), EDEMA (56.4%), PERIPHERAL NEUROPATHY (49.5%), COGNITIVE EFFECTS (31.3%), Dyspnoea (31.3%), FATIGUE (30.5%) and Arthralgia (30.5%).

Phase 2 Incidence of Treatment-Related AEs

In 275 participants of Phase 2 SAS, the most frequently reported treatment-related AEs (reported in ≥30% participants) in decreasing frequency were Hypertriglyceridaemia (64.7%), Hypercholesterolaemia (55.3%), Oedema peripheral (37.5%) and Blood cholesterol increased (35.6%).

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Phase 2 DDI Substudy Incidence of AEs:

Phase 2 DDI Substudy Incidence of All-Causality AEs

All 32 participants of DDI substudy SAS had all-causality AEs. The most frequently reported all-causality AEs (with clustering, reported in ≥30% participants) in decreasing frequency were HYPERCHOLESTEROLEMIA (93.8%), HYPERTRIGLYCERIDEMIA (84.4%), EDEMA (59.4%), PERIPHERAL NEUROPATHY (43.8%), FATIGUE (37.5%), COGNITIVE EFFECTS (31.3%) and Dyspnoea (31.3%).

Phase 2 DDI Substudy Incidence of Treatment-Related AEs

In 32 participants of DDI substudy SAS, the most frequently reported treatment-related AEs (reported in ≥30% participants) in decreasing frequency were Hypertriglyceridaemia (71.9%), Blood cholesterol increased (53.1%) and Hypercholesterolaemia (46.9%).

Deaths

Phase 1 Deaths:

In 54 participants of Phase 1 SAS, 35 deaths were reported, including 8 (14.8%) participants who died on study treatment or within 28 days after their last dose of lorlatinib, and 27 (50.0%) participants who died after 28 days after their last dose of lorlatinib. None of the deaths were treatment-related; 33 of the deaths were due to disease under study, 2 were due to unknown cause, none were due to "Other" cause.

In 10 participants who had fatal (Grade 5) all-causality AEs, 9 had Grade 5 disease progression (1 participant each in 10 mg QD group, 25 mg QD group, 75 mg QD group, 150 mg QD group and 75 mg BID group, 4 participants in 100 mg QD group), and 1 participant in 150 mg QD group had Grade 5 hypoxia caused by disease under study.

Phase 2 Deaths:

In 275 participants of Phase 2 SAS, 151 deaths were reported, including 39 (14.2%) participants who died on study treatment or within 28 days after their last dose of lorlatinib, and 112 (40.7%) participants who died after 28 days after their last dose of lorlatinib. None of the deaths were treatment-related; 129 of the deaths were due to disease under study, 13 were due to unknown cause, and 9 were due to "Other" cause.

In 43 participants who had fatal (Grade 5) all-causality AEs, 29 had Grade 5 disease progression, 2 participants had Grade 5 pneumonia, and the following Grade 5 events were reported in 1 participant each: Embolism, Acute pulmonary oedema, Chronic obstructive pulmonary disease, General physical health deterioration, Acute myocardial infarction, Asphyxia, [redacted] Myocardial infarction, Neoplasm progression, Peripheral artery occlusion, Pulmonary tumour thrombotic microangiopathy, Respiratory distress.

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Phase 2 DDI Substudy Deaths:

In 32 participants of Phase 2 DDI substudy SAS, 17 deaths were reported, including 5 (15.6%) participants who died on study treatment or within 28 days after their last dose of lorlatinib, and 12 (37.5%) participants who died after 28 days after their last dose of lorlatinib; none of the deaths were treatment-related. All 17 deaths were due to disease under study.

In 5 participants who had fatal (Grade 5) all-causality AEs, all of the AEs were Grade 5 disease progression.

SAEs

Phase 1 SAEs:

In 54 participants of Phase 1 SAS, 33 (61.1%) had all-causality SAEs (with clustering). The most frequent all-causality SAE was Disease progression (9 [16.7%] participants), which was required to be reported as an SAE if the outcome was fatal and if it occurred within 28 days after the last dose of lorlatinib. Other frequent (in >5% of participants) SAEs were Dyspnoea and Pneumonia (4 [7.4%] participants each), Haemoptysis, Mental status changes and Seizure (3 [5.6%] participants each).

In 54 participants of Phase 1 SAS, 8 (14.8%) had treatment-related SAEs (with clustering), including Seizure reported in 2 participants (3.7%), and Mental status change, COGNITIVE EFFECTS, Cataract, Dermatomyositis, Hallucination, Headache, Lipase increased, Neurological symptom reported in 1 participant each.

Phase 2 SAEs:

In 275 participants of Phase 2 SAS, 135 (49.1%) had all-causality SAEs. The most frequent all-causality SAE (with clustering) was Disease progression (29 [10.5%] participants). The other SAE reported in more than 5% of participants was Pneumonia (19 [6.9%] participants).

In 275 participants of Phase 2 SAS, 27 (9.8%) had treatment-related SAEs. Treatment-related SAE (with clustering) reported in more than 1 participant included COGNITIVE EFFECTS (3 [1.1%] participants) and Acute respiratory failure (2 participants).

Phase 2 DDI Substudy SAEs:

In 32 participants of the DDI substudy SAS, 13 (40.6%) had all-causality SAEs. All-causality SAE (with clustering) reported in more than 1 participant included Disease progression (5[15.6%] participants) and COGNITIVE EFFECTS (2 [6.3%] participants).

In 32 participants of the DDI substudy SAS, 1 (3.1%) participant experienced treatment-related SAE of Pneumonitis.

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AEs Resulting in Permanent Discontinuation From Study Intervention

Phase 1 AEs Resulting in Permanent Discontinuation From Study Intervention:

In 54 participants of Phase 1 SAS, lorlatinib was permanently discontinued due to all-causality AE in 6 (11.1%) participants. Two participants in the 100 mg BID group had treatment-related AEs resulting in permanent discontinuation from lorlatinib . One participant in the 10 mg QD and 2 participants in the 150 mg QD group had serious AEs resulting in permanent discontinuation from lorlatinib; none of these SAEs were treatment-related.

Phase 2 AEs Resulting in Permanent Discontinuation From Study Intervention:

In 275 participants of Phase 2 SAS, lorlatinib was permanently discontinued due to all-causality AE in 35 (12.7%) participants, and due to treatment-related AE in 13 (4.7%) participants. All-causality AEs leading to permanent discontinuation of treatment reported in more than 1 participant included Acute respiratory failure, Dyspnoea and Respiratory failure (2 participants each). None of the treatment-related AEs leading to permanent discontinuation of treatment was reported in more than 1 participant.

Treatment-related SAEs that resulted in permanent discontinuation included Grade 3 Confusional state (1 participant in EXP-1), Grade 3 Cognitive disorder (1 participant in EXP-3), Grade 4 Schizophreniform disorder (1 participant in EXP-3), Grade 3 Nervous system disorder (1 participant in EXP-4), Grade 4 Pneumonitis (1 participant in EXP-4), Grade 2 Headache (1 participant in EXP-5), Grade 3 Delirium (1 participant in EXP-6), and Grade 3 Pericardial effusion (1 participant in EXP-6)

Phase 2 DDI Substudy AEs Resulting in Permanent Discontinuation From Study Intervention:

In 32 participants enrolled in the DDI substudy, lorlatinib was permanently discontinued due to all-causality AE in 4 (12.5%) participants, and due to treatment-related AE in 3 (9.4%) participants.

One participant in the DDI substudy experienced a treatment-related SAE of Grade 2 Pneumonitis that resulted in permanent discontinuation from treatment.

AEs Resulting in Dose Reduction or Temporary Discontinuation From Study Intervention

Phase 1 AEs Resulting in Dose Reduction or Temporary Discontinuation From Study Intervention:

In 54 participants of Phase 1 SAS, lorlatinib was temporarily discontinued due to all-causality AEs for 29 (53.7%) participants. The most frequently reported all-causality AEs

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associated with a temporary treatment discontinuation were Lipase increased, Hypercholesterolaemia and Pneumonia.

In 54 participants of Phase 1 SAS, 14 (25.9%) participants required dose reduction in association with all-causality AEs. The most frequently reported all-causality AEs that were associated with a dose reduction were Hypercholesterolaemia, Fatigue and Seizure.

Phase 2 AEs Resulting in Dose Reduction or Temporary Discontinuation From Study Intervention:

In 275 participants of Phase 2 SAS, lorlatinib was temporarily discontinued due to all-causality AEs for 158 (57.5%) participants. The most frequently reported all-causality AEs associated with a temporary treatment discontinuation were Hypertriglyceridaemia, Oedema peripheral and Pneumonia.

In 275 participants of Phase 2 SAS, 77 (28.0%) participants required dose reduction in association with all-causality AEs. The most frequently reported all-causality AEs that were associated with a dose reduction were Oedema peripheral, Cognitive disorder and Hypertriglyceridaemia.

Phase 2 DDI Substudy AEs Resulting in Dose Reduction or Temporary Discontinuation From Study/Study Intervention:

In 32 participants of the DDI substudy, lorlatinib was temporarily discontinued due to all-causality AEs for 14 (43.8%) participants. The most frequently reported all-causality AEs associated with a temporary treatment discontinuation were Confusional state, Hypercholesterolaemia and Hyertriglyceridaemia.

In 32 participants of the DDI substudy, 11 (34.4%) participants required dose reduction in association with all-causality AEs. The most frequently reported all-causality AEs that were associated with a dose reduction were Confusional state and Neuropathy peripheral.

AEs of Special Interest

Phase 1 AESIs:

Phase 1 Hyperlipidemia Adverse Events: (ie. HYPERCHOLESTEROLEMIA and HYPERTRIGLYCERIDEMIA)

All-causality Hyperlipidemia AEs included HYPERCHOLESTEROLEMIA reported in 41 (75.9%) participants (40 [74.1%] experienced treatment-related events) and HYPERTRIGLYCERIDEMIA reported in 25 (46.3%) participants (all participants had treatment-related events). None of the Hyperlipidemia AEs were SAEs or resulted in permanent discontinuation from treatment. Most episodes were managed by temporary discontinuation, dose reduction and/or concomitant treatment.

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Phase 1 EDEMA

All-causality EDEMA AEs were reported in 35 (64.8%) participants; 29 (53.7%) participants experienced treatment-related EDEMA. None of the EDEMA AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 1 PERIPHERAL NEUROPATHY

All-causality PERIPHERAL NEUROPATHY AEs were reported in 33 (61.1%) participants; 21 (38.9%) participants experienced treatment-related PERIPHERAL NEUROPATHY AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 1 CNS Effects

- *Phase 1 COGNITIVE EFFECTS*: All-causality COGNITIVE EFFECTS AEs were reported in 22 (40.7%) participants; 14 (25.9%) participants experienced treatment-related COGNITIVE EFFECTS AEs. None of these AEs resulted in permanent discontinuation from treatment. Two participants experienced serious COGNITIVE EFFECTS AEs: 1 participant in 100 mg QD group experienced 1 episode of Grade 3 SAE Delirium and another episode of Grade 2 SAE Delirium, and both events were considered treatment related; 1 participant in the 150 mg QD group experienced 1 episode of Grade 2 SAE Confusional state, which was determined to be unrelated to study treatment.

- *Phase 1 MOOD EFFECTS*: All-causality MOOD EFFECTS AEs were reported in 15 (27.8%) participants; 11 (20.4%) participants experienced treatment-related events. None of these AEs were SAEs or resulted in permanent discontinuation from treatment. One participant in the 35 mg BID group experienced a Grade 4 MOOD EFFECTS AE of anxiety, which was not treatment-related.

- *Phase 1 SPEECH EFFECTS*: All-causality SPEECH EFFECTS AEs were reported in 16 (29.6%) participants; 11 (20.4%) participants experienced treatment-related events. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

- *Phase 1 PSYCHOTIC EFFECTS*: Two participants in the 150 mg QD group experienced all-causality PSYCHOTIC EFFECTS AEs: 1 participant experienced a Grade 1 non-serious adverse event (NSAE) and a Grade 2 NSAE of hallucination; the other participant experienced two Grade 2 SAEs of hallucination. Two NSAEs and 1 of the SAEs of hallucination were treatment-related. None of these events resulted in permanent discontinuation from treatment or study.

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Phase 1 Weight Gain

All-causality Weight gain AEs were reported in 15 (27.8%) participants; 12 (22.2%) participants experienced treatment-related Weight gain AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 1 VISION DISORDER

All-causality VISION DISORDER AEs were reported in 14 (25.9%) participants; 7 (13.0%) participants experienced treatment-related VISION DISORDER AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 1 Liver Function Tests Increased

All-causality Liver function tests increased AEs were reported in 14 (25.9%) participants; 12 (22.2%) participants experienced treatment-related Liver function tests increased AEs. One participant in the 100 mg BID group experienced 2 episodes of Grade 3 AST increased and 1 episode of Grade 4 AST increased (which was an SAE), 1 episode of Grade 3 ALT increased, 4 episodes of Grade 3 Gamma-glutamyltransferase increased, 2 episodes of Grade 4 Gamma-glutamyltransferase increased; this participant permanently discontinued from treatment due to NSAEs of Grade 2 ALT increased and Grade 2 AST increased, both of which were treatment-related.

Phase 1 QT Interval Prolongation

All-causality QT interval prolongation AEs (PT = Electrocardiogram QT prolonged) were reported in 4 (7.4%) participants; 2 (3.7%) participants experienced treatment-related events. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 1 Interstitial Lung Disease/Pneumonitis

In Phase 1, no AEs of Interstitial lung disease or Pneumonitis were reported.

Phase 1 Atrioventricular Block

In Phase 1, no AEs of AV block were reported.

Phase 1 Pancreatitis

All-causality Pancreatitis was reported in 15 (27.8%) participants; 12 (22.2%) participants experienced treatment-related Pancreatitis. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

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Phase 2 AESIs:

Phase 2 Hyperlipidemia Adverse Events: (ie. HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA)

All-causality Hyperlipidemia AEs included HYPERCHOLESTEROLEMIA reported in 232 (84.4%) participants (231 [84.0%] experienced treatment-related events) and HYPERTRIGLYCERIDEMIA reported in 189 (68.7%) participants (188 [68.4%] experienced treatment-related events). None of the events resulted in permanent discontinuation from treatment.

In phase 2, 1 participant in the EXP-3 group experienced a treatment-related SAE of Grade 4 HYPERCHOLESTEROLEMIA (blood cholesterol increased); 1 participant in the EXP-5 group experienced a treatment-related SAE of Grade 4 hypertriglyceridaemia.

Phase 2 EDEMA

All-causality EDEMA AEs were reported in 155 (56.4%) participants; 125 (45.5%) participants experienced treatment-related EDEMA AEs.

Two participants experienced all-causality EDEMA SAEs: 1 participant in the EXP-3 group experienced a Grade 3 SAE of peripheral swelling, which was not treatment-related, and resulted in permanent discontinuation from study and treatment; 1 participant in the EXP-3 group experienced a Grade 2 SAE of generalized oedema, and 2 episodes of SAEs of oedema peripheral (Grade 3 and Grade 2 respectively), which were all considered treatment-related.

Phase 2 PERIPHERAL NEUROPATHY

All-causality PERIPHERAL NEUROPATHY AEs were reported in 136 (49.5%) participants; 97 (35.3%) participants experienced treatment-related PERIPHERAL NEUROPATHY AEs. None of these events resulted in permanent discontinuation from treatment.

Three participants experienced PERIPHERAL NEUROPATHY SAEs; 1 participant in the EXP-5 cohort had a Grade 2 SAE of Peripheral sensory neuropathy, which was considered treatment-related and resulted in temporary discontinuation from treatment.

Phase 2 CNS Effects

- *Phase 2 COGNITIVE EFFECTS*: All-causality COGNITIVE EFFECTS AEs were reported in 86 (31.3%) participants; 67 (24.4%) participants experienced treatment-related events. Seven participants experienced serious COGNITIVE EFFECTS AEs in Phase 2, and 6 of these participants had Grade 3 COGNITIVE EFFECTS SAEs; 3 participants experienced serious COGNITIVE EFFECTS AEs that were treatment-related. One participant in the EXP-1 cohort experienced a Grade 3 SAE of

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Confusional state, which was considered treatment-related, and resulted in permanent discontinuation from treatment; 1 participant in the EXP-3 cohort experienced a Grade 3 SAE of Cognitive disorder, which was considered treatment-related, and resulted in permanent discontinuation from treatment.

- *Phase 2 MOOD EFFECTS*: All-causality MOOD EFFECTS AEs were reported in 68 (24.7%) participants; 44 (16.0%) participants experienced treatment-related events. None of these events were SAEs. One participant in the EXP-3 cohort experienced a Grade 2 NSAE of affect lability, which was considered treatment-related, and resulted in permanent discontinuation from both treatment and study.

- *Phase 2 SPEECH EFFECTS*: All-causality SPEECH EFFECTS AEs were reported in 26 (9.5%) participants; 21 (7.6%) participants experienced treatment-related events. None of these events were SAEs or resulted in permanent discontinuation from treatment or study.

- *Phase 2 PSYCHOTIC EFFECTS*: All-causality PSYCHOTIC EFFECTS AEs were reported in 23 (8.4%) participants; 19 (6.9%) participants experienced treatment-related events. None of these events were SAEs. One participant in the EXP-3 cohort experienced a Grade 2 NSAEs of hallucination, auditory and a Grade 2 NSAE of hallucination, visual, which were considered treatment-related, and resulted in permanent discontinuation from treatment.

Phase 2 Weight Gain

All-causality Weight gain AEs was reported in 77 (28.0%) participants; 66 (24.0%) participants experienced treatment-related events. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 2 VISION DISORDER

All-causality VISION DISORDER AEs were reported in 47 (17.1%) participants; 26 (9.5%) participants experienced treatment-related VISION DISORDER AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 2 Liver Function Tests Increased

All-causality AEs of Liver function tests increased were reported in 56 (20.4%) participants; 44 (16.0%) participants experienced treatment-related Liver function tests increased AEs. None of these events resulted in permanent discontinuation from treatment. Two participants experienced Liver function tests increased SAEs: 1 participant in the EXP-1 group experienced a Grade 3 SAE of ALT increased and a Grade 3 SAE of AST increased (both events were treatment-related); 1 participant in the EXP-4 cohort experienced a Grade 4 SAE of ALT increased and a Grade 4 SAE of AST increased (both events were not related to treatment).

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Phase 2 QT Interval Prolongation

All-causality QT interval prolongation AEs (PT = Electrocardiogram QT prolonged) were reported in 19 (6.9%) participants; 16 (5.8%) participants experienced treatment-related events. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 2 Interstitial Lung Disease/Pneumonitis

All-causality pneumonitis was reported in 7 (2.5%) participants; 2 (0.7%) participants experienced treatment-related events. Three participants experienced SAE of Pneumonitis; 1 participant in the EXP-4 cohort experienced a Grade 4 SAE of Pneumonitis that was determined to be related to lorlatinib treatment.

Phase 2 Atrioventricular Block

All-causality AV block AE was reported in 4 (1.5%) participants; 3 (1.1%) participants experienced treatment-related events. One participant in the EXP-6 cohort experienced a Grade 3 SAE of AV block complete, which was determined as not related to treatment.

Phase 2 Pancreatitis

All-causality pancreatitis was reported in 56 (20.4%) participants; 41 (14.9%) participants experienced treatment-related Pancreatitis. One participant in the EXP-4 cohort experienced a Grade 3 SAE of Pancreatitis, which was considered treatment-related, and resulted in temporary discontinuation and dose reduction of lorlatinib.

Phase 2 DDI Substudy AESIs:

Phase 2 DDI Substudy Hyperlipidemia Adverse Events: (ie. HYPERCHOLESTEROLEMIA and HYPERTRIGLYCERIDEMIA)

All-causality hyperlipidemia AEs included HYPERCHOLESTEROLEMIA reported in 30 (93.8%) participants (all of these participants experienced treatment-related events) and HYPERTRIGLYCERIDEMIA reported in 27 (84.4%) participants (all of these participants experienced treatment-related events). None of these events were SAEs or resulted in permanent discontinuation from treatment or study.

Phase 2 DDI Substudy EDEMA

All-causality EDEMA AEs were reported in 19 (59.4%) participants; 11 (34.4%) participants experienced treatment-related EDEMA AEs. None of these events were SAEs or resulted in permanent discontinuation from treatment or study.

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Phase 2 DDI Substudy PERIPHERAL NEUROPATHY

All-causality PERIPHERAL NEUROPATHY AEs were reported in 14 (43.8%) participants; 11 (34.4%) participants experienced treatment-related PERIPHERAL NEUROPATHY. None of these events were SAEs. One participant experienced 2 episodes of Grade 3 NSAEs of paraesthesia, the first one resulted in temporary discontinuation, and the second one resulted in permanent discontinuation from lorlatinib treatment and from study; neither episode was treatment-related.

Phase 2 DDI Substudy CNS Effects

- *Phase 2 DDI Substudy COGNITIVE EFFECTS*: All-causality COGNITIVE EFFECTS AEs were reported in 10 (31.1%) participants; 6 (18.8%) participants experienced treatment-related events) COGNITIVE EFFECTS AEs. One participant experienced a Grade 3 SAE of Confusional state, which was not related to treatment, and resulted in temporary discontinuation and dose reduction of lorlatinib; another participant experienced 2 episodes of Grade 3 SAE of Confusional state, which were not considered to be treatment-related, and 1 of the episodes resulted in temporary discontinuation from lorlatinib.

- *Phase 2 DDI Substudy MOOD EFFECTS*: All-causality MOOD EFFECTS AEs were reported in 7 (21.9%) participants; 4 (12.5%) participants experienced treatment-related events. None of these events were serious or resulted in permanent discontinuation from treatment.

- *Phase 2 DDI Substudy SPEECH EFFECTS*: Only 1 participant in the DDI substudy experienced SPEECH EFFECTS AEs (not treatment-related), including a Grade 1 SAE of Dysarthria.

- *Phase 2 DDI Substudy PSYCHOTIC EFFECTS*: All-causality PSYCHOTIC EFFECTS AEs were reported in 5 (15.6%) participants; 4 (12.5%) participants experienced treatment-related events. None of the PSYCHOTIC EFFECTS AEs were SAEs or resulted in permanent discontinuation from treatment or study.

Phase 2 DDI Substudy Weight Gain

All-causality Weight gain AEs was reported in 9 (28.1%) participants; 8 (25.0%) participants experienced treatment-related Weight gain AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 2 DDI Substudy VISION DISORDER

All-causality VISION DISORDER AEs were reported in 3 (9.4%) participants; none of the events were treatment-related. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

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Phase 2 DDI Substudy Liver Function Tests Increased

All-causality AEs of Liver function tests increased were reported in 3 (9.4%) participants; 2 (6.3%) participants experienced treatment-related Liver function tests increased AEs. None of these AEs were SAEs or resulted in permanent discontinuation from treatment.

Phase 2 DDI Substudy QT Interval Prolongation

No participant had QTc interval prolongation AEs in DDI substudy.

Phase 2 DDI Substudy Interstitial Lung Disease/Pneumonitis

One participant experienced 2 episodes of Grade 2 SAEs of Pneumonitis, which were considered treatment-related; 1 of the event resulted in temporary discontinuation and dose reduction, and the other resulted in permanent discontinuation from lorlatinib treatment.

Phase 2 DDI Substudy Atrioventricular Block

No participant had AV block AE in the DDI substudy.

Phase 2 DDI Substudy Pancreatitis

All-causality Pancreatitis was reported in 5 (15.6%) participants; 4 (12.5%) participants experienced treatment-related Pancreatitis. None of these events were SAEs or resulted in permanent discontinuation from treatment.

Clinical Laboratory Results

Phase 1 Clinical Laboratory Results:

Phase 1 Hematology

The most frequently reported all-grade hematology laboratory abnormality was anemia (51/54, 94.4%). Most participants had hematology baseline values of Grade 0 or Grade 1. No Grade 4 hematology shifts and minor Grade 3 shifts were observed in Phase 1.

Phase 1 Chemistry

The most frequently reported chemistry laboratory abnormality was creatine increased (44/54, 81.5%). Most participants had chemistry baseline values of Grade 0 or Grade 1. Very few of shifts to Grade 3 or Grade 4 were observed. One participant had abnormal liver test values meeting the criteria of potential Hy's Law case.

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Phase 1 Other Laboratory Results

The most frequently reported other laboratory abnormalities were cholesterol high (45/50, 90.0%) and hypertriglyceridemia (42/49, 85.7%). Most participants had other laboratory baseline values of Grade 0 or Grade 1. Shifts to Grade 3 post-baseline occurred for 5 participants for cholesterol high, 7 participants for hypertriglyceridemia, 1 participant for INR increased, 1 participant for prothrombin time. Shifts to Grade 4 post-baseline occurred for 3 participants for cholesterol high, 1 participant for hypertriglyceridemia.

Phase 2 Clinical Laboratory Results:

Phase 2 Hematology

The most frequently reported all-grade hematology laboratory abnormality was anemia (218/273, 79.9%). Most participants had hematology baseline values of Grade 0 or Grade 1. Shifts to Grade 3 post-baseline occurred for 14 participants for anemia, 15 participants for lymphocyte count decreased, 2 participants for white blood cell decreased. Minor shifts to Grade 4 were observed.

Phase 2 Chemistry

The most frequently reported chemistry laboratory abnormalities were aspartate aminotransferase increased (139/272, 51.1%), creatinine increased (209/273, 76.6%), hyperglycemia (185/273, 67.8%), and hypoalbuminemia (180/271, 66.4%). Most participants had chemistry baseline values of Grade 0 or Grade 1. Minor shifts to Grade 3 or Grade 4 were observed. One participant had abnormal liver test values meeting the criteria of potential Hy's Law case.

Phase 2 Other Laboratory Results

The most frequently reported other laboratory abnormalities were cholesterol high (267/272, 98.2%) and hypertriglyceridemia (261/272, 96.0%). Most participants had other laboratory baseline values of Grade 0 or Grade 1. Shifts to Grade 3 post-baseline occurred for 1 patient for activated partial thromboplastin time prolonged, 50 participants for cholesterol high, 43 participants for hypertriglyceridemia, and 1 participant for INR increased. Shifts to Grade 4 post-baseline occurred for 6 participants for cholesterol high, and 10 participants for hypertriglyceridemia.

Phase 2 DDI Substudy Clinical Laboratory Results:

Phase 2 DDI Substudy Hematology

The most frequently reported all-grade hematology laboratory abnormality was anemia (25/32, 78.1%). Most participants had hematology baseline values of Grade 0 or Grade 1. Very few shifts to Grade 3 post-baseline occurred. No Grade 4 abnormal values were reported.

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Phase 2 DDI Substudy Chemistry

The most frequently reported chemistry laboratory abnormalities were creatinine increased (20/32, 62.5%), hyperglycemia (23/32, 71.9%), and hypoalbuminemia (18/32, 56.3%). Most participants had chemistry baseline values of Grade 0 or Grade 1. Very few of shifts to Grade 3 were observed. No Grade 4 abnormal values were reported. No participant met the criteria of a potential Hy's law case.

Phase 2 DDI Substudy Other Laboratory Results

The most frequently reported (>50% participants) other laboratory abnormalities were cholesterol high (31/32, 96.9%), hypertriglyceridemia (31/32, 96.9%). Most participants had other laboratory baseline values of Grade 0 or Grade 1. Minor shifts to Grade 3 were observed. No Grade 4 abnormal values were reported.

Other Safety Results

Phase 1 Other Safety Results:

Phase 1 Vital Signs and Body Weight

A few participants had vital signs and body weight data meeting categorical values; 6 participants experienced all-causality AE of Hypertension, in which 2 participants had treatment-related AE of Hypertension; 15 participants experienced all-causality AE of Weight increased, in which 12 participants had treatment-related AE of Weight increased.

Phase 1 Electrocardiograms

Among 54 participants in Phase 1 who had both baseline and post-baseline QTcF interval measurements, 44 participants had maximum QTcF interval <450 msec at post-baseline, none of the Phase 1 participants had maximum QTcF interval ≥500 msec post baseline. Electrocardiogram QT prolonged was reported as AE in 4 (7.4%) participants.

Phase 1 Left Ventricular Ejection Fraction

In Phase 1, 15 (27.8%) out of 54 participants had a maximum decrease of ≥20% from baseline in LVEF, including 5 (29.4%) out of 17 participants in the 100 mg QD dosing cohort. Four (7.4%) participants had all-causality Ejection fraction decreased (only 1 participant had treatment-related event).

Phase 2 Other Safety Results:

Phase 2 Vital Signs and Body Weight

Among 270 participants in Phase 2 SAS with both baseline and post-baseline BP data, 45 (16.7%) participants had ≥40 mmHg increase from baseline and 2 (0.7%) participants had

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≥60 mmHg increase from baseline in sitting systolic BP; 86 (31.9%) participants had ≥20 mmHg increase from baseline and 8 (3.0%) participants had ≥40 mmHg increase from baseline in sitting diastolic BP. Thirty-five participants experienced all-causality AE of Hypertension, in which 15 participants had treatment-related AE of Hypertension.

Among 262 participants in Phase 2 SAS with both baseline and post-baseline weight data, 80 (30.5%) participants had maximum ≥10% and <20% increase from baseline in weight, and 58 (22.1%) participants had maximum ≥20% increase from baseline in weight. Seventy-seven participants experienced all-causality AE of Weight increased, in which 66 participants had treatment-related AE of Weight increased.

Phase 2 Electrocardiograms

Among 275 participants in Phase 2 who had both baseline and post-baseline QTcF interval measurements, 210 participants had maximum QTcF interval <450 msec at post-baseline, 3 participants had maximum QTcF interval ≥500 msec post baseline. Electrocardiogram QT prolonged was reported as AE in 19 (6.9%) participants.

Phase 2 Left Ventricular Ejection Fraction

In Phase 2, 41 (14.9%) out of 275 participants had a maximum decrease of ≥20% from baseline in LVEF. Eleven (4.0%) participants had the AE of Ejection fraction decreased, and 8 (2.9%) had treatment-related events.

Phase 2 DDI Substudy Other Safety Results:

Phase 2 DDI Substudy Vital Signs and Body Weight

Among 32 participants in the SAS of DDI substudy with both baseline and post-baseline BP data, 4 (12.5%) participants had ≥40 mmHg increase from baseline in sitting systolic BP, 7 (21.9%) participants had ≥20 mmHg increase from baseline in sitting diastolic BP, no participant had increase from baseline ≥60 mmHg in sitting systolic BP or increase from baseline ≥40 mmHg in sitting diastolic BP. Two participants experienced all-causality AE of Hypertension, and both had treatment-related AE of Hypertension.

Among 32 participants in the SAS of DDI substudy with both baseline and post-baseline weight data, 9 (28.1%) participants had maximum ≥10% and <20% increase from baseline in weight, and 3 (9.4%) participants had maximum ≥20% increase from baseline in weight. Nine participants experienced all-causality AE of Weight increased, in which 8 participants had treatment-related AE of Weight increased.

Phase 2 DDI Substudy Electrocardiograms

Among 275 participants in Phase 2 who had both baseline and post-baseline QTcF interval measurements, 210 participants had maximum QTcF interval <450 msec at post-baseline,

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3 participants had maximum QTcF interval ≥500 msec post baseline. Electrocardiogram QT prolonged was reported as AE in 19 (6.9%) participants.

Phase 2 DDI Substudy Left Ventricular Ejection Fraction

In the DDI substudy, 2 (6.3%) out of 32 participants had a maximum decrease of ≥20% from baseline in LVEF. One participant had a Grade 3 NSAE of Ejection fraction decreased, which was considered treatment-related, and resulted in temporary discontinuation and dose reduction of lorlatinib.

Biomarker Results:

Phase 1 Biomarker Results

Plasma CNA: In Phase 1, 40 participants with ALK+ NSCLC had plasma samples available for the analysis at baseline. No ALK kinase domain mutation was detected in 26 (65.0%) participants; at least 1 ALK kinase domain mutation was detected in 14 (35.0%) participants.

Tumor Tissue Analysis: In Phase 1, 40 participants with ALK+ NSCLC had tumor tissue samples available for the analysis at baseline. No ALK kinase domain mutation was detected in 23 (57.5%) participants; at least 1 ALK kinase domain mutation was detected in 7 (17.5%) participants; tumor tissue ALK mutation was not analyzable for 10 (25.0%) participants.

Phase 2 Biomarker Results

In participants who have failed 1 or more second-generation ALK TKIs, lorlatinib showed greater efficacy in participants with ALK mutations (including ALK G1202R) compared with participants without ALK mutations.

Plasma CNA: In Phase 2 participants with ALK+ NSCLC and plasma samples available for the analysis at baseline, no ALK kinase domain mutation was detected in 28/30 (93.3%) participants in EXP-1, 19/26 (73.1%) participants in EXP-2, 49/59 (83.1%) participants in EXP-3, 42/61 (68.9%) participants in EXP-4, and 31/46 (67.4%) participants in EXP-5. At least 1 ALK kinase domain mutation was detected in 6/26 (23.1%) participants in EXP-2, 8/59 (13.6%) participants in EXP-3, 17/61 (27.9%) participants in EXP-4, and 14/46 (30.4%) participants in EXP-5.

Tumor Tissue Analysis: In Phase 2 participants with ALK+ NSCLC and tumor tissue samples available for the analysis at baseline, no ALK kinase domain mutation was detected in 27/29 (93.1%) participants in EXP-1, 19/26 (73.1%) participants in EXP-2, 46/58 (79.3%) participants in EXP-3, 38/63 (60.3%) participants in EXP-4, and 21/44 (47.7%) participants in EXP-5. At least 1 ALK kinase domain mutation was detected in 7/26 (26.9%) participants in EXP-2, 8/58 (13.8%) participants in EXP-3, 12/63 (19.0%) participants in EXP-4, and 13/44 (29.5%) participants in EXP-5.

CLINICAL STUDY REPORT SYNOPSIS

Patient-Reported Outcomes Results:

The majority of participants had clinically meaningful improvement (at least 10-point increase in QOL/functioning scales, or at least 10-point decrease in symptom scales) or stable scores (<10-point change) for each of the QOL, functioning or symptom domains of EORTC QLQ-C30 and EORTC QLQ-LC13.

Conclusions:

Efficacy

- Lorlatinib treatment provided a clinically meaningful benefit in patients with advanced ALK-positive or ROS1-positive NSCLC as evidenced by rapid, deep, and durable systemic and intracranial responses.

- Across expansion cohorts, in ALK-positive NSCLC patients who were treatment-naïve or had received up to 3 prior ALK inhibitors, ORRs as assessed by independent review ranged between 37.0% and 90.0%, which numerically exceeded historical controls in comparable segments.

- Across expansion cohorts, lorlatinib produced rapid, deep, and durable intracranial responses consistent with its ability to cross the blood-brain barrier with ORRs as assessed by independent central review ranging from 43.2% to 75.0%, including complete intracranial responses, irrespective of prior lines of therapy, which numerically exceeded historical controls in comparable segments.

- Lorlatinib demonstrated antitumor activity across a variety of ALK kinase domain resistance mutations, including the difficult-to-treat G1202R/G1202del mutations. Lorlatinib also evoked tumor responses in tumors resistant to prior ALK TKIs that did not contain ALK resistance mutations.

- Lorlatinib treatment showed improvement from baseline in global quality of life that was maintained over time. In addition, there was improvement in physical, emotional, social, and role functioning, while cognitive functioning neither improved nor worsened. Improvements were shown in appetite loss and key lung cancer symptoms such as pain, dyspnea, cough, and fatigue. An increase in peripheral neuropathy was noted.

Safety

- Lorlatinib was generally tolerable and, when needed, AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy.

- Lorlatinib 100 mg QD was established as the RP2D in patients with advanced ALK-positive and ROS1-positive NSCLC.

CLINICAL STUDY REPORT SYNOPSIS

Overall

In summary, lorlatinib conferred a clinically meaningful benefit in patients with advanced ALK- and ROS1-positive NSCLC across a range of treatment with prior ALK inhibitors and/or chemotherapies, including in treatment settings with a high unmet medical need. Lorlatinib was generally tolerable, as AEs were primarily mild to moderate in severity, and manageable as rates of permanent discontinuations due to AEs were low and could be managed by dosing interruption, dose reduction, and/or standard supportive medical therapy.

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GENERIC DRUG NAME AND/OR COMPOUND NUMBER

Lorlatinib / PF-06463922

PROTOCOL NO.:

B7461001

PROTOCOL TITLE:

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

Study Centers:

A total of 47 centers randomized patients into the study: Australia (2), Canada (3), France (4), Germany (1), Hong Kong (1), Italy (4), Japan (11), Korea (1), Singapore (2), Spain (4), Switzerland (2), Taiwan (1), and United States (US) (11).

Study Initiation Date and Primary Completion or Final Completion Dates:

08 January 2014 (First Patient First Visit) to 15 March 2017 (Primary Completion Date).
The planned study completion date (Last Patient Last Visit) is 10 April 2018.

Phase of Development:

Phase 1/2

Study Objectives:

Phase 1 Portion of Study

Primary Objective:

- The primary objective of the Phase 1 portion of the study was to assess safety and tolerability of lorlatinib as a single agent at increasing dose levels in patients with advanced anaplastic lymphoma kinase (ALK) -positive or advanced ROS1-positive non-small cell lung cancer (NSCLC) in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D).

Secondary Objectives:

- To evaluate the overall safety and tolerability of lorlatinib.

- To evaluate the single- and multiple-dose pharmacokinetic (PK) profiles of single-agent lorlatinib.

- To detect early signs of cognitive dysfunction.

- To evaluate patient-reported outcomes (PRO) of global Quality of Life (QOL) functioning, and the impact of lorlatinib on disease/treatment-related symptoms of lung cancer.

- To evaluate the potential of single-agent lorlatinib to cause cytochrome P450 (CYP) 3A inhibition/induction using midazolam (MDZ) as a probe.

- To characterize the effects of single-agent lorlatinib on the QT interval corrected for heart rate (QTc).

- To evaluate tumor and blood-based molecular markers of response and resistance to single-agent lorlatinib.

- To characterize the effect of food on lorlatinib.

- To evaluate preliminary anti-tumor activity of single-agent lorlatinib in patients with advanced ALK-positive NSCLC or advanced ROS1-positive NSCLC.

- To evaluate response to prior systemic therapies.

Phase 2 Portion of Study

Primary Objective

- The primary objective of the Phase 2 portion of the study was to evaluate overall (intra- and extra-cranial) and intra-cranial anti-tumor activity of single-agent lorlatinib at RP2D in patients with advanced ALK-positive NSCLC and advanced ROS1-positive NSCLC.

Secondary Objectives

- To confirm the safety and tolerability of single-agent lorlatinib at the RP2D.

- To confirm single- and multiple-dose PK profiles of single-agent lorlatinib at the RP2D.

- To assess secondary measures of clinical efficacy.

- To detect early signs of changes in mood, cognitive function, or suicidal ideation and behavior (SIB).

- To evaluate PRO of global QOL, functioning and the impact of lorlatinib on disease/treatment-related symptoms of lung cancer at the RP2D.

- To further evaluate the effects of single-agent lorlatinib at the RP2D on the QTc interval.

- To further evaluate tumor and blood-based molecular markers of response and resistance to single-agent lorlatinib at the RP2D.

- To evaluate the safety and efficacy of single-agent crizotinib following lorlatinib in treatment-naïve patients with advanced ALK-positive NSCLC.

- To evaluate response to prior systemic therapies.

METHODS

Study Design:

This is an ongoing Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamics and anti-cancer efficacy exploration study of lorlatinib as a single agent in patients with advanced ALK-positive or advanced ROS1-positive NSCLC. This clinical study consisted of 2 parts, Phase 1 and Phase 2. The Phase 1 portion of the study estimated the MTD for single-agent lorlatinib in dose escalation cohorts in patients with advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic central nervous system (CNS) metastases. The Phase 1 portion was also the basis for selecting the RP2D. The Phase 2 portion of the study employed single-agent lorlatinib at the RP2D identified in Phase 1 and was designed to evaluate the anti-cancer activity of lorlatinib in multiple subpopulations of patients with advanced ALK-positive NSCLC and in patients with advanced ROS1-positive NSCLC based on prior type and lines of therapy received.

Phase 1 Dose Escalation

In the Phase 1 portion, lorlatinib was to be evaluated at escalating doses of 10, 25, 50, 75, 100, 150, 200, 250, 300, and 400 mg/once daily (QD), depending on toxicities observed. The goal of the Phase 1 portion was to determine the dose of lorlatinib that was the closest to but no higher than a 33% probability of a dose-limiting toxicity (DLT). DLT definitions were defined as any of the following adverse events (AEs) occurring in the first cycle of treatment (21 days) which were attributable to lorlatinib:

Hematologic:

- Grade 4 neutropenia lasting >7 days.

- Febrile neutropenia (defined as absolute neutrophil count [ANC] $<1000/mm^3$ with a single temperature of ≥38.3°C [≥101°F) or a sustained temperature of ≥38°C [≥100.4°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 (eg, anti-emetics, anti-diarrheals).
- Symptomatic Grade ≥3 QTc prolongation (QTc ≥501 msec on at least 2 separate ECGs), or asymptomatic Grade ≥3 QTc prolongation that has been confirmed by repeat testing and re-evaluation by a qualified person, and persists after correction of reversible causes such as electrolyte abnormalities or hypoxia.
- ≥20% decrease in Left Ventricular Ejection Fraction (LVEF) compared to baseline echocardiogram or Multi Gated Acquisition Scan (MUGA) using the same method.

Others:

- Failure to deliver at least 16 out of the 21 prescribed daily total doses (approximately 75% planned dose for Cycle 1) due to toxicities attributable to study drug.
- Failure to restart dosing after 21 days (1 cycle) delay due to toxicities attributable to study drug.

Twice daily (BID) dosing was not originally planned, but was also tested to support identification of the RP2D.

Severity of AEs was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

<u>Phase 2</u>

The Phase 2 portion enrolled patients at the RP2D identified in Phase 1 and included patients from the following subpopulations based on mutation status and prior therapies received:

- Expansion (EXP)-1: Treatment-naïve patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases. Additionally, EXP-1 patients were eligible to receive single-agent crizotinib following treatment with lorlatinib if allowed per local guidelines and appropriate per investigator discretion.
- EXP-2: Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after only crizotinib therapy. No prior chemotherapy was allowed in the metastatic setting.
- EXP-3: Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after crizotinib therapy and 1 or 2 prior regimens of chemotherapy given before or after crizotinib therapy, or patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after

1 ALK inhibitor therapy other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting.

Note: EXP-3 was further subgrouped into EXP-3A and EXP-3B. EXP-3A included patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after crizotinib therapy and 1 or 2 prior regimens of chemotherapy given before or after crizotinib therapy and EXP-3B included patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 1 ALK inhibitor therapy other than crizotinib with or without any number of prior chemotherapy regimens in any disease setting.

- EXP-4: Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 2 prior lines of ALK inhibitor therapies. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting.

- EXP-5: Patients with advanced ALK-positive NSCLC with or without asymptomatic CNS metastases relapsing after 3 prior lines of ALK inhibitor therapies. Patients were permitted to have any number of prior chemotherapy regimens in any disease setting.

- EXP-6: Patients with advanced ROS1-positive NSCLC who were treatment naïve or have had any number of prior cancer therapies, with or without asymptomatic CNS metastases.

The schedule of activities and PK assessments for Phase 1 and Phase 2 is detailed in Table 1 and Table 2 (Phase 1 portion), Table 3 and Table 4 (Phase 2 portion).

Table 1. Schedule of Activities - Phase 1 Portion

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			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[a] (≤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[aa]**	**Follow- Up[z]**
Visit Window (days)	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Informed consent[b]	X									
Tumor history	X									
Medical history	X									
Physical examination including weight	X	(X)	(X)			X	X	X		
Baseline signs and symptoms[c]		X	X							
Height	X									
Weight	X		X			X	X	X		
Vital signs[d]		X	X	X	X	X	X	X	X	
Performance status[e]	X		X			X	X	X	X	
Laboratory										
Hematology[f]	X		(X)		X	X	X	X	X	
Blood chemistry[g]	X		(X)		X	X	X	X	X	
Coagulation[h]	X		(X)						X	
Lipids[i]	X		(X)		X	X	X	X	X	
Urinalysis[j]	X		(X)						X	
Pregnancy test[k]	X	X	(X)			X	X	X	X	
(12-lead) ECG[l]	X	X	X	X	X	X	X		X	
LVEF assessments (echocardiogram or MUGA)[bb]	X					X	X	Every 4 Cycles	X	
Registration and Treatment										
Registration[m]		X								
Lorlatinib treatment[n,o]		X	Once a day or twice a day, continuously							
MDZ treatment for patients participating in the MDZ sub-study[p]		X (MDZ only)			X					
Tumor Assessments										
CT and MRI scan or equivalent[q]	X						X and then every 6 weeks ±1 week	Every 12 weeks ±1 week	(X)	

Table 1. Schedule of Activities - Phase 1 Portion (Continued)

Page 2 of 5

			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[a] (≤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[aa]**	**Follow- Up[z]**
Visit Window (days)	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±7**
Cerebrospinal fluid[r]	X						X	X		
Other Clinical Assessments										
AEs[s]		X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[t]	X		X			X	X	X		X
EORTC QLQ-C30, QLQ-LC13[y]		X				X	X	X	X	
Neurological examination[cc]	X	Only as clinically indicated								
Survival follow-up										X
Other Samples										
Archival tumor tissue specimen[u]	X									
De novo tumor specimens[v]	'X'								'X'	
Blood specimens for CNA profiling[w]	X								X	
Banked biospecimen[x]	X									

Footnotes (X) refer to specific footnote when the measurement could have been optional/repeat measurement could have not been required.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; CAP = chest abdomin pelvis; cfDNA = circulating free DNA; cfRNA = circulating free RNA; C_{max} = maximum plasma concentration; CNA = circulating nucleic acid; CNS = central nervous system; CRF = case report form; CSF = cerebrospinal fluid; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DNA = dehydroxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; EOT = End of Treatment; FFPE = formalin-fixed paraffin embedded; FNA = fine needle aspiration; IEC = Institutional Ethics Committee; IRB = Institutional Review Boards; K_2EDTA = dipotassium ethylenediamine tetra acetic acid; LVEF = left ventricular ejection fraction; MDZ = midazolam; MRI = Magnetic Resonance Imaging; MUGA = multiple gated acquisition; N/A = not applicable; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OLQ-C30 = Quality of Life Questionnaire Core-30; OLQ-LC13 = Quality of Life Questionnaire Supplement Module for Lung Cancer (LC13); PE = pleural effusion; PK = pharmacokinetic(s); QTc = QT corrected for heart rate; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; ROS1-positive = ROS oncogene 1 positive; SAE = serious adverse event.

a. Screening: to be obtained within 28 days prior to registration.

b. Informed consent: to be obtained prior to undergoing any study-specific procedures.

Table 1. Schedule of Activities - Phase 1 Portion (Continued)

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c. Baseline signs and symptoms: patients were asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening of baseline signs and symptoms were recorded on the AEs CRF page.
d. Vital signs: blood pressure and pulse rate were recorded in sitting position.
e. Performance status: use ECOG.
f. Hematology: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date.
g. Blood chemistry: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date.
h. Coagulation: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date.
i. Lipids: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date.
j. Urinalysis: dipstick was acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date.
k. Serum pregnancy test: for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, was performed on 2 occasions prior to starting study therapy - once at the start of Screening and once at the baseline visit, immediately before investigational product administration. Adequate contraception (2 forms) was initiated after the first negative pregnancy test was obtained at Screening. Pregnancy tests were also routinely repeated at every cycle during the active treatment period (every other cycle beyond 18 months), at the end of study therapy and additionally whenever 1 menstrual cycle was missed or when potential pregnancy was otherwise suspected. Additional pregnancy tests could also be undertaken if requested by IRB/IECs or if required by local regulations.
l. Triplicate 12-lead ECGs: at each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine mean QTc interval. ECGs were collected as follows: 1) at Screening, 2) Day -7 (lead-in) after single-dose administration at pre-dose, at projected C_{max} (1 hour), and at 4 hours post dose, 3) Cycle 1 Day 1, Day 8, and Day 15 at pre-dose (0 hour) and 1 hour post dose. For Cycles 2-5, 1 hour post dose (time matched with PK), and 4) End of Treatment. In addition to these time points, ECGs were repeated as clinically indicated. Additional ECG time points could be included based on the emerging data.
When coinciding with blood sample draws for PK, ECG assessment were performed prior to blood sample collection such that the blood sample was collected at the nominal time. If the mean QTc was prolonged (≥501 msec), the ECGs were re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs could be performed as clinically indicated. All ECG assessments were matched with a PK sample.
m. Registration: patient number and dose level allocation operated by Pfizer Inc. Registration was within 2 days prior to lead-in single dose as appropriate.
n. Trial treatment.
o. Lead-in lorlatinib dose: a single dose of lorlatinib was given on Day –7 (lead-in period) for all patients in the Phase 1 except the patients who were scheduled for the MDZ interaction substudy. The timing of the lead-in dose was allowed to be modified based on PK data obtained.
p. MDZ treatment: for patients who were scheduled for the MDZ interaction sub-study only. A single 2-mg oral dose of MDZ was given on Day –7 and Cycle 1 Day 15. On Cycle 1 Day 15, MDZ was given concurrently with lorlatinib. Patients participating in the MDZ substudy did not receive any lead-in dose of lorlatinib on Day -7.

Table 1. Schedule of Activities - Phase 1 Portion (Continued)

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q. Tumor assessment: tumor assessments included all known or suspected disease sites. CT or MRI scans of CAP and MRI of the brain were performed at Screening. Gadolinium contrast enhanced MRI was used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm - 10 mm in size, 5 mm for lesions greater than 10 mm. Bone scans (or bone MRI if preferred by investigator) were performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases were observed at baseline. For all tumor assessments, the method of assessment that was used at baseline was required to be the same method used throughout the study. For patients who were without documented disease progression, CT and MRI scans were done every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ± 1 week beyond 18 months, and responses were confirmed ≥4 weeks later (RECIST version 1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment were done every 6 weeks ±1 week up to approximately 18 months, and then every 12 weeks ±1 week beyond 18 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses were confirmed ≥4 weeks later (RECIST version 1.1) until documented progression of disease. For patients who had documented disease progression but were still receiving lorlatinib, CT and MRI scans were done according to local institutional standard of care. Every effort was made to maintain the assessment scheduling relative to Cycle 1 Day 1 especially if there were dosing cycle interruptions due to toxicities. Tumor assessment was repeated at the end of treatment visit if more than 6 weeks (more than 12 weeks beyond 18 months) had passed since the last evaluation. CSF sampling in patients with asymptomatic leptomenigeal disease/carcinomatous meningitis were performed at baseline, and if clinically safe and feasible, further CSF cytology was to be performed on study every 2 cycles of treatment (every 12 weeks beyond 18 months) to assess disease.

r. CSF: CSF was mandatory for patients who had asymptomatic radiologically suspected leptomeningeal disease or carcinomatous meningitis but negative spinal fluid. CSF was collected at baseline and on study to determine lorlatinib concentrations. A blood sample for PK analysis was also collected at approximately the same time as the post dose CSF sample.

s. AE assessments: AEs were documented and recorded at each visit using NCI CTCAE version 4.03. Patients were followed for AEs for 28 days after the last treatment administration or until all drug related toxicities had resolved, whichever was later; or earlier than 28 days should the patient have had commenced another anti-cancer therapy in the meantime. For SAEs, the active reporting period to the Sponsor or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period had ended were reported to the Sponsor if the investigator became aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to study drug were reported to the Sponsor.

t. Concomitant medications and non-drug supportive interventions: all concomitant medications and non-drug supportive interventions were recorded in the CRF.

u. Archival tumor tissue specimen: all patients were provided a FFPE archival tumor specimen, specifically a FFPE tissue block that contained sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that were 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block was not submitted. If an archival tumor tissue sample was not available, a de novo tumor specimen was obtained. Specimens were sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to lorlatinib (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1-positive NSCLC patients specimens were sent to the Sponsor-designated central laboratory for ROS1 status confirmation.

v. De novo tumor specimens: optional de novo tumor biospy at Screening and at the time of progression was encouraged. If presented, PE cell pellet was substituted for tumor core biopsy, as appropriate. FNA samples (2-3 pathes prepared as FFPE cell block) were not preferred and were only performed in the event a biopsy or PE cell pellet was not safe or feasible. If local country regulations did not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) were acceptable. In all cases, this specimen was provided in addition to the archival tumor tissue specimen that was required for enrollment. Tissue specimens from all patients were used for additional biomarker analyses.

w. Blood specimens for CNA profiling: 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, cfDNA or cfRNA) were collected at Screening and at EOT.

Table 1. Schedule of Activities - Phase 1 Portion (Continued)

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x. Banked biospecimen: unless prohibited by local regulations, a blood specimen (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, was collected at Screening.

y. EORTC QLQ-C30 and QLQ-LC13: Patients were required to complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points prior to dosing. At Day -7 (lead- in period) site staff (eg, site coordinators) instructed patients that the assessment should be completed without help from friends or family members and also recommend that this assessment was to be completed in the morning. All scheduled assessments of the EORTC QLQ-C30 and QLQ-LC13 were not allowed to be taken home and were required to be completed in the clinic prior to any other study or medical procedures.

z. Follow-up: at least 28 days, and no more than 35 days after discontinuation of treatment patients returned to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment were continued to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement was expected. Patients discontinuing treatment for reasons other than progression of disease were continued to perform tumor assessments until progression disease or a new anti-cancer therapy was commenced. Survival follow-up every 2 months after progression disease or new anti-cancer therapy had commenced were performed (telephone contact was acceptable).

aa. EOT visit: obtained these assessments if not completed in the last week (last 6 weeks for tumor assessments if during the first 18 months, then last 12 weeks if beyond month 18).

bb. LVEF assessments: echocardiogram or MUGA was performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every 2 cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.) up to approximately 18 months, and then every 4 cycles thereafter, and at the EOT visit (±2-day time window applicable at the discretion of the investigator). The same method was used at each time point.

cc. Neurological examination: a neurological examination by a licensed neurologist was conducted in at least 12 patients in Phase 1 at baseline and, if clinically indicated, at any time point thereafter.

Table 2. Pharmacokinetic Assessments - Phase 1 Portion

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			CYCLE 1 (21 days)			CYCLE 2-5 (21 days)
Protocol Activity	**Screen (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**
Visit Window	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**
All patients						
Plasma sampling for full lorlatinib PK in patients not participating in the MDZ or the food effect substudy[a]		X	X	X	X	X
MDZ Substudy						
Plasma sampling for full lorlatinib PK in patients participating in the MDZ substudy[b]			X	X	X	X
Plasma sampling for full MDZ PK[c]		X			X	
Food Effect Substudy						
Blood sample for lorlatinib in food effect study[d]		X	X	X	X	X
Blood sample for lorlatinib metabolite profiling[e]					X	
24-hour urine collection for lorlatinib PK[f]					X	
All Patients						
Urine sample for 6 beta-hydroxycortisol/cortisol (6β-OHC/C) ratio[g]		X	X	X	X	X (Cycle 2 only)
4β-hydroxycholesterol/ Cholesterol blood sample[h]		X	X	X	X	X
Cerebrospinal fluid for PK concentration (optional)[i]					Anytime at steady state	

Abbreviations: 6β-OHC/C = 6 beta-hydroxycortisol/cortisol; BID = twice daily; CSF = cerebrospinal fluid; ECG = electrocardiogram; MDZ = midazolam; N/A = not applicable; PK = pharmacokinetic(s).

Table 2. Pharmacokinetic Assessments - Phase 1 Portion (Continued)

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a. Lorlatinib PK sampling: Blood samples were collected for PK sampling on the following days: 1) Day-7 (lead-in) pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96 and 120 hours post dose (2 samples between 48 to 120 hours), 2) Cycle 1 Day 1 and Day 8 at pre-dose, 1 hour and 4 hours post dose, 3) Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hours. For patients on BID dosing, the 24-hour time point sample was not required to be collected, 4) Day 1 of Cycles 2 to 5: pre-dose and 1 hour post dose (time matched with ECG).

b. Lorlatinib PK sampling for patients who participated in the MDZ interaction substudy: Blood samples were collected on Cycle 1 Day 1 and Cycle 1 Day 15 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hours post dose. On Cycle1 Day 8, a blood sample was collected at pre-dose, 1 and 4 hours post dose. Cycles 2-5: pre-dose and 1 hour (time matched with ECG).

c. MDZ PK samples: In MDZ interaction substudy, a PK profile of MDZ was collected after a single oral MDZ dose on Day –7 (lead-in period) and Cycle 1 Day 15 at the following time points: 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 9, and 24 hours post dose.

d. Food-effect substudy: PK samples were collected on Day -7 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, 24, 48, 72, 96, and 120 hours post dose (2 samples between 48 to 120 hours) and Cycle 1 Day 1 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hours post dose. For patients on BID dosing, the 24 hour time point sample was not required to be collected. Each patient served as their own control in which lorlatinib was administered in the morning under either "fed" or "fasted" conditions on Day -7 and Day 1 of Cycle 1. PK samples after Cycle 1 Day 1 followed same schedule as footnote a. The testing order for fed versus fasted conditions was as follows: The first half of the patients in this substudy were tested under fed followed by fasted conditions and the second half of the patients were tested under fasted followed by fed conditions.

e. Blood sample for lorlatinib metabolite profiling: Metabolite profiling was conducted in the food effect cohort for all patients. Blood samples were collected at steady-state on Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9 and 24 hours post dose.

f. Urine for lorlatinib PK: Urine was collected for 24 hours after lorlatinib dosing on Cycle 1 Day 15 from food effect cohorts over the following intervals: 0 to 4 hours, 4 to 12 hours and 12 to 24 hours post dose. For patients on BID dosing, 12-24-hour post dose urine collection was not required.

g. Urine sample for 6β-OHC/C ratio: Morning urine sample (pre-dose) was collected on Day -7, Day 1 of Cycle 1, Day 8 and Day 15 of Cycle 1 and Day 1 of Cycle 2.

h. Blood sample for 4β-hydroxycholesterol/cholesterol: Blood sample was collected at pre-dose on Day -7, Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycles 2 to 5 Day 1.

i. CSF Sample (optional): If a patient underwent a lumber puncture, a sample of CSF was to be collected for exploratory analysis of lorlatinib concentration, if possible. If this CSF sample was collected, a blood sample for PK analysis was also to be collected at approximately the same time as the CSF sample.

Table 3. Schedule of Activities - Phase 2 Portion

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			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[a] (≤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[aa]**	**Follow- Up[z]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2 days**	**±2**	**±7**
Informed consent[b]	X									
Tumor history	X									
Medical history	X									
Physical examination	X	(X)	(X)			X	X	X		
Baseline signs and symptoms[c]		X	X							
Height	X									
Weight	X		X			X	X	X		
Vital signs[d]			X	X	X	X	X	X	X	
Performance status[e]	X		X			X	X	X	X	
Contraceptive check (as appropriate)		(X)	X			X	X	X		
Laboratory										
Hematology[f]	X		(X)		X	X	X	X	X	
Blood chemistry[g]	X		(X)		X	X	X	X	X	
Lipids[h]	X		(X)		X	X	X	X	X	
Hypogonadism (male patients)[i]	X				X	X	Cycle 5 Day 1 and every 4 cycles thereafter	Every 4 Cycles	X	
Coagulation[j]	X		(X)						X	
Urinalysis[k]	X		(X)						X	
Pregnancy test[l]	X	X	(X)			X	X	X	X	
(12-lead) ECG[m]	X	X	X	X	X	X	X (up to Cycle 5)		X	
LVEF assessments (echocardiogram or MUGA)[bb]	X					X	X	Every 4 Cycles	X	
Registration and Treatment										

Table 3. Schedule of Activities - Phase 2 Portion (Continued)

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			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[a] (≤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[aa]**	**Follow- Up[z]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**± 2 days**	**±2**	**±7**
Registration[n]		X	(X)							
Lorlatinib treatment[o,p]		X	Once a day continuously							
Tumor Assessments										
CT and MRI scan or equivalent[q]	X						X and then every 6 weeks ±1 week	Every 12 weeks ± 1	(X)	(X)
CSF if leptomenigeal/carcinomatous meningitis disease is present[r]	X									
Other Clinical Assessments										
AEs[s]		X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[t]	X		X			X	X	X		X
EORTC QLQ-C30, QLQ-LC13[y]		X	X			X	X	X	X	
Cognitive assessment[cc]	X	X	X			X	X up to Cycle 6 and then Day 1 of every other cycle	X	X	
Mood assessment[dd]		X	X			X	X up to Cycle 6 and then Day 1 of every other cycle	X	X	
Suicidal ideation and behavior[ee]		X	X			X	X up to Cycle 6 and then Day 1 of every other cycle	X	X	
Survival Follow-up										X
Other Samples										

Table 3. Schedule of Activities - Phase 2 Portion (Continued)

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			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[a] (≤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[aa]**	**Follow- Up[z]**
Visit or Assessment Window (days) Unless Otherwise Noted	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**	**± 2 days**	**±2**	**±7**
Archival tumor tissue specimen[u]	X									
De novo tumor specimens[v]	X								'X'	
Blood specimens for CNA profiling[w]	X						X		X	
Banked biospecimen[x]	X									

Footnotes (X) refer to specific footnote when the measurement could have been optional/repeat measurement might not have been required. For example, if a patient was not to have the lead-in (Day -7) visit, some assessments could have been required on Cycle 1 Day 1 instead of Day -7 and vice versa.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; BDI-II = Beck Depression Inventory-II; C-SSRS = Columbia Suicide Severity Rating Scale; CAP = chest abdomin pelvis; cfDNA = circulating free DNA; cfRNA = circulating free RNA; C_{max} = maximum plasma concentration; CNA = circulating nucleic acid; CNS = central nervous system; CRF = case report form; CSF = cerebrospinal fluid; C-SSRS = Columbia Suicide Severity Rating Scale; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; EOT = End of Treatment; FFPE = formalin-fixed paraffin embedded; FNA = fine needle aspiration; IEC = Institutional Ethics Committee; IRB = Institutional Review Boards; K_2EDTA = dipotassium ethylenediamine tetra acetic acid; LIC = lead-in cohort; LVEF = left ventricular ejection fraction; MDZ = midazolam; MRI = Magnetic Resonance Imaging; MUGA = multiple gated acquisition; N/A = not applicable; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OLQ-C30 = Quality of Life Questionnaire Core-30; OLQ-LC13 = Quality of Life Questionnaire Supplement Module for Lung Cancer (LC13); PE = pleural effusion; PK = pharmacokinetic(s); QTc = QT corrected for heart rate; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; ROS1-positive = ROS oncogene 1 positive; SAE = serious adverse event.

a. Screening: to be obtained within 28 days prior to registration.
b. Informed consent: to be obtained prior to undergoing any study-specific procedures that were not considered standard of care.
c. Baseline signs and symptoms: patients were asked about any signs and symptoms experienced within the 14 days prior to study entry. Worsening baseline signs and symptoms were recorded on the AEs CRF page.
d. Vital signs: blood pressure and pulse rate were recorded in sitting position.
e. Performance status: use ECOG.
f. Hematology: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date. For those visits after Cycle 1 Day 1, hematology laboratories were done within 72 hours of dosing with results checked prior to dosing.

Table 3. Schedule of Activities - Phase 2 Portion (Continued)

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g. Blood chemistry: No need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date. For those visits after Cycle 1 Day 1, blood chemistry was done within 72 hours of dosing with results checked prior to dosing.

h. Lipids: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date. For those visits after Cycle 1 Day 1, lipids were done within 72 hours of dosing with results checked prior to dosing.

i. Hypogonadism laboratory test was performed in male patients only. Blood draws were done between 08.00-11.00 AM. Should a decrease of ≥25% from baseline have been observed in total testosterone or free testosterone a repeat laboratory analysis of both these parameters were required to be performed at the next clinical visit to confirm hypogonadism.

j. Coagulation: no need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date. For those visits after Cycle 1 Day 1, coagulation was done within 72 hours of dosing with results checked prior to dosing.

k. Urinalysis: dipstick was acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on Cycle 1 Day 1 if baseline assessment performed within 7 days prior to that date. For those visits after Cycle 1 Day 1, urinalysis was done within 72 hours of dosing with results checked prior to dosing.

l. Serum pregnancy test: for female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, was performed on 2 occasions prior to starting study therapy - once at the start of Screening and once at the baseline visit, immediately before investigational product administration. Pregnancy tests were also routinely repeated at every cycle during the active treatment period (every other cycle beyond 30 months), at the EOT therapy and additionally whenever 1 menstrual cycle was missed or when potential pregnancy was otherwise suspected. Additional pregnancy tests were also undertook if requested by IRB/IECs or if required by local regulations.

m. Triplicate 12-lead ECGs: At each time point, 3 consecutive 12-lead ECGs were performed approximately 2 minutes apart to determine mean QTc interval. ECGs were collected as follows: 1) at Screening, 2) Day -7 (lead-in) at pre-dose, 1 hour, 2 hours and 4 hours post dose, 3) Cycle 1 Day 1, Day 8, and Day 15 at pre-dose, 1 hour and 2 hours post dose, 4) Cycles 2-5 Day 1 at pre-dose and 1 hour and 2 hours post dose and 5) EOT. If at any of these time-points the mean QTc was prolonged (≥501 msec), the ECGs were re-evaluated by a qualified person at the institution for confirmation. Additional triplicate ECGs were allowed to be performed as clinically indicated. When an ECG and PK sample were scheduled at the same time, ECG assessments were performed prior to PK sample such that the PK sample was collected at the nominal time (but regardless, the exact time of ECG assessment and PK collection were always recorded).

n. Registration: registration was within 2 days prior to lead-in or study treatment start.

o. Trial treatment.

p. Lead-in lorlatinib dose: a single dose of lorlatinib was given on Day –7 (lead-in period) for 10 non-Japanese and 3 Japanese (non-LIC) patients, after which exemptions to this lead- in period requirement were granted after discussion with Sponsor. Consideration was given by the Sponsor to shorten the duration of the lead-in period for those patients who experienced disease related symptom flare.

Table 3. Schedule of Activities - Phase 2 Portion (Continued)

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q. Tumor assessment: Tumor assessments included all known or suspected disease sites. CT or MRI scans of CAP and MRI of the brain were performed at Screening. Gadolinium contrast enhanced MRI was used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5mm for lesions greater than 10mm. Bone scans (or bone MRI if preferred by investigator) were performed at baseline for all patients and repeated every 12 weeks on study only if evidence of bone metastases was observed at baseline. For all tumor assessments, the method of assessment that was used at baseline should have been the same method used throughout the study. CT and MRI scans were to be done at every 6 weeks ±1 week up to approximately 30 months, and then every 12 weeks ± 1 week beyond 30 months, and responses were confirmed ≥4 weeks later (RECIST version 1.1) until documented progression of disease. For patients with bone involvement at Screening, CT or MRI or other appropriate imaging for bone assessment were done every 6 weeks ± 1 week up to approximately 30 months, and then every 12 weeks ± 1 week beyond 30 months (in addition to the every 12 week bone scan or bone MRI for detection of new disease) and responses were confirmed ≥4 weeks later (RECIST version 1.1) until documented progression of disease. For patients who had documented disease progression but were still receiving lorlatinib, CT and MRI scans were done according to local institutional standard of care. Every effort was made to maintain the assessment scheduling relative to Cycle 1 Day 1 especially if there were dosing cycle interruptions due to toxicities. Tumor assessment was repeated at the EOT and study visits if more than 6 weeks (more than 12 weeks beyond 30 months) had passed since the last evaluation. Tumor assessments continued until progression of disease or a new anti-cancer therapy had commenced. For all patients, copies of radiologic images were required to be available for independent central radiology review as determined by the Sponsor.

r. Diagnostic CSF: CSF analysis was not required unless patients had suspected or confirmed leptomeningeal carcinomatosis not visualized on MRI. When applicable, CSF sample was collected at Screening (optional CSF collection post Screening).

s. AE assessments: AEs were documented and recorded at each visit using NCI CTCAE version 4.03. Patients were followed for AEs for 28 days after the last treatment administration or until all drug related toxicities had resolved, whichever was later; or earlier than 28 days should the patient had commenced another anti-cancer therapy in the meantime. For SAEs, the active reporting period to the Sponsor or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period had ended were required to be reported to the Sponsor if the investigator became aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to study drug were reported to the Sponsor.

t. Concomitant medications and non-drug supportive interventions: all concomitant medications and non-drug supportive interventions were recorded in the CRF.

u. Archival tumor tissue specimens: all patients were provided a FFPE archival tumor specimen, specifically a FFPE tissue block that contained sufficient tissue to generate at least 6 (preferably 12) unstained slides, each with tissue sections that were 5 microns thick, or at least 6 (preferably 12) unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block was not submitted. Specimens were sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to lorlatinib (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1-positive NSCLC patients, specimens were sent to the Sponsor-designated central laboratory for ROS1 status confirmation.

Table 3. Schedule of Activities - Phase 2 Portion (Continued)

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v. De novo tumor specimens: de novo tumor core biopsy collection was mandatory at Screening unless it was considered to pose a safety risk to the patient, in the opinion of the investigator, and only after discussion with the Sponsor. For patients who were treatment naïve at Screening (ie, no previous systemic therapy in the metastatic setting), a de novo tumor biopsy was not required if a previous tumor biopsy was performed within 4 months of first dose of lorlatinib. PE cell pellets were substituted for tumor core biopsy as appropriate. FNA samples (2-3 pathes prepared as FFPE cell block) were not preferred and were only performed in the event a biopsy or PE cell pellet was not safe or feasible. If local country regulations did not allow for tissue block to be submitted, 5-micron FFPE tumor tissue slides (at least 12 slides) were acceptable. Specimens were sent to the Sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to lorlatinib (eg, ALK mutations, mutations/copy number variation of candidate genes, expression and/or phosphorylation of candidate proteins, etc); for ROS1-positive NSCLC patient specimens were sent to the Sponsor-designated central laboratory for ROS1 status confirmation. In addition, optional de novo tumor biopsy collection at the time of progression was encouraged. Tumor tissue specimens from all patients were used for additional biomarker analyses.

w. Blood specimens for CNA profiling: 10 mL blood specimen optimized for plasma preparation for nucleic acid analysis (eg, cfDNA or cfRNA) was collected at Screening, at the end of Cycle 2 (matching the first tumor restaging, in practical terms this could be Cycle 3 Day 1 pre-dose) and at EOT.

x. Banked biospecimens: unless prohibited by local regulations, a blood sample (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis), retained for pharmacogenomic analyses, was collected at Screening.

y. EORTC QLQ-C30 and QLQ-LC13: Patients were required to complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the clinic at the specified time points prior to dosing. At Day -7, or Cycle 1 Day 1 if this was the first dose, site staff (eg, site coordinators) instructed patients that the assessment should have been completed without help from friends or family members and also recommended that this assessment to be completed in the morning. All scheduled assessments of the EORTC QLQ-C30 and QLQ LC13 were not allowed to be taken home and were required to be completed in the clinic prior to any other study or medical procedures.

z. Follow-up: at least 28 days, and no more than 35 days after discontinuation of treatment patients returned to undergo review of concomitant medications and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment were continued to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement was expected. Patients discontinuing treatment for reasons other than progression of disease were continued to perform tumor assessments until progression disease or a new anti-cancer therapy was commenced. Bimonthly survival follow-up after progression disease or new anti-cancer therapy had commenced were performed (telephone contact was acceptable).

aa. EOT visit: obtained these assessments if not completed in the last week (last 6 weeks for tumor assessments up to 30 months and then last 12 weeks beyond 30 months).

bb. LVEF assessments: echocardiogram or MUGA was performed at Screening, before dosing at Day 1 Cycle 2, before dosing at Day 1 Cycle 3, before dosing at Day 1 Cycle 5 and every 2 cycles thereafter (ie, before dosing at Day 1 Cycle 7, Day 1 Cycle 9, etc.) up to approximately 30 months, and then every 4 Cycles thereafter, and at the EOT visit. A ±2 days time window applicable at the discretion of the investigator was allowed at all time points. The same method was used at each time point.

cc. Cognitive assessment: a computerized cognitive test compromised of verbal learning, psychomotor function, attention and memory were administered to patients prior to study drug dosing. This test took approximately 10-20 minutes to complete and was administered via qualified site personnel. A practice test was performed at Screening and a baseline test was done on the first day of lorlatinib dosing (ie, Day -7 or Cycle 1 Day 1, whichever was their first dose), and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After Cycle 6 Day 1, this test was administered prior to dosing on Day 1 of every other cycle ±1 week (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.).

dd. Mood assessment: an assessment of mood via the BDI-II scale was administered to patients prior to the first day of lorlatinib dosing (ie, day -7 or Cycle 1 Day 1, whichever was their first dose) and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After Cycle 6 Day 1, this test was administered prior to dosing on Day 1 of every other cycle ±1 week (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.).

ee. Suicidal ideation and behavior assessment: an assessment of suicidal ideation and behavior via the C-SSRS was administered to patients prior to study drug dosing (ie, Day -7 or Cycle 1 Day 1, whichever was their first dose) and then prior to dosing on Day 1 of Cycle 2 –Cycle 6 (±1 week). After Cycle 6 Day 1, this was administered prior to dosing on Day 1 of every other cycle ±1 week (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.).

Table 4. Pharmacokinetic Assessments - Phase 2 Portion

			CYCLE 1 (21 days)			CYCLE 2-5 (21 days)	CYCLE 6, 8 and 10 (21 days)
Protocol Activity	**Screen (≤28 days)**	**Lead-in PK (Day -7)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**
Visit Window	**N/A**	**+1**	**±1**	**±1**	**±1**	**±2**	**±2**
Sparse lorlatinib PK samples[a]			X			X	X
CSF lorlatinib concentration (optional)[b]					Any time during steady state, ideally 4-6 hours and 8-9 hours post dose		
Blood sample (whenever CSF for lorlatinib was collected)[c]					Same time as CSF lorlatinib concentration sample collected		

Abbreviations: CSF = cerebrospinal fluid; LIC = lead-in cohort; N/A = not applicable; PK = pharmacokinetic(s).

a. Sparse plasma sampling for lorlatinib (in all patients after 10 non-Japanese and 3 Japanese [non-LIC] patients with full PK sampling): Blood samples were collected pre-dose on Day 1 of Cycles 1-5 and pre-dose on Day 1 of Cycle 6,Day 1 of Cycle 8 and Day 1 of Cycle 10. Sites were notifed via letter when sparse PK sampling was in effect.

b. CSF lorlatinib concentration sample (optional): if a patient underwent a lumber puncture, a sample of CSF was collected for exploratory analysis of lorlatinib concentration, if possible. If this CSF sample was collected, a blood sample for PK analysis was also collected at approximately the same time as the CSF sample. If scheduling permitted, 1 CSF sample was taken between 4 and 6 hours post dose. If it was possible to take a second sample, collection was between 8 and 9 hours post dose.

c. If a CSF lorlatinib concentration sample was collected, a blood sample for PK analysis was collected at approximately the same time as the CSF sample.

Number of Subjects (Planned and Analyzed):

Phase 1 and Phase 2 portion of the study originally planned to enroll approximately 50 patients and 260 patients, respectively; the actual numbers of patients assigned and analyzed were 55 patients for Phase 1, and 276 patients for Phase 2, respectively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Eligible patients should have been 18 years or older and had evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC that carried an ALK rearrangement, as determined by the Food and Drug Administration (FDA)-approved fluorescent in situ hybridization (FISH) assay or by Immunohistochemistry (IHC), or a ROS1 rearrangement as determined by FISH or reverse transcription-polymerase chain reaction (RT-PCR) or Next Generation Sequencing (NGS) via a local diagnostic test. All patients (ALK positive or ROS1 positive) had to have archival tissue sample available and collected prior to enrollment. Patients should have had adequate bone marrow, pancreatic function, renal function and liver function. For females of childbearing potential, negative serum pregnancy test was required.

Disease status should have met the following requirements:

- Phase 1: ALK-positive NSCLC and ROS1-positive patients must either have been treatment naïve in the advanced setting or have had disease progression after at least 1 previous ALK or ROS1 inhibitor therapy(ies), respectively.

- Phase 2:

    - ALK-positive NSCLC patients must either have been or have had:

        - Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ALK inhibitor therapy allowed).

        - Disease progression after crizotinib only. No prior chemotherapy was allowed in the metastatic disease setting.

        - Disease progression after crizotinib and 1 or 2 prior regimens of chemotherapy in the metastatic disease setting.

        - Disease progression after 1 prior ALK inhibitor therapy other than crizotinib. Patients may have had any number of prior chemotherapy regimens in any disease setting.

        - Disease progression after 2 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting.

        - Disease progression after 3 prior ALK inhibitor therapies. Patients may have had any number of prior chemotherapy regimens in any disease setting.

- ROS1-positive NSCLC patients were to have had:
    - Treatment naïve (ie, no prior chemotherapy in the metastatic disease setting and no prior ROS inhibitor therapy).
    - Any number of prior therapies (ie, chemotherapy and/or ROS inhibitor therapies).

Tumor Requirements:

- All patients must have had at least 1 measurable target extracranial lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In addition patients with asymptomatic CNS metastases (including patients asymptomatic by means of stable or decreasing doses of steroids within the last 2 weeks prior to study entry) were eligible. Phase 1 only: patients who had leptomeningeal disease (LM) or carcinomatous meningitis (CM) and negative cerebrospinal fluid (CSF) were eligible. Phase 2 only: Patients who had LM or CM were eligible if the LM/CM was visualized on magnetic resonance imaging (MRI) or if documented baseline CSF positive cytology was available.

Patients were ineligible if they have received radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Whole brain radiation had to be completed at least 4 weeks prior to study entry. Following prior therapies were not allowed: 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, including, but not limited to, anti- programmed cell death receptor-1 (PD-1), anti-anti PD-ligand 1(PD-L1), anti-PD ligand 2 (PD-L2), anti-CD137 (4-1BB), or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody. Patients were excluded if they had active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness. Patients should have had no clinically significant cardiovascular disease (ie, active or <3 months prior to enrollment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure, second-degree or third-degree atrioventricular (AV) block (unless paced) or any AV block with PR interval>220 msec. Additionally patients should have had no ongoing cardiac dysrhythmias of NCI (CTCAE) Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 beats per minute (bpm) (unless patient was otherwise healthy such as long-distance runners, etc.), machine-read ECG with QT corrected for heart rate (QTc) >470 msec, or congenital long QT syndromes. The following medical histories were not allowed: 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 were ineligible if they had current use or anticipated need for food or drugs that are known strong or moderate CYP3A4 inhibitors, inducers and substrates; drugs that are CYP2C9 substrates; drugs that are sensitive CYP2B6 substrates; drugs that are strong CYP2C19 inhibitors; drugs that are strong inhibitors; and drugs that are P-glycoprotein substrates.

Study Treatment:

In Phase 1, lorlatinib supplied for oral administration as 5 mg, 25 mg and 100 mg acetate solvate tablets in high density polyethylene (HDPE) bottles with desiccant. Tablets had different sizes and shapes according to different strengths. Study medication was supplied by the Sponsor. MDZ (2 mg/mL, oral syrup) was used in the study and supplied by the Sponsor.

In Phase 2, lorlatinib was supplied for oral administration as 25 mg free base tablets in HDPE bottles with desiccant. Study medication was supplied by the Sponsor.

In all study parts, lorlatinib was administered orally QD (or BID dosing in Phase 1) continuously in 21-day cycles. Patients self-administered lorlatinib in the outpatient setting.

In Phase 1, dose level allocation was performed by the Sponsor after patients gave their written informed consent and completed the necessary baseline (defined as the time period up to 28 days before start of dosing) assessments. In Phase 2, an automated registration system was used where a randomization number was assigned.

Efficacy, Pharmacokinetic, Biomarker, and Outcomes Research Endpoints:

Efficacy Endpoints-Phase 1:

Primary Efficacy

None.

Secondary Efficacy

- Objective tumor response, as assessed by RECIST version 1.1. In patients with asymptomatic CNS metastases, up to 5 intra-cranial target lesions in addition to the 5 extracranial target lesions were planned to be assessed.
- Disease Control Rate (DCR) at 12 weeks defined as the percent of patients with a confirmed complete response (CR), partial response (PR) or stable disease (SD) according to RECIST version 1.1 at 12 weeks.
- Time-to-event endpoints: Progression-Free Survival (PFS), Overall Survival (OS) at 1 year and 18 months, Duration of Response (DOR), and Time to Tumor Response (TTR).
- Probability of first event being a CNS progression, non-CNS progression, or death.

Pharmacokinetic Endpoints-Phase 1:

- PK parameters of lorlatinib: Single Dose - maximum observed plasma concentration (C_{max}), Time for C_{max} (T_{max}), area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}), area under the concentration-time profile from time 0 to time τ (AUC_{τ}), apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F) and terminal plasma half-life ($t_{½}$), area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) as data permitted. Multiple Dose (assuming steady-state was

achieved) - C_{max} at steady state ($C_{ss,max}$), T_{max} at steady state ($T_{ss,max}$), T_{max} at steady state ($AUC_{ss,\tau}$), $t_{½}$, minimum observed plasma concentration at steady state ($C_{ss,min}$), average observed plasma concentration at steady state ($C_{ss,av}$), CL/F, V_z/F, steady state accumulation ratio (R_{ss} [$AUC_{ss,\tau}/AUC_{sd,inf}$]) as data permitted. Urine PK parameters (percent of dose recovered unchanged in urine [Ae%], and renal clearance [CL_r]) of PF-06463922 from MDZ and food effect substudy.

- PK parameters of MDZ: C_{max}, T_{max}, AUC_{last}, CL/F, and V_z/F and $t_{½}$, AUC_{inf} as data permitted.

Biomarker Endpoints-Phase 1

- Selected molecular profiling of tumor tissue, eg, ALK kinase domain mutations and circulating nucleic acid (CNA), eg, ALK kinase domain mutations.

Outcome Research Endpoints-Phase 1:

- Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL.

Efficacy Endpoints-Phase 2:

Primary Efficacy

- Objective tumor response, as assessed by RECIST version 1.1. In patients with asymptomatic CNS metastases, up to 5 intra-cranial target lesions in addition to the 5 extracranial target lesions were planned to be assessed.

Secondary Efficacy

- DCR at 12 weeks defined as the percent of patients with a confirmed CR, PR or SD according to RECIST version 1.1 at 12 weeks.
- Time-to-event endpoints: PFS, OS at 1 year and 18 months, DOR, and TTR.
- Probability of first event being a CNS progression, non-CNS progression, or death.
- Time to Progression (TTP).

Pharmacokinetic Endpoints-Phase 2:

- PK parameters of lorlatinib: Single Dose - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{½}$, AUC_{inf} as data permitted. Multiple Dose (assuming steady-state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{½}$, $C_{ss,min}$, $C_{ss,av}$, CL/F, V_z/F, R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}/AUC_{sd,inf}$) as data permitted.

Biomarker Endpoints-Phase 2:

- Selected molecular profiling of tumor tissue, eg, ALK kinase domain mutations and CNA, eg, ALK kinase domain mutations.

Outcome Research Endpoints-Phase 2:

- Patient reported functioning and impact on disease/treatment-related symptoms of lung cancer and global QOL.

Safety Evaluations:

Safety evaluations included collection of adverse events (AEs), serious AEs (SAEs), vital signs, 12-lead ECGs, physical examinations, safety laboratory tests and echocardiogram or Multi Gated Acquisition (MUGA) scan, and neurological assessments.

Statistical Methods:

Analysis Populations

The following main analysis populations were defined:

Full Analysis Set

The full analysis (FA) set included all enrolled patients, regardless of whether or not treatment was received.

Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set was all enrolled patients with documented ALK or ROS1 rearrangement and who received at least 1 dose of lorlatinib (including Day -7 dose).

Patients without documentation of an ALK or ROS1 rearrangements were excluded from the ITT analysis sets.

Per Protocol Analysis Set

For Phase 1, the Per Protocol (PP) analysis set was all enrolled patients evaluable for MTD as defined by patients who received at least 75% of the planned lorlatinib doses in the first cycle (ie 16 out of 21 dosing days). Patients who received less than 75% of the planned lorlatinib doses in the first cycle due to DLT were also considered evaluable for MTD.

For Phase 2, the PP analysis set was all patients with CNS metastases at study entry based on investigator assessment and separately, patients with CNS metastases at study entry based on Independent Central Review (ICR).

Safety Analysis Set

The safety analysis (SA) set was all enrolled patients who received at least 1 dose of lorlatinib (including lead-in dose).

PK Analysis Set

PK Concentration for Lorlatinib

The PK concentration analysis set of lorlatinib was defined as all patients treated (including Day -7 dose) who had at least 1 concentration of lorlatinib.

PK Concentration for Midazolam (Phase 1 only)

The PK concentration analysis set of MDZ was defined as all patients treated with MDZ (including Day -7 dose) who had at least 1 concentration of MDZ.

PK Parameters for Lorlatinib

The PK parameter analysis population was defined as all enrolled patients who received at least 1 dose of study medication (including Day -7 dose, not including midazolam) and had sufficient information to estimate at least 1 of the PK parameters of interest (C_{max} or AUC) for lorlatinib.

PK Parameters for Midazolam (Phase 1 only)

The MDZ analysis set included patients who had received at least 1 dose of midazolam and for which at least 1 MDZ PK parameter of interest (C_{max} or AUC) was available.

CNA Peripheral Blood Analysis Set

The CNA Peripheral Blood analysis set was defined as all patients of the ITT analysis set who had at least 1 molecular biomarker (analyte mutation) assayed.

Paired CNA Peripheral Blood Analysis Set

The Paired CNA Peripheral Blood analysis set was defined as all patients in the ITT analysis set who had valid paired results from at least 1 molecular biomarker (analyte mutation) assayed at Screening and post-treatment (ie, End of Treatment [EOT] for Phase 1, Cycle 3 Day 1 and/or EOT for Phase 2).

Tumor Tissue Analysis Set

The Tumor Tissue analysis set was defined as all patients in the ITT analysis set who had at least 1 molecular tumor biomarker assayed from either the screening archival or screening de novo tumor biopsy sample (or both).

Paired Tumor De Novo Analysis Set

The Paired Tumor De Novo analysis set was defined as all patients in the ITT analysis set who had both a) either archival tumor tissue or de novo biopsy at Screening, and b) an EOT de novo biopsy with at least 1 molecular tumor biomarker assayed.

Patient Reported Outcome Evaluable Population

The Patient Reported Outcome (PRO) evaluable analysis set was defined as all enrolled patients who received at least 1 dose of study medication who completed a baseline (last PRO assessment prior to first dose of lorlatinib, which could have been Day -7 or Cycle 1 Day 1) and at least 1 post-baseline PRO assessment.

Mini Mental State Examination (Phase 1 Only)/Mood/Cognitive/SIB Assessment Evaluable Population

The evaluable analysis set for Mini Mental State Examination (MMSE) (Phase 1 only) and the Mood/Cognitive/SIB assessment was defined as all enrolled patients who received at least 1 dose of study medication who completed a baseline (last assessment prior to first dose of lorlatinib, which could have been Day -7 or Cycle 1 Day 1) and at least 1 post-baseline assessment.

Efficacy Analysis

Analyses of the efficacy endpoints are presented by ALK-positive and ROS1-positive status for the Phase 1 part of the study and by cohorts EXP-1, EXP-2, EXP-3A, EXP-3B, EXP-4, EXP-5 and EXP-6 for the Phase 2 part of the study.

All efficacy analyses, except OS, were performed according to ICR assessment and derived investigator assessment. The analyses based on the ICR assessment were considered primary.

Efficacy parameters were calculated on the groups resulting from pooling ITT analysis set (defined below) of the following subpopulations:

- EXP-2:5 (treatment after at least 1 prior ALK tyrosine kinase inhibitors [TKIs])
- EXP-4:5 (treatment after at least 2 prior ALK TKIs)
- EXP-2:3A (treatment after prior crizotinib +/- chemotherapy)

For patients treated in the EXP-3, efficacy parameters were also summarized separately for the following subgroups:

- EXP-3A: Patients with prior crizotinib therapy and prior regimens of chemotherapy.
- EXP-3B: Patients with 1 prior non-crizotinib ALK TKI therapy +/- prior regimens of chemotherapy.

Primary Efficacy Parameters:

- Analysis of Objective Response Rate (ORR) and intra-cranial ORR were performed for the intention-to-treat (ITT) analysis set. The point estimate of the ORR was to be provided along with the corresponding 95% confidence interval (CI) using the exact

method based on the binomial distribution. Intra-cranial ORR was also provided with the corresponding 95% CI.

- Disagreement rates between independent assessment and investigator assessment of objective overall responses and intracranial responses were calculated using the following formula: Response Disagreement Rate = (c+d)/N × 100%, where c = investigator assessment indicates response; ICR assessment indicates no response or no scan available and d = ICR assessment indicates response; investigator assessment indicates no response or no scan available; N=number of patients.

Analysis of Secondary Efficacy Parameters:

- DCRs and intra-cranial DCRs (IC-DCRs) are provided along with the corresponding 95% CI.

- For PFS, estimates of the time-to-event curves using the Kaplan-Meier method are presented relative to the analysis set. Two-sided 95% CIs for the 1-year PFS probability were calculated for the log [-log(1-year (18-month) PFS probability)] using a normal approximation and then back transformed to give a CI for the 1-year PFS. The 18-month PFS probability was calculated in an identical manner.

- For OS, estimates of the time-to-event curves using the Kaplan-Meier method are presented relative to the analysis set. Two-sided 95% CIs for the 1-year survival probability were calculated for the log [-log(1-year survival probability)] using a normal approximation and then back transformed to give a CI for the 1-year survival probability itself. The 18-month survival probability was calculated in an identical manner.

- DOR was summarized in the populations of patients with a confirmed CR or PR using the Kaplan‑Meier method. The median event time (if appropriate) and two‑sided 95% CI for the median was provided.

- TTR was only calculated for the subgroup of patients with a confirmed objective tumor response. TTR was summarized based on both ICR and investigator assessments using descriptive statistics.

- For TTP, estimates of the TTP curve using the Kaplan-Meier method are presented relative to the analysis set. This method was applied to derive the median event time and a CI for the median, calculated using normal approximation methods. Two-sided 95% CIs for the 1-year TTP probability were calculated for the log [-log(1-year TTP probability)] using a normal approximation and then back transformed to give a CI for the 1-year TTP probability. The 18-month TTP probability was calculated in an identical manner.

- Intra-cranial (IC)-TTP was calculated in a similar manner to TTP for the ITT analysis set and for subgroups of patients with and without brain metastases at baseline. For

the subgroup of patients without brain metastases at baseline, only the appearance of new brain metastases was considered events.

- The probability of the first event being a CNS progression, a non-CNS progression, or death was evaluated with a competing risk approach by estimating cumulative incidence functions relative to the analysis set based on both ICR and investigator assessments. All the analyses were repeated on patients with brain lesions at study entry in the analysis set.

Pharmacokinetic Analysis:

Single- and Multiple-Dose Lorlatinib Pharmacokinetic Analysis in Phase 1 and Phase 2

Plasma PK parameters including the C_{max}, T_{max}, and AUC_{last} for lorlatinib were estimated using non-compartmental analysis. AUC_{inf}, $t_{½}$, CL/F, V_z/F, R_{ac} and R_{ss} were also estimated. R_{ac} and R_{ss} were summarized descriptively. The single dose and steady-state PK parameters were summarized descriptively by dose, cycle and day.

Lorlatinib concentrations were summarized descriptively by dose, cycle, day and nominal time.

Dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} were plotted against dose (using a logarithmic scale) by cycle and day.

The observed R_{ac} and R_{ss} were summarized descriptively.

Trough concentrations were plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

Urine PK parameters (Ae%, CL_r) for lorlatinib were also estimated and summarized.

Effect of Food on Lorlatinib Pharmacokinetics in Phase 1

For the evaluation of the food effect, lorlatinib plasma concentration-time data were compared on Day -7 to Cycle 1 Day 1.

Effect of Lorlatinib on MDZ Pharmacokinetics in Phase 1

Plasma concentration-time data of MDZ in the absence and presence of lorlatinib were analyzed using non-compartmental methods to estimate the following PK parameters in individual patient: C_{max}, T_{max}, AUC_{last}, and, if data permitted, AUC_{inf}, $t_{½}$, CL/F and V_z/F.

Urine 6 beta-Hydroxycortisol/Cortisol and Serum 4 beta-Hydroxycholesterol/Cholesterol Ratio Analysis in Phase 1

Urine 6 beta-hydroxycortisol/cortisol (6β-OHC/C) and serum
4 beta-hydroxycholesterol/cholesterol ratio data ratio data were summarized using graphical methods and descriptive statistics in tabular form, as appropriate.

CSF Analysis in Phase 1 and Phase 2

CSF concentrations of lorlatinib were listed along with corresponding bound and unbound plasma concentrations of lorlatinib.

Biomarker Analysis:

CNA Mutations in Phase 1 and Phase 2

Analyses of CNA mutations were based on the CNA Peripheral Blood analysis set.

CNA mutations were measured at Screening, EOT in Phase 1 and at Screening, Cycle 3 Day 1 and EOT in Phase 2. For Phase 1, patients were expected to have none or 1 or more than 1 of the 12 (and later 17 or more) possible ALK or 3 possible ROS1 mutations included in the panel, and patients could have had a change in mutation after treatment. For Phase 2, patients were expected to have none or 1 or more mutations (no panel restriction), and patients could have had a change in mutation while on treatment (Cycle 3 Day 1) or at EOT.

Tumor Tissue Analysis in Phase 1 and Phase 2

Analyses of tumor tissues were based on the Tumor Tissue analysis set.

DNA mutations in tumor tissue were measured at Screening. Patients were expected to have none or 1 or more of 9 possible mutations.

Tumor De Novo Analysis in Phase 1 and Phase 2

Analyses of tumor de novo were to be based on the Paired Tumor De Novo analysis set.

DNA mutations were measured at Screening and optionally at EOT. Patients were expected to have none or 1 or more of 9 possible mutations, and patients could have had a change in mutations after treatment.

Tumor Versus Blood Analyses in Phase 1 and Phase 2

Mutations were measured in both blood and tumor for all patients.

Safety Analysis:

AEs were graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0). The focus of AE summaries was on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment related SAE was summarized according to worst toxicity grades. Cluster term AEs were summarized by maximum CTCAE grade and causality (all-causality and treatment-related) together with other AEs. Clustered terms are presented using capital letters while MedDRA preferred terms (PTs) are written with only the first letter capitalized.

The number and percentage of patients who experienced laboratory test abnormalities were summarized according to worst toxicity grade observed on treatment for each laboratory assay. Worst case was defined as the maximum post-baseline CTCAE grade using scheduled and unscheduled visits. The analyses summarized laboratory tests on the entire study period. Shift tables of baseline grade by maximum post-baseline CTCAE grade were also presented.

Coagulation assays (collected at Screening, EOT and as needed) were summarized in a listing by visit reporting the value and the CTCAE grade for each visit.

Baseline and the change from baseline in blood pressure, weight and pulse rate were summarized using descriptive statistics by visit.

The analysis of ECG results was based on the Safety Analysis set patients with baseline and on-treatment ECG data. Changes from baseline for the ECG parameters were summarized by treatment and time. Shift tables were provided for baseline versus worst values on study.

For physical examinations, individual patient data were listed.

For total cholesterol and triglycerides abnormalities, in addition to the summary tables included in the set produced for the biochemistry assays, the n, mean, standard deviation (Std Dev), median, minimum, and maximum time from start of concomitant medication were presented for the concomitant medications used.

For patients with MUGA scans or echocardiograms, individual LVEF (%) and its changes from baseline was summarized by time point (changes from baseline should only have been calculated for the on treatment evaluation using the same method used for baseline). The number of patients and the percentage whose maximum relative decrease from baseline in LVEF was greater than 20% was calculated.

A shift table of baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) by maximum post-baseline value was presented. Individual patient data was listed.

The assessments of cognitive function, mood and suicidal ideation and behaviors were to be analyzed by Cogstate.

Patient Reported Outcomes Analysis:

The PRO evaluable analysis set was the primary population for the analyses of change from baseline in Phase 1 and Phase 2. In Phase 2, PRO analyses were performed by the pre-defined subgroups, EXP-1:EXP-6 and on the group pooling EXP-1:EXP-6, EXP-2:EXP-5, EXP-2:EXP-3A, and EXP-4:EXP-5.

RESULTS

Subject Disposition and Demography:

Phase 1:

Patient disposition for Phase 1 is summarized in Table 5. A total of 55 Phase 1 patients were assigned to treatment with lorlatinib: 3 patients each in the 10, 25, 50, 150, and 200 mg QD

cohorts, 13 patients in the 75 mg QD cohort, 17 patients in the 100 mg QD cohort, 3 patients in the 35 and 75 mg BID dosing cohorts, and 4 patients in the 100 mg BID cohort. Patients treated at 100 mg QD, which was determined to be the RP2D, are presented separately from the other Phase 1 dosing cohorts.

All patients received lorlatinib except for 1 patient in the 75 mg QD cohort who was enrolled but was never treated with lorlatinib.

A total of 19 (35.2%) patients were ongoing on treatment and 35 (64.8%) patients had permanently discontinued from treatment as of the database cutoff date (15 March 2017). The primary reason for permanent discontinuation of treatment was objective progression or relapse in 20 (37.0%) patients.

As of the data cutoff date (15 March 2017), 22 out of 54 patients (40.7%) were ongoing in the study and 33 out of 54 patients (61.1%) permanently discontinued the study. Of the patients that discontinued from the study, 27 out of 55 patients (49.1%) died, 2 (3.6%) patients were lost to follow-up, 3 (5.5%) patients refused further follow-up, and 1 (1.8%) patient discontinued for a reason provided as "other".

Table 5. Patient Disposition (Phase 1) - Full Analysis Population

Number (%) of Patients	Total	100 mg QD
Assigned to study treatment[a]	55	17
Treated	54 (100)	17 (100)
Ongoing on treatment at data cutoff	19 (35.2)	7 (41.2)
Discontinued from treatment	35 (64.8)	10 (58.8)
Reason for discontinuation		
AEs[b]	5 (9.3)	0
Global deterioration of health status	4 (7.4)	1 (5.9)
Objective progression or relapse	20 (37.0)	8 (47.1)
Patient died	2 (3.7)	1 (5.9)
Patient no longer willing to participate in the study	2 (3.7)	0
Other[c]	2 (3.7)	0

Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; QD=once daily.

a. Included 1 patient who was neither ALK-positive nor ROS1-positive.
b. Calculated by the addition of the number of patients who discontinued owing to all causality AEs.
c. Reason provided for 1 patient was "patient held study drug for longer than 42 days" and for the other patient was "go back to his country".

Thirty-two (32) (59.3%) female patients and 22 (40.7%) male patients were enrolled in Phase 1, and the mean age was 51.9 years old. The majority of patients enrolled were White (68.5%). Most of the ITT population had disease at more than 1 site; the frequently involved disease sites at the time of study entry were lung (81.5%), brain (72.2%), and lymph node (61.1%). Of the 39 (72.2%) patients who had brain metastasis at baseline according to investigator assessment, 24 (44.4%) had measurable baseline CNS disease.

Phase 2:

Patient disposition for Phase 2 is summarized in Table 6. A total of 276 Phase 2 patients were assigned to selected cohorts. A total of 275 patients received lorlatinib treatment: 30, 27, 60, 65, 46 and 47 patients in cohorts EXP-1, EXP-2, EXP-3, EXP-4, EXP-5 and EXP-6, respectively.

As of the database cutoff date (15 March 2017), 157 (57.1%) patients were ongoing on treatment and 118 (42.9%) patients permanently discontinued treatment from Phase 2 at the cutoff date. Similar to the Phase 1 results, the primary reason for discontinuation of treatment across all EXP groups was objective progression or relapse.

One hundred and ninety three (193) patients (70.2%) were ongoing in the study and 83 (30.2%) patients permanently discontinued the study. Of the patients that discontinued from the study, 63 (22.8%) patients died, 1 (0.4%) patient was lost to follow-up, 17 (6.2%) patients refused further follow-up, and 2 patients (0.7%) discontinued for a reason provided as "other".

One (1) patient, in cohort EXP-4, was assigned to lorlatinib but never received lorlatinib as the patient died before the start of treatment, so was therefore excluded from the safety analysis set and ITT population. In addition, 1 patient in cohort EXP-3 was included in the safety analysis set, but was excluded from the ITT population as the patient had no confirmed ALK-positive status.

Table 6. Patient Disposition (Phase 2) - Full Analysis Population

Number (%) of Patients	EXP-1	EXP-2	EXP-3	EXP-4	EXP-5	EXP-6	Total
Assigned to study treatment	30	27	60	66	46	47	276
Treated	30	27	60	65	46	47	275
Ongoing on treatment at data cutoff	25 (83.3)	21 (77.8)	39 (65.0)	31 (47.7)	20 (43.5)	21 (44.7)	157 (57.1)
Discontinued from treatment	5 (16.7)	6 (22.2)	21 (35.0)	34 (52.3)	26 (56.5)	26 (55.3)	118 (42.9)
Reason for discontinuation							
AEs[a]	1 (3.3)	2 (7.4)	4 (6.6)	3 (4.6)	5 (10.9)	5 (10.6)	20 (7.2)
Global deterioration of health status	0	0	1 (1.7)	3 (4.6)	2 (4.3)	2 (4.3)	8 (2.9)
Objective progression or relapse	4 (13.3)	2 (7.4)	14 (23.3)	22 (33.8)	15 (32.6)	13 (27.7)	70 (25.5)
Patient died	0	1 (3.7)	2 (3.3)	2 (3.1)	2 (4.3)	1 (2.1)	8 (2.9)
Patient no longer willing to participate in the study	0	1 (3.7)	0	2 (3.1)	2 (4.3)	5 (10.6)	10 (3.6)
Protocol violation	0	0	0	1 (1.5)[b]	0	0	1 (0.4)
Other	0	0	0	1 (1.5)	0	0	1 (0.4)

Abbreviation: AE = adverse event; EXP = expansion cohort.

a. Calculated by the addition of the number of patients who discontinued owing to all causality AEs.

b. One (1) patient had a machine read that the QTc results were >500 msec.

One hundred and fifty seven (157) (51.7%) female patients and 118 (42.9%) male patients were enrolled in Phase 2 and the mean (Std Dev) age was 53.6 (12.1) years. The majority of patients enrolled were either White (48.0%) or Asian (37.5%) (Safety Analysis Set). Most patients in the safety population had disease at more than 1 site; the most frequently involved disease sites at the time of study entry were lung (87.3%), brain (55.3%), and lymph node (50.9%). Among the 152 patients in the safety population who had brain metastasis at baseline according to investigator assessment, 53 (34.6%) had measurable baseline CNS disease.

Efficacy, Pharmacokinetic, Biomarker, and Outcomes Research Results:

Efficacy Results-Phase 1:

Primary Efficacy

There were no primary efficacy evaluations done in the Phase 1 portion of the study.

Secondary Efficacy

- Objective Response Rate: The confirmed ORRs based on independent assessment were 39.0% (95% CI: 24.2, 55.5) in patients with ALK-positive NSCLC and 50.0% (95% CI: 21.1, 78.9) in patients with ROS1-positive NSCLC.

- Intra-cranial Objective Response Rate(IC-ORR): The confirmed IC-ORRs based on independent assessment were 41.2% (95% CI: 24.6, 59.3) in patients with ALK-positive NSCLC patients with CNS metastases and 50.0% (95% CI: 15.7, 84.3) in patients with ROS1-positive NSCLC with CNS metastases.

- Disagreement in Response Assessment: The overall discordance rate for objective overall response was 20.8% and for intra-cranial responses was 23.8%.

- Time to Tumor Response: Among the 16 patients with ALK-positive NSCLC with a confirmed objective tumor response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 15.2 months). Among the 6 patients with ROS1-positive NSCLC with a confirmed objective tumor response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 2.8 months).

- Intra-cranial Time to Tumor Response (IC-TTR): For patients with CNS metastases and a confirmed objective response by independent assessment, the median IC-TTR was 1.4 months (range: 1.2 to 20.1 months) for patients with ALK-positive NSCLC and 1.7 months (range: 1.1 to 2.8 months) for patients with ROS1-positive NSCLC.

- Duration of Response: The median follow-up time for DOR was 27.8 months (95% CI: 20.4, 31.8) for patients with ALK-positive NSCLC and 21.6 months (95% CI: 19.4, 23.5) for patients with ROS-positive NSCLC. The Kaplan-Meier estimate of median DOR based on independent assessment was 14.1 months (95% CI: 4.17, not reached [NR]) for patients with ALK-positive NSCLC with 50% of patients censored. The DOR was >6 months for 7/8 patients with subsequent progressive disease (PD) or death at the time

of data cutoff. The DOR in patients without subsequent PD or death at the date of data cutoff was >6 months in 1/8 patients. For patients with ROS1-positive NSCLC, the number of patients with subsequent progression or death was limited (2/6), but both patients had a DOR of >6 months and the median DOR was not reached at the time of data cutoff using the Kaplan-Meier method, with 66.7% of responding patients censored.

- Intra-cranial Duration of Response: For patients with ALK-positive NSCLC and a confirmed intra-cranial response, the median IC-DOR could not be estimated (78.6% of patients censored). However, the lower boundary of the 95% CI, per independent review, was 14.1 months. Also, the IC-DOR was >6 months for 2/3 patients with subsequent PD or death at the time of data cutoff. The IC-DOR in patients without subsequent PD or death at the date of data cutoff was >6 months in 8/11 patients. For patients with ROS1-positive NSCLC, and a confirmed intra-cranial response, the median IC-DOR could not be estimated either, because none of the patients had an event and all patients were censored at the time of data cutoff. Among these patients, the IC-DOR was >18 months in 3/4 patients.

- Disease Control Rate at 12 Weeks: The DCRs based on independent assessment were 53.7% (95% CI: 37.4, 69.3) for patients with ALK-positive NSCLC and 58.3% (95% CI: 27.7, 84.8) for patients with ROS1-positive NSCLC.

- Intra-cranial Disease Control Rate (IC-DCR) at 12 Weeks: The IC-DCRs based on independent assessment were 50.0% (95% CI: 32.4, 67.6) for patients with ALK-positive NSCLC and 37.5% (95% CI: 8.5, 75.5) for patients with ROS1-positive NSCLC.

- Time to Tumor Progression: The median TTP based on independent assessment was 5.4 months (95% CI: 2.7, 11.8) for patients with ALK-positive NSCLC and 11.1 months (95% CI: 1.6, NR) for patients with ROS1-positive NSCLC.

- Probability of First Event Being a CNS Progression, non-CNS Progression, or Death: The cumulative incidence rate of progression within the brain was comparable with the cumulative incidence rate of progression outside the brain in all patients, while in patients who had CNS metastases at baseline, the cumulative incidence rate of progression within the brain was higher than the cumulative incidence rate of progression outside the brain.

- Progression-Free Survival: The median PFS based on independent assessment was 5.3 months (95% CI: 2.5, 11.8) for patients with ALK positive NSCLC and 10.1 months (95% CI: 1.6, NR) for patients with ROS1-positive NSCLC.

- Overall Survival: A total of 26 patients (49.1%) died during Phase 1. The survival probability at 12 and 18 months was 62.7 (95% CI: 47.9, 74.4) and 56.6 (95% CI: 41.9, 69.0).

Pharmacokinetic Results-Phase 1:

- Following single doses of 10 mg to 200 mg, lorlatinib was absorbed rapidly with median time to reach C_{max} (T_{max}) values of 1.09 and 2.00 hours and showed biphasic decline with mean $t_{½}$ value of 17.2 to 27.2 hours across all doses.

- Lorlatinib exposures increased in a dose-proportional manner after single doses of 10-200 mg and in a slightly less than dose-proportional manner after multiple doses of 10-200 mg QD.

- The pilot food effect evaluation showed that total plasma lorlatinib exposure based on $AUC_{\tau}$and C_{max} were similar following administration of a single lorlatinib 100 mg dose under fed and fasted conditions, indicating that food appeared not to affect lorlatinib plasma exposure.

- Co-administration with repeated 25 mg and 150 mg QD lorlatinib dosing decreased oral AUC_{inf} and C_{max} of MDZ, indicating that continuous dosing with lorlatinib had a net induction effect on CYP3A.

- Urinary recovery of unchanged lorlatinib following multiple doses was low (<0.5%).

- Both urinary 6β-OHC/C ratio and blood 6β-hydroxycholesterol/cholesterol ratios indicated that maximum induction of CYP3A was reached by 8 days of multiple dosing with lorlatinib 100 mg QD.

Biomarker Results-Phase 1

- Plasma Circulating Nucleic Acid: Out of the 41 patients with ALK positive NSCLC included in Phase 1, 39/41 (95.1%) had plasma samples available for the analysis at baseline. No ALK kinase domain mutation was detected in 25 out of 39 (64.1%) patients; 9 out of 25 (36%) patients who did not harbor an ALK kinase domain mutation experienced a response. The median treatment duration for this group of patients was 20.8 months (range: 0.07, 35.02). ALK kinase domain mutations were detected in 14 out of 39 (35.9%) patients; 5 out of 14 (35.7%) patients harboring at least 1 ALK mutation experienced a PR. The median treatment duration for these patients was 8.6 months (range: 1.41, 35.68). One (1) patient experienced a best overall response (BOR) of SD with duration of stable disease of 2.7 months, while 8 experienced a BOR of PD. Three (3) G1202R mutations were detected, and 1 patient harboring this mutation experienced a BOR of SD with duration of stable disease of 2.7 months; the other 2 patients harboring this mutation had a BOR of PD.

- Tumor Tissue Analysis: Out of the 41 patients with ALK-positive NSCLC included in Phase 1, 39/41 (95.1%) had tumor tissue samples available for the analysis. No ALK kinase domain mutation was detected in 23 out of 39 (59.0%) patients; 11 out of 23 (47.8%) patients who did not harbor an ALK mutation experienced a response (1 CR and 10 PR). The median treatment duration for this group of patients was 9.2 months (range: 0.07, to 35.7 months).

- Circulating Nucleic Acid Peripheral Blood and Tumor Tissue comparison: The same mutations and/or mutational status was found in 18 (43.9%) patients while different mutations between the blood based and the tumor based assay results were found for 10 (24.4%) patients.

Patient Reported Outcomes-Phase 1:

- Completion Rates: During Phase 1, the percentage of patients completing at least 1 question on the EORTC QLQ-C30 questionnaire and QLQ-LC13 module ranged from 61.1% to 100% over the first 33 cycles.

- EORTC QLQ-C30 and EORTC QLQ-LC13

  Global QOL: a statistically significant and clinically meaningful improvement from Baseline was observed for global QOL for Cycles 3 to 5, 9, and 11. A statistically significant improvement from Baseline was observed for global QOL in Cycle 2, but did not cross the 10-point threshold, so was not clinically meaningful. The majority of patients had either improved (46.5%) or stable (30.2%) scores in global QOL during treatment (including all cycles).

  Functioning: a statistically significant and clinically meaningful improvement from Baseline was observed for the following functional domains at the following time points: role functioning (Cycles 5 and 9), emotional functioning (Cycles 9, 10, and 32), and social functioning (Cycles 3, 5, and 9). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a clinically meaningful improvement, for the following functional domains: physical functioning (Cycles 3 and 5), role functioning (Cycles 2 and 3), and emotional functioning (Cycles 1, 5, 15, and 20). The majority of patients had improved or stable scores for each of the functioning domains of the EORTC QLQ-C30.

  Symptoms (EORTC QLQ-C30): a statistically significant and clinically meaningful improvement from Baseline was observed for the following symptoms: fatigue (Cycles 4 to 6, 9, 10, 11, 24, and 32), pain (Cycles 2, 3, 5, 7, 9, and 13 to 15), dyspnoea (Cycles 4 and 5), insomnia (Cycles 4, 6, 7, 9, 11, 13 to 15, 17 to 21, 24, and 26), and appetite loss (Cycles 2, 3, 5, and 6). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a clinically meaningful improvement, for the following symptoms: fatigue (Cycles 2 and 3), nausea and vomiting (Cycles 26, 28, and 29), appetite loss (Cycles 4, 7, 8, 11, 13), and diarrhoea (Cycle 12). The majority of patients were improved or stable for symptoms.

  Symptoms (EORTC QLQ-LC13): a statistically significant and clinically meaningful improvement from Baseline was observed for the following symptoms at the following timepoints: coughing (Cycles 3 to 7, 9 to 11, 13 to 16, s 18 to 21, 23, 27, and 30), pain in chest (Cycles 2, 4, 7, 9 to 13, 16, 17, 23, 24, 26, 27, 29, and 30) and pain in other parts (Cycles 2, 5, 7 to 9, 13 to 15, 22, 24, and 27). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a clinically meaningful improvement, for the following symptoms: coughing (Cycle 2), dyspnoea (Cycle 4), pain in chest (Cycle 5), pain in arm or shoulder (Cycle 27). The majority of patients were improved or stable for symptoms.

Efficacy Results-Phase 2:

Primary Efficacy

- Objective Response Rate: The confirmed ORRs based on independent assessment were 90% (95% CI: 73.5, 97.9) for cohort EXP-1, 74.1% (95% CI: 53.7, 88.9) for cohort EXP-2, 65.6% (95% CI: 46.8, 81.4) for cohort EXP-3A, 33.3% (95% CI: 16.5, 54.0) for cohort EXP-3B, 41.5% (95% CI: 29.4, 54.4) for cohort EXP-4, 34.8% (95% CI: 21.4, 50.2) for cohort EXP-5, and 36.2% (95% CI: 22.7, 51.5) for cohort EXP-6, respectively.

- Intra-cranial Objective Response Rate: The confirmed IC-ORRs based on independent assessment were 75.0% (95% CI: 34.9, 96.8) for cohort EXP-1, 58.8% (95% CI: 32.9, 81.6) for cohort EXP-2, 40.0% (95% CI: 19.1, 63.9) for cohort EXP-3A, 41.7% (95% CI: 15.2, 72.3) for cohort EXP-3B, 55.6% (95% CI: 40.0, 70.4) for cohort EXP-4, 39.5% (95% CI: 24.0, 56.6) for cohort EXP-5, and 56.0% (95% CI: 34.9, 75.6) for cohort EXP-6, respectively.

- Disagreement in Response Assessment: The overall discordance rate was 16.4% and for intra-cranial responses was 29.6%.

Secondary Efficacy

- Time to Tumor Response: For patients with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 5.4 months) for cohort EXP-1, 1.4 months (range: 1.2 to 11.0 months) for cohort EXP-2, 1.4 months (range: 1.1 to 5.7 months) for cohort EXP-3A, 1.4 months (range: 1.3 to 3.0 months) for cohort EXP-3B, 2.6 months (range: 1.2 to 9.9 months) for cohort EXP-4, 1.4 (range: 1.2 to 4.0 months) for cohort EXP-5, and 1.4 months (range: 1.3 to 4.2 months) for cohort EXP-6.

- Intra-cranial Time to Tumor Response: For patients with baseline CNS metastases and a confirmed objective response by independent assessment, the median IC-TTR was 2.1 months (range: 1.2 to 2.8 months) for cohort EXP-1, 1.4 months (range: 1.2 to 1.5 months) for cohort EXP-2, 1.4 months (range: 1.1 to 5.7 months) for cohort EXP-3A, 1.4 months (range: 1.3 to 3.0 months) for cohort EXP-3B, 1.5 months (range: 1.2 to 6.2 months) for cohort EXP-4, 1.4 (range: 1.2 to 3.3 months) for cohort EXP-5, and 1.4 months (range: 1.2 to 5.5 months) for cohort EXP-6.

- Duration of Response: The median DOR could not be reliably estimated in any of the expansion cohorts with the exception of EXP-4 (median DOR: 6.93 months) and EXP-6 (median DOR: 13.83 months). Overall, 72% of patients were censored (range for EXP-1 to EXP-6 was 59 to 89%). The lower boundaries of the 95% CIs (months), by independent assessment, were 10.02 for EXP-1, NR for EXP-2, 11.10 for EXP-3A, 4.14 for EXP-3B, 5.22 for EXP-4, 4.17 for EXP-5, and 11.10 for EXP-6. The total number of patients with a DOR of >6 months with and without subsequent PD or death was 10/38 and 61/99, respectively.

- Intra-cranial Duration of Response: The median IC-DOR was 9.2 months (95% CI: 8.28, 10.02) for EXP-1, NR (95% CI: NR) for EXP-2, NR (95% CI: 8.38, NR) for EXP-3A, NR (95% CI: 4.11, NR) for EXP-3B, 14.52 months (95% CI: NR) for EXP-4, 8.3 months (95% CI: 6.93, NR) for EXP-5, and NR (95% CI: 4.99, NR) for EXP-6. The total number of patients with baseline CNS metastases with an IC-DOR of >6 months with and without subsequent progressive disease or death was 9/21 and 39/69, respectively with overall approximately 77% of responding patient censored (range for EXP-1 to EXP-6 was 60.0% to 100%).

- Disease Control Rate at 12 Weeks: The DCRs at 12 weeks based on independent assessment were 93.3% (95% CI: 77.9, 99.2) for cohort EXP-1, 85.2% (95% CI: 66.3, 95.8) for cohort EXP-2, 78.1% (95% CI: 60.0, 90.7) for cohort EXP-3A, 55.6% (95% CI: 35.3, 74.5) for cohort EXP-3B, 63.1% (95% CI: 50.2, 74.7) for cohort EXP-4, 52.2% (95% CI: 36.9, 67.1) for cohort EXP-5, and 63.8% (95% CI: 48.5, 77.3) for cohort EXP-6, respectively.

- Intra-cranial Disease Control Rate at 12 Weeks: The IC-DCRs at 12 weeks based on independent assessment were 76.4% (95% CI: 69.1, 82.6) overall, 87.5% (95% CI: 47.3, 99.7) for cohort EXP-1, 94.1% (95% CI: 71.3, 99.9) for cohort EXP-2, 78.1% (95% CI: 60.0, 90.7) for cohort EXP-3A, 55.6% (95% CI: 35.3, 74.5) for cohort EXP-3B, 77.8% (95% CI: 62.9, 88.8) for cohort EXP-4, 68.4% (95% CI: 51.3, 82.5) for cohort EXP-5, and 72.0% (95% CI: 50.6, 87.9) for cohort EXP-6.

- Time to Tumor Progression on the Last Prior Treatment Regimen Before Lorlatinib: For patients who had received systemic therapy prior to lorlatinib, the median TTP was 11.5 months (95% CI: 7.2, 19.6) for cohort EXP-2, 12.8 months (95% CI: 9.2, 16.9) for cohort EXP-3, 10.2 months (95% CI: 7.6, 14.9) for cohort EXP-4, and 3.7 months (95% CI: 2.1, 6.4) for cohort EXP-5. The corresponding hazard ratios were 0.511 (95% CI: 0.229, 1.143) for EXP-2, 0.606 (95% CI: 0.342, 1.073) for EXP-3, 0.814 (95% CI: 0.541, 1.225) for EXP-4, and 0.608 (95% CI: 0.366, 1.008) for EXP-5. For patients who had received ALK /ROS1 TKI treatment prior to lorlatinib, the median TTP was 11.5 months (95% CI: 7.2, 19.6) for cohort EXP-2, 12.9 months (95% CI: 11.2, 18.1) for cohort EXP-3, 12.1 months (95% CI: 7.9, 16.4) for cohort EXP-4, and 3.7 months (95% CI: 2.1, 6.6) for cohort EXP-5. The corresponding hazard ratios were 0.511 (95% CI: 0.229, 1.143) for EXP-2, 0.572 (95% CI: 0.342, 1.010) for EXP-3, 0.757 (95% CI: 0.489, 1.173) for EXP-4, and 0.628 (95% CI: 0.382, 1.034) for EXP-5. For patients who had received systemic therapy other than ALK/ROS1 TKI treatment prior to lorlatinib, the median TTP was 19.6 months (95% CI: 16.1, 30.7) for cohort EXP-2, 8.5 months (95% CI: 5.0, 12.6) for EXP-3, 5.0 months (95% CI: 3.1, 10.8) for cohort EXP-4, and 5.6 months (95% CI: 4.7, 11.2) for cohort EXP-5. The corresponding hazard ratios were NR for EXP-2, 0.314 (95% CI: 0.086, 1.148) for EXP-3, 0.745 (95% CI: 0.357, 1.552) for EXP-4, and 0.886 (95% CI: 0.398, 1.972) for EXP-5.

- Time to Tumor Progression: The median TTP based on independent assessment was NR (95% CI: 11.4, NR) for cohort EXP-1, NR (95% CI: NR, NR) for cohort EXP-2, 9.0 months (95% CI: 5.5, NR) for cohort EXP-3, 8.4 months (95% CI: 5.6, 13.7) for cohort EXP-4, 7.1 months (95% CI: 4.1, 12.5) for cohort EXP-5, and 12.5 months

(95% CI: 8.2, NR) for cohort EXP-6. Analyses for TTP by EXP-3A or EXP-3B were not performed.

- Intra-cranial Time to Tumor Progression: The median IC-TTP based on independent assessment was 11.4 months (95% CI: 9.6, 11.4) for cohort EXP-1, NR (95% CI: NR, NR) for cohort EXP-2, NR months (95% CI: 6.9, NR) for cohort EXP-3, 15.7 months (95% CI: 11.0, 15.7) for cohort EXP-4, NR (95% CI: 8.3, NR) for cohort EXP-5, and NR (95% CI: NR, NR) for cohort EXP-6.

- Probability of First Event Being a CNS Progression, non-CNS Progression, or Death: The cumulative incidence rate of progression within the brain was lower than the cumulative incidence rate of progression outside the brain in all patients and in patients who had CNS metastases at baseline.

- Progression-Free Survival: The median PFS based on independent assessment was NR (95% CI: 11.4, NR) for cohort EXP-1, NR for cohort EXP-2, 12.5 months (95% CI: 6.9, NR) for cohort EXP-3A, 5.5 months (95% CI: 2.9, 9.0) for cohort EXP-3B, 7.3 months (95% CI: 5.4, 11.0) for cohort EXP-4, 5.6 months (95% CI: 4.0, 12.5) for cohort EXP-5, and 9.6 months (95% CI: 4.7, NR) for cohort EXP-6.

- Overall Survival: The median duration of follow-up for OS was 9.9 months (95% CI: 9.2, 10.7). A total of 64 patients (23.4%) died during Phase 2. The survival probability, for the total population, at 12 months was 74.2% (95% CI: 67.5, 79.8).

Pooled Analyses-Phase 2

- Pooled Objective Response Rate: The pooled ORRs based on independent assessment were 47.2% (95% CI: 40.1, 54.4) for EXP-2:EXP-5, 69.5% (95% CI: 56.1, 80.8) for EXP-2:EXP-3A, and 38.7% (95% CI: 29.6, 48.5) for EXP-4:EXP-5.

- Pooled Intra-cranial Objective Response Rate: The pooled IC-ORRs based on independent assessment were 53.0% (95% CI: 44.2, 61.8) for EXP-2:EXP-5, 48.2% (95% CI: 37.1, 59.4) for EXP-4:EXP-5, and 67.6% (95% CI: 50.2, 82.0) for EXP-2:EXP-3A.

- Pooled Time to Tumor Response: Among the 93 patients from pooled EXP-2:EXP-5 with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.1 to 11.0 months). Among the 41 patients from pooled EXP-2:EXP-3A with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.1 to 11.0 months). Among the 43 patients from pooled EXP-4:EXP-5 with a confirmed objective response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 9.9 months).

- Pooled Intra-cranial Time to Tumor Response: Among the 70 patients from pooled EXP-2:EXP-5 with a confirmed objective tumor response by independent assessment, the median IC-TTR was 1.4 months (range: 1.1 to 6.2 months). Among the 25 patients from pooled EXP-2:EXP-3A with CNS metastases and a confirmed objective tumor response

by independent assessment, the median IC-TTR was 1.4 months (range: 1.1 to 5.7 months). Among the 40 patients from pooled EXP-4:EXP-5 with CNS metastases and a confirmed objective tumor response by independent assessment, the median IC-TTR was 1.4 months (range: 1.2 to 6.2 months).

- Pooled Duration of Response: The median follow-up time for DOR was 6.9 months (95% CI: 6.9, 7.2) for EXP-2:EXP-5, 6.9 months (95% CI: 5.7, 6.9) for EXP-2:EXP-3A, and 7.2 months (95% CI: 6.9, 8.3) for EXP-4:EXP-5. A reliable estimate of median DOR was not reached in any pooled group at the time of data cutoff using the Kaplan-Meier method with 67.7% of responding patients in EXP-2:EXP-5, 78.0% of patients in EXP-2:EXP-3A, and 60.5% of patients in EXP-4:EXP-5 censored. The lower boundaries of the 95% CIs were 11.1 months for EXP-2:EXP-5, 11.1 months for EXP-2:EXP-3A, and 5.5 months for EXP-4:EXP-5, respectively. The frequency of patients with a DOR of >6 months with and without subsequent PD or death was 5/30 and 38/63, respectively, in pooled EXP-2: EXP-5, 2/9 and 18/32, respectively, in pooled EXP-2:EXP-3A, and 3/17 and 17/26, respectively, in pooled EXP-4:EXP-5.

- Pooled Intra-cranial Duration of Response: The median IC-DOR per independent review was 14.5 months (95% CI: NR, NR) for EXP-2:EXP-5, not reported for EXP-2:EXP-3A, and 14.5 months (95% CI: 8.25, 14.5 months) for EXP-4:EXP-5. The frequency of patients with CNS metastases with an IC-DOR of >6 months with and without subsequent PD or death was 7/16 and 32/54, respectively, in pooled EXP-2: EXP-5, 1/3 and 14/22, respectively, in pooled EXP-2:EXP-3A, and 6/11 and 17/29, respectively, in pooled EXP-4:EXP-5 with 77.1% of responding patients in EXP-2:EXP-5, 88.0% of patients in EXP-2:EXP-3A, and 72.5% of patients in EXP-4:EXP-5 censored.

- Pooled Disease Control Rate at 12 Weeks: The DCRs at 12 weeks based on independent assessment were 65.0% (95% CI: 57.9, 71.6) for pooled EXP-2:EXP-5, 81.4% (95% CI: 69.1, 90.3) for pooled EXP-2:EXP-3A, and 58.6% (95% CI: 48.8, 67.8) for pooled EXP-4:EXP-5.

- Pooled Intra-cranial Disease Control Rate at 12 Weeks: The IC-DCRs at 12 weeks based on independent assessment were 76.5% (95% CI: 68.4, 83.5) for pooled EXP-2:EXP-5, 86.5% (95% CI: 71.2, 95.5) for pooled EXP-2:EXP-3A, and 73.5% (95% CI: 62.7, 82.6) for pooled EXP-4:EXP-5.

- Pooled Progression-Free Survival: Of the 197 pooled EXP-2:EXP-5 patients, 100 (50.8%) patients had disease progression or died and 78 (39.6%) patients were still in follow-up for PFS at the date of data cutoff. Of the 59 pooled EXP-2:EXP-3A patients, 19 (32.2%) patients had disease progression or died and 36(61.0%) were still in follow-up for PFS. Of the 111 pooled EXP-4:EXP-5 patients, 55 (49.5%) patients had disease progression or died and 34 (30.6%) patients were still in follow-up for PFS. The median PFS based on independent assessment was 7.4 months (95% CI: 5.6, 11.0) for pooled EXP-2:EXP-5, was NR for EXP-2:EXP-3A (95% CI: 12.5, NR), and 6.9 months (95% CI: 5.4, 9.5) for pooled EXP-4:EXP-5.

- Pooled Overall Survival: A total of 53 patients (26.9%) died in pooled EXP-2:EXP-5, 9 patients (15.3%) died in pooled EXP-2:EXP-3A, and 35 patients (31.5%) died in pooled EXP-4:EXP-5. The survival probability at 12 months was 70.2% (95% CI: 61.9, 77.1) for EXP-2:EXP-5, 84.5% (95% CI: 67.4, 93.0) for EXP-2:EXP-3A, and 64.9% (95% CI: 53.8, 74.0) for EXP-4:EXP-5.

Pharmacokinetic Results-Phase 2:

- Lorlatinib PK following single and multiple doses of 100 mg QD were similar to those observed in Phase 1.

- After multiple oral doses of 100 mg QD, lorlatinib steady-state was reached by 15 days. There was no evidence for changes in lorlatinib exposure with long term dosing of 100 mg QD (up to 20 cycles) after steady state was reached.

- The AUC_{τ} of PF-06895751, the major human circulating metabolite, was about 80% higher than that of lorlatinib, after repeated 100 mg QD dosing.

- No overt differences in single- and multiple-dose PK parameters between the Asian and non-Asian groups were evident, with the exception of a 52% higher lorlatinib C_{max} after a single dose of 100 mg lorlatinib in Asian patients compared to that observed in non-Asian patients.

- Following multiple oral doses of lorlatinib at 100 mg QD or 150 mg QD, mean CSF/free plasma ratios were 0.7481 and 0.6791, respectively, for Phase 1 and Phase 2 and Japan LIC. The CSF/free plasma ratios of lorlatinib provided direct evidence that lorlatinib partitioned across the blood brain barrier.

Biomarker Results-Phase 2:

- Plasma Circulating Nucleic Acid Analysis:

  EXP-1 CNA Analysis: A single ALK kinase domain mutation (R1120W) was detected in the plasma sample from 1 patient. The patient did not demonstrate intrinsic resistance to lorlatinib.

  EXP-2 CNA Analysis: Six (6) out of 27 patients harbored ALK kinase domain mutations in their plasma circulating free DNA (cfDNA). No G1202R mutation was detected in this patient group.

  EXP-3 CNA Analysis: Eight (8) out of 59 patients had ALK kinase domain mutations in their plasma cfDNA.

  EXP-4 CNA Analysis: Seventeen (17) out of 65 patients harbored ALK kinase domain mutations in their plasma cfDNA.

  EXP-5 CNA Analysis: Fourteen (14) out of 46 patients harbored ALK kinase domain mutations in their plasma cfDNA.

EXP-2:EXP-5 CNA Pooled Analysis: Out of this group of 190 patients, 139 (73.2%) did not harbor any detectable ALK kinase domain mutation while 45 (23.7%) did harbor a mutation.

EXP-4:EXP-5 CNA Pooled Analysis: Out of 46 patients harboring ALK kinase domain mutations in their plasma cfDNA samples reported in this study, 31 (67.4%) were part of this group of heavily pretreated patients (N=106). Out of the 106 patients in this combined group, 72 (67.9%) did not harbor ALK kinase domain mutation in their plasma cfDNA. Twenty one (21) out of the 72 patients (29.2%) experienced a response (2 CR and 19 PR).

EXP-2:EXP-3A CNA Pooled Analysis: Out of this group of 58 patients who received crizotinib as only ALK TKI (with or without chemotherapy), 45 (77.6%) did not harbor any detectable ALK kinase domain mutation while 11 (19.0%) did harbor a mutation.

- Tumor Tissue Analysis:

  EXP-1 Tumor Tissue Analysis: No ALK kinase domain mutation was detected in any patient's tumor sample.

  EXP-2 Tumor Tissue Analysis: Seven (7) patients harbored ALK kinase domain mutations in their tumor tissue.

  EXP-3 Tumor Tissue Analysis: Eight (8) patients harbored ALK kinase domain mutations in their tumor tissue sample.

  EXP-4 Tumor Tissue Analysis: Eleven (11) patients harbored ALK kinase domain mutations in their tumor tissue sample.

  EXP-5 Tumor Tissue Analysis: Thirteen (13) patients harbored ALK kinase domain mutations in their tumor tissue sample.

  EXP-2:EXP-5 Tumor Tissue Pooled Analysis: Out of this group of 188 patients, 120 (63.8%) did not harbor any detectable ALK kinase domain mutation while 39 (20.7%) did harbor a mutation.

  EXP-4:EXP-5 Tumor Tissue Pooled Analysis: Out of this group of 105 patients, 57 (54.3%) did not harbor any detectable ALK kinase domain mutation while 24 (22.9%) did.

  EXP-2:EXP-3A Tumor Tissue Pooled Analysis: Out of this group of 56 patients who received crizotinib as only ALK TKI (with or without chemotherapy), 42 (75.0%) did not harbor any detectable ALK kinase domain mutation while 11 (19.6%) did harbor a mutation.

  Tumor Versus Blood Analyses: A total of 65 patients had 1 or both samples harboring 1 or more ALK kinase domain mutations.

Patient Reported Outcomes-Phase 2

- Completion Rates: During Phase 2, questionnaire compliance was high. The percentage of patients completing at least 1 question on the EORTC QLQ-C30 questionnaire and QLQ-LC13 module ranged from approximately 94.5% to 100% over the first 24 cycles.

- EORTC QLQ-C30 and EORTC QLQ-LC13

  Global QOL (EORTC QLQ-C30): A statistically significant and clinically meaningful improvement from Baseline was observed for global QOL for Cycles 2, 3, and 5. A statistically significant improvement from Baseline was observed for global QOL for Cycles 4, 6 to 17 and 20, but did not cross the 10-point threshold, so was not clinically meaningful. The majority of patients had either improved (42.7%) or stable (39.6%) scores in global QOL during treatment (including all cycles).

  Functioning (EORTC QLQ-C30): A statistically significant and clinically meaningful improvement from Baseline was observed for the following functional domains at the following time points: role functioning (Cycle 2, 4 to 8, 10, 12, and 14) and emotional functioning (Cycle 10). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a clinically meaningful improvement, for the following functional domains: physical functioning (Cycles 2 to 15), role functioning (Cycles 3, 9, 11, 13, and 15), emotional functioning (Cycles 2 to 9 and 11 to 18), and social functioning (Cycles 2 to 15). The domains with the highest proportion of patients 'improved' from Baseline (≥10 point increase in mean change), were emotional functioning (38.4%), role functioning (37.6%), and social functioning (33.7%). The majority of patients had 'stable' scores for cognitive functioning with similar proportions showing improvement (24.3%) and worsening (23.9%).

  Symptoms (EORTC QLQ-C30): A statistically significant and clinically meaningful improvement from Baseline was observed for the following symptoms at the following time points: fatigue (Cycles 2 to 15, and 20 to 23), pain (Cycles 2 to 10, 13 to 14, and 21), insomnia (Cycles 2 to 24), and appetite loss (Cycles 2 to 16, and 21 to 24). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a clinically meaningful improvement, for the following symptoms. fatigue (Cycles 16 to 19), dyspnoea (Cycles 2 to 12), nausea and vomiting (Cycles 2 to 17), pain (Cycles 11, 12, 15 to 18), appetite loss (Cycles 17, 18, and 20), constipation (Cycles 2, 4 to 8, 10, and 15), diarrhoea (Cycles 8 and 14), and financial difficulties (Cycles 2 to 7, and 10). The symptoms that had the highest of patients 'improved' from Baseline (≥10 point decrease) were fatigue (49.0%) insomnia (45.1%), pain (40.8%), and appetite loss (41.6%).

  Symptoms (EORTC QLQ-LC13): A statistically significant and clinically meaningful improvement from Baseline was observed for the following symptoms at the following time points: coughing (Cycles 2 to 15, 17 to 18, 21 to 24) and pain in chest (Cycles 6 to 7, 9 to 11, 13, 16, 20, 21 and 23). In addition, a statistically significant improvement from Baseline was observed in other cycles, but did not reach a

clinically meaningful improvement, for the following symptoms: coughing (Cycles 16 and 19), hemoptysis (Cycles 2 to 6, 8, and 10 to 13), dyspnoea (Cycles 2 to 3, 5 to 10, and 12), dysphagia (Cycle 2), alopecia (Cycle 2), pain in Chest (Cycles 2 to 5, 8, 12, 14, 15, and 17 to 19), pain in arm or shoulder (Cycles 2 to 4, 6 to 11, 16, and 20), and pain in other parts (Cycles 2, 3, 8, and 10). A statistically significant and clinically meaningful worsening from Baseline was observed for peripheral neuropathy for Cycles 5 to 18. In addition, a statistically significant worsening from Baseline was observed for peripheral neuropathy for Cycles 3, 4, and 19, but was not clinically meaningful. The symptoms for which the highest proportion of patients 'improved' from Baseline (≥10 point decrease) were coughing (43.5%), pain in other parts (32.5%), pain in chest (29.8%), and dyspnoea (28.2%). The symptom for which the highest proportion of patients 'worsened' (≥10-point increase) from Baseline was peripheral neuropathy (38.4%)

Safety Results:

Dose-Limiting Toxicity (Phase 1 only) and RP2D

One (1) patient treated at 200 mg QD met the criteria for DLT. This patient failed to receive 16 of the planned 21 doses of lorlatinib during Cycle 1 due to toxicities attributed to lorlatinib, which met the protocol definition of a DLT. This patient experienced Grade 1 and Grade 2 CNS effects during Cycle 1, including Grade 2 aphasia and cognitive disorder, and Grade 1 visual impairment and abnormal dreams. As a result, lorlatinib was temporarily discontinued and the patient did not receive at least 16 of the planned 21 doses in Cycle 1. The CNS effects resolved within 7 days. Lorlatinib was reduced to dose of 150 mg QD during Cycle 2. Additionally, at the 150 and 200 mg QD cohorts, the majority of patients had treatment-related AEs resulting in dose interruption and/or dose reduction. As a result, it was agreed upon by the Sponsor and the Phase 1 Investigators to evaluate doses lower than 200 mg QD and consider an alternative dosing regimen. BID dosing was evaluated to potentially modulate these AEs, but the patients did not tolerate the 75 mg or 100 mg BID dosing.

Overall, 100 mg QD was a well-tolerated dose. At the time of the RP2D selection, none of the patients at 100 mg QD required a dose reduction. Temporary discontinuations did occur, but they were not attributed to CNS effects, but rather to HYPERCHOLESTEROLEMIA or HYPERTRIGLYCERIDEMIA, or to disease-related events. Additionally, 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 minimum efficacious concentration (C_{eff}) of 150 ng/mL to inhibit ALK G1202, during the majority of the 24 hour dosing interval, once steady-state was reached. Therefore, while the MTD was not formally identified, 100 mg QD was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

Serious Adverse Event

Phase 1

Incidences of treatment-emergent all-causality and treatment-related SAEs (Phase 1) were summarized in Table 7 and Table 8, respectively. Overall, 28 (51.9%) of the 54 patients had

SAEs and 7 (13.0%) patients had treatment-related SAEs. In the 100 mg QD cohort, 9 (52.9%) patients had SAEs and 1 (5.9%) patient had treatment-related SAEs.

Table 7. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Number (%) of Patients:										
Evaluable for AEs	3	3	3	12	17	3	3	3	3	4
With AEs	3 (100.00)	1 (33.33)	1 (33.33)	4 (33.33)	9 (52.94)	3 (100.00)	1 (33.33)	2 (66.67)	2 (66.67)	2 (50.00)
Number (%) of Patients with AEs by: System Organ Class and MedDRA (version 20.0) Preferred Term										
Cardiac Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1 (33.33)**	**2 (66.67)**	**0**	**0**
Cardiac arrest	0	0	0	0	0	0	0	1 (33.33)	0	0
Pericardial effusion	0	0	0	0	0	0	1 (33.33)	1 (33.33)	0	0
Eye Disorders	**0**	**0**	**0**	**1 (8.33)**	**0**	**0**	**0**	**0**	**0**	**1 (25.00)**
Cataract	0	0	0	1 (8.33)	0	0	0	0	0	0
Eye pain	0	0	0	0	0	0	0	0	0	1 (25.00)
Gastrointestinal Disorders	**0**	**0**	**0**	**1 (8.33)**	**0**	**0**	**0**	**0**	**1 (33.33)**	**1 (25.00)**
Abdominal pain	0	0	0	0	0	0	0	0	1 (33.33)	0
Crohn's disease	0	0	0	0	0	0	0	0	0	1 (25.00)
Ileus	0	0	0	0	0	0	0	0	0	1 (25.00)
Intestinal perforation	0	0	0	1 (8.33)	0	0	0	0	0	0
Large intestinal obstruction	0	0	0	1 (8.33)	0	0	0	0	0	0
General Disorders and Administration Site Conditions	**1 (33.33)**	**1 (33.33)**	**0**	**1 (8.33)**	**3 (17.65)**	**1 (33.33)**	**0**	**0**	**1 (33.33)**	**0**
Asthenia	0	0	0	1 (8.33)	0	0	0	0	0	0
Disease progression	1 (33.33)	1 (33.33)	0	1 (8.33)	3 (17.65)	1 (33.33)	0	0	1 (33.33)	0
Pyrexia	0	0	0	1 (8.33)	0	0	0	0	0	0
Hepatobiliary Disorders	**0**	**0**	**0**	**0**	**1 (5.88)**	**0**	**0**	**0**	**0**	**0**
Biloma	0	0	0	0	1 (5.88)	0	0	0	0	0
Infections and Infestations	**0**	**0**	**0**	**1 (8.33)**	**2 (11.76)**	**2 (66.67)**	**1 (33.33)**	**0**	**0**	**1 (25.00)**
Bronchitis	0	0	0	0	1 (5.88)	0	0	0	0	0
Influenza	0	0	0	1 (8.33)	0	0	0	0	0	0

Table 7. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Lower respiratory tract infection	0	0	0	0	0	0	0	0	0	1 (25.00)
Lung infection	0	0	0	0	0	1 (33.33)	0	0	0	0
Pneumonia	0	0	0	0	0	1 (33.33)	0	0	0	0
Pyelonephritis	0	0	0	0	0	0	1 (33.33)	0	0	0
Respiratory tract infection	0	0	0	0	0	0	1 (33.33)	0	0	0
Urinary tract infection	0	0	0	0	1 (5.88)	0	0	0	0	0
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**0**	**1 (5.88)**	**0**	**0**	**0**	**0**	**0**
Subdural hematoma	0	0	0	0	1 (5.88)	0	0	0	0	0
Investigations	**1 (33.33)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (25.00)**
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	0	1 (25.00)
Lipase increased	1 (33.33)	0	0	0	0	0	0	0	0	0
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**0**	**0**	**2 (66.67)**	**0**	**0**	**0**	**1 (25.00)**
Decreased appetite	0	0	0	0	0	0	0	0	0	1 (25.00)
Hypercalcemia	0	0	0	0	0	1 (33.33)	0	0	0	0
Hyperuricemia	0	0	0	0	0	1 (33.33)	0	0	0	0
Nervous System Disorders	**0**	**1 (33.33)**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**	**1 (33.33)**	**1 (25.00)**
Cerebrovascular accident	0	1 (33.33)	0	0	0	0	0	0	0	0
Hemorrhage intra-cranial	0	0	0	0	0	1 (33.33)	0	0	0	0
Headache	0	0	0	0	0	0	0	0	0	1 (25.00)
Presyncope	0	0	0	0	0	0	0	0	1 (33.33)	0
Seizure	0	0	0	0	0	1 (33.33)	0	0	0	1 (25.00)
Psychiatric Disorders	**1 (33.33)**	**0**	**0**	**0**	**2 (11.76)**	**2 (66.67)**	**0**	**0**	**0**	**0**
Confusional state	0	0	0	0	0	1 (33.33)	0	0	0	0
Delirium	0	0	0	0	1 (5.88)	0	0	0	0	0
Hallucination	0	0	0	0	0	1 (33.33)	0	0	0	0
Mental status changes	1 (33.33)	0	0	0	1 (5.88)	1 (33.33)	0	0	0	0

Table 7. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Respiratory, Thoracic and Mediastinal Disorders	**1 (33.33)**	**0**	**1 (33.33)**	**0**	**1 (5.88)**	**1 (33.33)**	**1 (33.33)**	**0**	**0**	**1 (25.00)**
Dyspnea	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	1 (25.00)
Hemoptysis	0	0	1 (33.33)	0	1 (5.88)	0	1 (33.33)	0	0	0
Hypoxia	1 (33.33)	0	0	0	0	1 (33.33)	0	0	0	0
Pleural effusion	0	0	0	0	1 (5.88)	0	0	0	0	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**	**0**	**0**
Dermatomyositis	0	0	0	0	0	1 (33.33)	0	0	0	0
Vascular Disorders	**0**	**1 (33.33)**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**	**0**	**0**
Embolism	0	1 (33.33)	0	0	0	1 (33.33)	0	0	0	0
Embolism venous	0	0	0	0	0	1 (33.33)	0	0	0	0

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; QD = once daily.

Table 8. Treatment-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1

	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Number (%) of Patients:										
Evaluable for AEs	3	3	3	12	17	3	3	3	3	4
With AEs	1 (33.33)	0	0	1 (8.33)	1 (5.88)	3 (100.00)	0	0	0	1 (25.00)
Number (%) of Patients with AEs by: System Organ Class and MedDRA (version 20.0) Preferred Term										
Eye Disorders	**0**	**0**	**0**	**1 (8.33)**	**0**	**0**	**0**	**0**	**0**	**0**
Cataract	0	0	0	1 (8.33)	0	0	0	0	0	0
Investigations	**1 (33.33)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (25.00)**
Aspartate aminotransferase increased	0	0	0	0	0	0	0	0	0	1 (25.00)
Lipase increased	1 (33.33)	0	0	0	0	0	0	0	0	0
Nervous System Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (25.00)**
Headache	0	0	0	0	0	0	0	0	0	1 (25.00)
Seizure	0	0	0	0	0	0	0	0	0	1 (25.00)
Psychiatric Disorders	**0**	**0**	**0**	**0**	**1 (5.88)**	**2 (66.67)**	**0**	**0**	**0**	**0**
Delirium	0	0	0	0	1 (5.88)	0	0	0	0	0
Hallucination	0	0	0	0	0	1 (33.33)	0	0	0	0
Mental status changes	0	0	0	0	0	1 (33.33)	0	0	0	0
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**	**0**	**0**
Dermatomyositis	0	0	0	0	0	1 (33.33)	0	0	0	0

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; QD = once daily.

Phase 2

Incidences of treatment-emergent all-causality and treatment-related SAEs (Phase 2) were summarized in Table 9 and Table 10, respectively. Overall, 89 (32.4%) patients had SAEs and 19 (6.9%) patients had treatment-related SAEs.

Table 9. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Page 1 of 4

	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Number (%) of Patients:						
Evaluable for AEs	30	27	60	65	46	47
With AEs	8 (26.67)	5 (18.52)	18 (30.00)	24 (36.92)	18 (39.13)	16 (34.04)
Number (%) of Patients with AEs by: System Organ Class and MedDRA (version 20.0) Preferred Term						
Cardiac Disorders	**1 (3.33)**	**0**	**0**	**4 (6.15)**	**1 (2.17)**	**3 (6.38)**
Atrial fibrillation	0	0	0	2 (3.08)	0	0
Atrioventricular block complete	0	0	0	0	0	1 (2.13)
Cardiac arrest	0	0	0	0	0	1 (2.13)
Myocardial infarction	0	0	0	0	0	1 (2.13)
Pericardial effusion	1 (3.33)	0	0	1 (1.54)	1 (2.17)	0
Sinus node dysfunction	0	0	0	1 (1.54)	0	0
Supraventricular tachycardia	0	0	0	1 (1.54)	0	0
Ear and Labyrinth Disorders	**1 (3.33)**	**0**	**0**	**1 (1.54)**	**0**	**0**
Vertigo	1 (3.33)	0	0	1 (1.54)	0	0
Eye Disorders	**0**	**0**	**0**	**1 (1.54)**	**0**	**0**
Blepharitis	0	0	0	1 (1.54)	0	0
Gastrointestinal Disorders	**3 (10.00)**	**0**	**0**	**3 (4.62)**	**2 (4.35)**	**1 (2.13)**
Abdominal pain upper	0	0	0	0	1 (2.17)	0
Abdominal wall hematoma	0	0	0	0	0	1 (2.13)
Gastric volvulus	1 (3.33)	0	0	0	0	0
Gastritis	0	0	0	0	1 (2.17)	0
Glossitis	1 (3.33)	0	0	0	0	0
Intestinal obstruction	1 (3.33)	0	0	0	0	0
Nausea	1 (3.33)	0	0	0	0	0
Pancreatitis	0	0	0	1 (1.54)	0	0
Vomiting	0	0	0	2 (3.08)	0	0
General Disorders and Administration Site Conditions	**3 (10.00)**	**0**	**8 (13.33)**	**7 (10.77)**	**8 (17.39)**	**6 (12.77)**
Chest pain	0	0	1 (1.67)	0	1 (2.17)	0
Disease progression	0	0	6 (10.00)	6 (9.23)	5 (10.87)	5 (10.64)

Table 9. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Fatigue	1 (3.33)	0	0	0	0	0
General physical health deterioration	0	0	0	0	1 (2.17)	0
Generalized edema	0	0	1 (1.67)	0	0	0
Pain	0	0	0	0	1 (2.17)	0
Peripheral swelling	0	0	1 (1.67)	0	0	0
Pyrexia	3 (10.00)	0	1 (1.67)	1 (1.54)	0	1 (2.13)
Hepatobiliary Disorders	**0**	**0**	**1 (1.67)**	**0**	**0**	**0**
Jaundice	0	0	1 (1.67)	0	0	0
Infections and Infestations	**3 (10.00)**	**2 (7.41)**	**5 (8.33)**	**5 (7.69)**	**1 (2.17)**	**0**
Diverticulitis	0	0	0	1 (1.54)	0	0
Erysipelas	0	0	1 (1.67)	0	0	0
Influenza	0	0	1 (1.67)	0	0	0
Lower respiratory tract infection	1 (3.33)	0	0	0	0	0
Lung abscess	0	0	1 (1.67)	0	0	0
Lung infection	0	1 (3.70)	0	0	1 (2.17)	0
Pneumonia	1 (3.33)	1 (3.70)	0	3 (4.62)	0	0
Respiratory tract infection	1 (3.33)	0	0	0	0	0
Sepsis	0	0	1 (1.67)	0	0	0
Septic shock	0	0	1 (1.67)	0	0	0
Upper respiratory tract infection	0	0	1 (1.67)	0	0	0
Vestibular neuronitis	0	0	0	1 (1.54)	0	0
Injury, Poisoning and Procedural Complications	**0**	**1 (3.70)**	**1 (1.67)**	**2 (3.08)**	**1 (2.17)**	**2 (4.26)**
Fall	0	0	0	1 (1.54)	0	0
Femoral neck fracture	0	0	1 (1.67)	1 (1.54)	0	0
Hip fracture	0	0	0	1 (1.54)	0	0
Humerus fracture	0	0	0	0	0	1 (2.13)
Pelvic fracture	0	0	0	1 (1.54)	0	0
Post procedural hemorrhage	0	0	0	0	1 (2.17)	0
Rib fracture	0	0	0	0	0	1 (2.13)
Road traffic accident	0	1 (3.70)	0	0	0	0
Toxicity to various agents	0	0	0	1 (1.54)	0	0

Table 9. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Investigations	**1 (3.33)**	**0**	**2 (3.33)**	**1 (1.54)**	**0**	**1 (2.13)**
Alanine aminotransferase increased	1 (3.33)	0	0	1 (1.54)	0	0
Aspartate aminotransferase increased	1 (3.33)	0	0	1 (1.54)	0	0
Blood cholesterol increased	0	0	1 (1.67)	0	0	0
Blood creatine phosphokinase increased	0	0	1 (1.67)	0	0	0
Ejection fraction decreased	0	0	0	0	0	1 (2.13)
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**0**	**1 (2.17)**	**0**
Hypertriglyceridemia	0	0	0	0	1 (2.17)	0
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (3.70)**	**1 (1.67)**	**1 (1.54)**	**1 (2.17)**	**0**
Back pain	0	0	0	1 (1.54)	1 (2.17)	0
Intervertebral disc protrusion	0	1 (3.70)	0	0	0	0
Spinal pain	0	0	1 (1.67)	0	0	0
Nervous System Disorders	**0**	**0**	**3 (5.00)**	**4 (6.15)**	**3 (6.52)**	**4 (8.51)**
Brain compression	0	0	0	0	0	1 (2.13)
Brain edema	0	0	0	0	1 (2.17)	0
Cognitive disorder	0	0	1 (1.67)	0	0	0
Hemorrhage intra-cranial	0	0	0	0	1 (2.17)	0
Headache	0	0	1 (1.67)	1 (1.54)	0	0
Hydrocephalus	0	0	0	1 (1.54)	0	0
Ischemic stroke	0	0	0	0	0	1 (2.13)
Lacunar stroke	0	0	0	1 (1.54)	0	0
Partial seizures	0	0	0	0	0	1 (2.13)
Peripheral sensory neuropathy	0	0	0	0	1 (2.17)	0
Presyncope	0	0	0	0	0	1 (2.13)
Syncope	0	0	1 (1.67)	0	0	0
Vagus nerve disorder	0	0	0	1 (1.54)	0	0
Psychiatric Disorders	**1 (3.33)**	**0**	**0**	**1 (1.54)**	**1 (2.17)**	**1 (2.13)**
Confusional state	1 (3.33)	0	0	0	0	0
Mental status changes	0	0	0	1 (1.54)	1 (2.17)	1 (2.13)
Respiratory, Thoracic and Mediastinal Disorders	**3 (10.00)**	**2 (7.41)**	**5 (8.33)**	**10 (15.38)**	**4 (8.70)**	**0**
Acute pulmonary edema	0	0	1 (1.67)	0	0	0

Table 9. All Causalities Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Acute respiratory failure	0	0	1 (1.67)	1 (1.54)	0	0
Asthma	1 (3.33)	0	0	0	0	0
Chronic obstructive pulmonary disease	0	0	1 (1.67)	0	0	0
Dyspnea	1 (3.33)	0	1 (1.67)	3 (4.62)	1 (2.17)	0
Dyspnea exertional	0	0	1 (1.67)	0	0	0
Epistaxis	1 (3.33)	0	0	0	0	0
Hypoxia	0	0	0	1 (1.54)	0	0
Interstitial lung disease	0	0	0	0	1 (2.17)	0
Lung disorder	0	0	0	1 (1.54)	0	0
Pleural effusion	0	0	1 (1.67)	1 (1.54)	0	0
Pleuritic pain	0	0	0	0	1 (2.17)	0
Pneumonitis	0	0	0	2 (3.08)	0	0
Pulmonary congestion	0	0	1 (1.67)	0	0	0
Pulmonary embolism	0	0	0	2 (3.08)	1 (2.17)	0
Pulmonary hypertension	0	1 (3.70)	0	0	0	0
Respiratory distress	0	1 (3.70)	0	0	0	0
Respiratory failure	0	0	1 (1.67)	1 (1.54)	0	0
Vascular Disorders	**0**	**0**	**0**	**5 (7.69)**	**3 (6.52)**	**1 (2.13)**
Aortic dissection	0	0	0	0	0	1 (2.13)
Deep vein thrombosis	0	0	0	1 (1.54)	0	0
Embolism	0	0	0	1 (1.54)	1 (2.17)	0
Hypertensive crisis	0	0	0	1 (1.54)	0	0
Peripheral artery occlusion	0	0	0	1 (1.54)	0	0
Superior vena cava syndrome	0	0	0	2 (3.08)	0	0
Thrombosis	0	0	0	0	2 (4.35)	0

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; EXP = expansion cohort; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients.

Table 10. Treatment-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2

Page 1 of 2

	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Number (%) of Patients:						
Evaluable for AEs	30	27	60	65	46	47
With AEs	3 (10.00)	0	5 (8.33)	4 (6.15)	5 (10.87)	2 (4.26)
Number (%) of Patients with AEs by:						
System Organ Class and						
MedDRA (version 20.0) Preferred Term						
Gastrointestinal Disorders	**1 (3.33)**	**0**	**0**	**1 (1.54)**	**1 (2.17)**	**0**
Gastritis	0	0	0	0	1 (2.17)	0
Glossitis	1 (3.33)	0	0	0	0	0
Pancreatitis	0	0	0	1 (1.54)	0	0
General Disorders and Administration Site Conditions	**0**	**0**	**1 (1.67)**	**0**	**0**	**0**
Generalized edema	0	0	1 (1.67)	0	0	0
Infections and Infestations	**1 (3.33)**	**0**	**1 (1.67)**	**0**	**0**	**0**
Erysipelas	0	0	1 (1.67)	0	0	0
Pneumonia	1 (3.33)	0	0	0	0	0
Investigations	**1 (3.33)**	**0**	**1 (1.67)**	**0**	**0**	**0**
Alanine aminotransferase increased	1 (3.33)	0	0	0	0	0
Aspartate aminotransferase increased	1 (3.33)	0	0	0	0	0
Blood cholesterol increased	0	0	1 (1.67)	0	0	0
Metabolism and Nutrition Disorders	**0**	**0**	**0**	**0**	**1 (2.17)**	**0**
Hypertriglyceridemia	0	0	0	0	1 (2.17)	0
Nervous System Disorders	**0**	**0**	**1 (1.67)**	**1 (1.54)**	**1 (2.17)**	**1 (2.13)**
Cognitive disorder	0	0	1 (1.67)	0	0	0
Peripheral sensory neuropathy	0	0	0	0	1 (2.17)	0
Presyncope	0	0	0	0	0	1 (2.13)
Vagus nerve disorder	0	0	0	1 (1.54)	0	0
Psychiatric Disorders	**1 (3.33)**	**0**	**0**	**0**	**0**	**1 (2.13)**
Confusional state	1 (3.33)	0	0	0	0	0
Mental status changes	0	0	0	0	0	1 (2.13)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**2 (3.33)**	**2 (3.08)**	**1 (2.17)**	**0**
Acute respiratory failure	0	0	1 (1.67)	0	0	0

Table 10. Treatment-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Dyspnea exertional	0	0	1 (1.67)	0	0	0
Interstitial lung disease	0	0	0	0	1 (2.17)	0
Pneumonitis	0	0	0	1 (1.54)	0	0
Respiratory failure	0	0	0	1 (1.54)	0	0
Vascular Disorders	**0**	**0**	**0**	**0**	**1 (2.17)**	**0**
Thrombosis	0	0	0	0	1 (2.17)	0

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; EXP = expansion cohort; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients.

Non-Serious Adverse Event

Phase 1

Incidence of treatment-emergent all-causality non-SAEs in >5% of patients (Phase 1) was summarized in Table 11. Overall, all 54 Phase 1 patients had treatment-emergent all-causality non-SAEs.

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Number (%) of Patients:										
Evaluable for AEs	3	3	3	12	17	3	3	3	3	4
With AEs	3 (100.00)	3 (100.00)	3 (100.00)	12 (100.00)	17 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	4 (100.00)
Number (%) of Patients with AEs by:										
System Organ Class and MedDRA (version 20.0) Preferred Term										
Blood and Lymphatic System Disorders	**1 (33.33)**	**1 (33.33)**	**0**	**5 (41.67)**	**8 (47.06)**	**3 (100.00)**	**1 (33.33)**	**1 (33.33)**	**2 (66.67)**	**3 (75.00)**
Anemia	0	0	0	2 (16.67)	6 (35.29)	3 (100.00)	1 (33.33)	1 (33.33)	2 (66.67)	2 (50.00)
Febrile neutropenia	0	0	0	0	0	0	0	0	0	1 (25.00)
Hemorrhagic diathesis	1 (33.33)	0	0	0	0	0	0	0	0	0
Iron deficiency anemia	0	0	0	0	0	1 (33.33)	0	0	0	0
Leukocytosis	0	0	0	2 (16.67)	0	0	0	0	0	0
Neutropenia	0	0	0	0	1 (5.88)	0	0	0	0	0
Thrombocytopenia	1 (33.33)	1 (33.33)	0	1 (8.33)	2 (11.76)	0	0	0	0	0
Thrombocytosis	0	0	0	0	1 (5.88)	0	0	0	0	0
Cardiac Disorders	**1 (33.33)**	**1 (33.33)**	**1 (33.33)**	**0**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**
Atrial fibrillation	0	1 (33.33)	0	0	0	0	0	1 (33.33)	0	0
Tachycardia	0	0	1 (33.33)	0	0	0	0	0	0	0
Ventricular dysfunction	1 (33.33)	0	0	0	0	0	0	0	0	0
Ear and Labyrinth Disorders	**0**	**1 (33.33)**	**1 (33.33)**	**4 (33.33)**	**4 (23.53)**	**1 (33.33)**	**0**	**0**	**0**	**1 (25.00)**
Ear discomfort	0	1 (33.33)	0	0	0	0	0	0	0	0
Hypoacusis	0	0	0	1 (8.33)	1 (5.88)	0	0	0	0	0
Tinnitus	0	0	1 (33.33)	3 (25.00)	3 (17.65)	1 (33.33)	0	0	0	1 (25.00)
Vertigo	0	0	0	1 (8.33)	0	0	0	0	0	0
Vertigo positional	0	1 (33.33)	0	0	0	0	0	0	0	0
Endocrine Disorders	**0**	**0**	**0**	**1 (8.33)**	**1 (5.88)**	**0**	**0**	**1 (33.33)**	**0**	**0**
Cushingoid	0	0	0	0	1 (5.88)	0	0	0	0	0
Hyperparathyroidism	0	0	0	0	0	0	0	1 (33.33)	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Hypothyroidism	0	0	0	1 (8.33)	0	0	0	0	0	0
Eye Disorders	**1 (33.33)**	**1 (33.33)**	**0**	**2 (16.67)**	**6 (35.29)**	**1 (33.33)**	**2 (66.67)**	**0**	**1 (33.33)**	**0**
Asthenia	0	0	0	0	0	0	0	0	1 (33.33)	0
Astigmatism	0	0	0	0	1 (5.88)	0	0	0	0	0
Conjunctival edema	0	0	0	0	1 (5.88)	0	0	0	0	0
Diplopia	0	0	0	1 (8.33)	0	0	0	0	0	0
Dry eye	1 (33.33)	0	0	0	0	0	0	0	0	0
Photophobia	0	0	0	0	0	0	1 (33.33)	0	0	0
Photopsia	0	0	0	0	1 (5.88)	0	0	0	0	0
Presbyopia	0	0	0	0	1 (5.88)	0	0	0	0	0
Retinal vein occlusion	0	0	0	0	0	0	1 (33.33)	0	0	0
Vision blurred	1 (33.33)	0	0	0	2 (11.76)	0	1 (33.33)	0	0	0
Visual acuity reduced	0	0	0	1 (8.33)	1 (5.88)	0	0	0	1 (33.33)	0
Visual impairment	0	1 (33.33)	0	1 (8.33)	0	1 (33.33)	1 (33.33)	0	0	0
Gastrointestinal Disorders	**2 (66.67)**	**2 (66.67)**	**2 (66.67)**	**5 (41.67)**	**11 (64.71)**	**2 (66.67)**	**3 (100.00)**	**2 (66.67)**	**3 (100.00)**	**4 (100.00)**
Abdominal discomfort	0	0	0	0	0	1 (33.33)	0	0	1 (33.33)	0
Abdominal distension	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	0
Abdominal pain	0	0	0	2 (16.67)	1 (5.88)	0	1 (33.33)	0	0	1 (25.00)
Abdominal pain upper	1 (33.33)	0	1 (33.33)	0	0	0	0	1 (33.33)	1 (33.33)	2 (50.00)
Ascites	0	0	0	0	0	0	0	0	1 (33.33)	0
Constipation	0	1 (33.33)	0	3 (25.00)	3 (17.65)	0	2 (66.67)	1 (33.33)	1 (33.33)	0
Crohn's disease	0	0	0	0	0	0	0	0	0	1 (25.00)
Diarrhea	0	0	1 (33.33)	3 (25.00)	3 (17.65)	1 (33.33)	2 (66.67)	0	0	3 (75.00)
Dry mouth	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	0
Dyspepsia	0	0	0	1 (8.33)	0	0	0	0	0	0
Dysphagia	0	0	0	1 (8.33)	0	0	0	0	0	0
Feces discolored	0	0	1 (33.33)	0	0	0	0	0	0	0
Gastrointestinal disorder	0	0	0	1 (8.33)	0	0	0	0	0	0
Gastroesophageal reflux disease	0	0	0	1 (8.33)	2 (11.76)	0	0	0	0	0
Intestinal obstruction	0	0	0	0	1 (5.88)	0	0	0	0	0
Nausea	1 (33.33)	1 (33.33)	0	2 (16.67)	2 (11.76)	0	1 (33.33)	0	1 (33.33)	2 (50.00)
Swollen tongue	1 (33.33)	0	0	0	0	0	0	0	0	0
Vomiting	0	2 (66.67)	1 (33.33)	1 (8.33)	3 (17.65)	0	0	0	0	2 (50.00)

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
General Disorders and Administration Site Conditions	**3 (100.00)**	**2 (66.67)**	**3 (100.00)**	**9 (75.00)**	**13 (76.47)**	**3 (100.00)**	**3 (100.00)**	**0**	**3 (100.00)**	**4 (100.00)**
Asthenia	1 (33.33)	0	2 (66.67)	3 (25.00)	3 (17.65)	0	1 (33.33)	0	0	0
Axillary pain	0	0	1 (33.33)	0	0	0	0	0	0	0
Catheter site extravasation	0	0	0	0	0	1 (33.33)	0	0	0	0
Chest discomfort	0	0	0	0	0	0	0	0	1 (33.33)	0
Chest pain	0	0	0	0	1 (5.88)	0	0	0	0	0
Chills	0	0	0	1 (8.33)	0	0	0	0	0	0
Disease progression	0	0	0	1 (8.33)	0	0	0	0	0	0
Face edema	0	0	0	1 (8.33)	0	0	0	0	0	0
Fatigue	1 (33.33)	1 (33.33)	0	4 (33.33)	4 (23.53)	2 (66.67)	1 (33.33)	0	1 (33.33)	3 (75.00)
Gait disturbance	1 (33.33)	1 (33.33)	1 (33.33)	1 (8.33)	1 (5.88)	0	1 (33.33)	0	0	0
Generalized edema	0	0	0	0	0	1 (33.33)	0	0	0	0
Mucosal inflammation	0	0	0	0	0	0	0	0	1 (33.33)	0
Non-cardiac chest pain	0	0	1 (33.33)	0	0	0	0	0	0	0
Edema	0	1 (33.33)	1 (33.33)	2 (16.67)	0	0	2 (66.67)	0	0	1 (25.00)
Edema peripheral	3 (100.00)	1 (33.33)	1 (33.33)	3 (25.00)	9 (52.94)	3 (100.00)	1 (33.33)	0	2 (66.67)	3 (75.00)
Pain	1 (33.33)	0	0	0	0	0	0	0	0	0
Performance status decreased	1 (33.33)	0	0	0	0	0	0	0	0	0
Peripheral swelling	1 (33.33)	0	0	2 (16.67)	0	0	1 (33.33)	0	0	0
Pyrexia	0	0	1 (33.33)	0	3 (17.65)	1 (33.33)	0	0	0	0
Swelling	1 (33.33)	0	0	0	0	0	0	0	0	0
Hepatobiliary Disorders	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (25.00)**
Hepatocellular injury	0	0	0	0	0	0	0	0	0	1 (25.00)
Immune System Disorders	**0**	**0**	**0**	**0**	**0**	**1 (33.33)**	**0**	**0**	**0**	**0**
Hypersensitivity	0	0	0	0	0	1 (33.33)	0	0	0	0
Infections and Infestations	**1 (33.33)**	**0**	**1 (33.33)**	**7 (58.33)**	**9 (52.94)**	**2 (66.67)**	**3 (100.00)**	**0**	**1 (33.33)**	**3 (75.00)**
Bacterial infection	0	0	0	0	1 (5.88)	0	0	0	0	0
Bronchitis	0	0	0	0	2 (11.76)	1 (33.33)	1 (33.33)	0	1 (33.33)	1 (25.00)
Candida infection	1 (33.33)	0	0	0	0	0	0	0	0	0
Cellulitis	0	0	0	1 (8.33)	0	0	0	0	0	0
Chronic sinusitis	0	0	0	0	0	0	0	0	0	1 (25.00)
Clostridium difficile colitis	0	0	0	0	1 (5.88)	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	25 mg QD n (%)	50 mg QD n (%)	75 mg QD n (%)	100 mg QD n (%)	150 mg QD n (%)	200 mg QD n (%)	35 mg BID n (%)	75 mg BID n (%)	100 mg BID n (%)
Enteritis infectious	0	0	0	1 (8.33)	0	0	0	0	0	0
Enterococcal bacteremia	0	0	0	0	0	1 (33.33)	0	0	0	0
Gastroenteritis	0	0	0	0	0	1 (33.33)	0	0	0	0
Helicobacter infection	0	0	0	0	1 (5.88)	0	0	0	0	0
Herpes virus infection	0	0	0	0	0	1 (33.33)	0	0	0	0
Influenza	0	0	0	0	1 (5.88)	0	0	0	0	0
Laryngitis	0	0	0	0	1 (5.88)	0	0	0	0	0
Lower respiratory tract infection	0	0	0	1 (8.33)	0	0	0	0	0	1 (25.00)
Lung infection	0	0	0	0	0	1 (33.33)	0	0	0	0
Nasopharyngitis	0	0	0	0	0	0	0	0	0	1 (25.00)
Oral candidiasis	0	0	0	0	1 (5.88)	0	0	0	0	0
Periodontitis	0	0	0	0	1 (5.88)	0	0	0	0	0
Pharyngitis	0	0	0	0	1 (5.88)	0	0	0	0	0
Pneumonia	0	0	1 (33.33)	0	0	0	0	0	0	1 (25.00)
Respiratory tract infection	0	0	0	1 (8.33)	2 (11.76)	0	0	0	0	0
Rhinitis	0	0	0	1 (8.33)	0	0	0	0	0	0
Sinusitis	0	0	0	1 (8.33)	0	0	0	0	0	0
Soft tissue infection	0	0	0	0	0	1 (33.33)	0	0	0	0
Tooth abscess	0	0	0	0	0	0	0	0	0	1 (25.00)
Upper respiratory tract infection	0	0	1 (33.33)	2 (16.67)	4 (23.53)	1 (33.33)	2 (66.67)	0	0	0
Urinary tract infection	0	0	0	1 (8.33)	2 (11.76)	0	2 (66.67)	0	0	1 (25.00)
Viral rhinitis	0	0	0	0	0	0	0	0	0	1 (25.00)
Viral upper respiratory tract infection	0	0	0	0	1 (5.88)	0	0	0	0	0
Injury, Poisoning and Procedural Complications	**0**	**2 (66.67)**	**0**	**0**	**4 (23.53)**	**0**	**0**	**1 (33.33)**	**0**	**0**
Contusion	0	0	0	0	1 (5.88)	0	0	0	0	0
Fall	0	0	0	0	1 (5.88)	0	0	0	0	0
Incision site pain	0	0	0	0	0	0	0	1 (33.33)	0	0
Joint dislocation	0	1 (33.33)	0	0	0	0	0	0	0	0
Laceration	0	1 (33.33)	0	0	1 (5.88)	0	0	0	0	0
Ligament sprain	0	0	0	0	1 (5.88)	0	0	0	0	0
Limb injury	0	1 (33.33)	0	0	0	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Toxicity to various agents	0	0	0	0	1 (5.88)	0	0	0	0	0
Investigations	**2 (66.67)**	**2 (66.67)**	**2 (66.67)**	**9 (75.00)**	**12 (70.59)**	**3 (100.00)**	**3 (100.00)**	**2 (66.67)**	**1 (33.33)**	**3 (75.00)**
Alanine aminotransferase increased	0	0	0	2 (16.67)	2 (11.76)	0	0	0	0	1 (25.00)
Amylase increased	2 (66.67)	0	0	1 (8.33)	4 (23.53)	0	1 (33.33)	0	0	0
Aspartate aminotransferase increased	0	1 (33.33)	1 (33.33)	2 (16.67)	2 (11.76)	0	2 (66.67)	0	0	1 (25.00)
Blood alkaline phosphatase increased	1 (33.33)	1 (33.33)	0	1 (8.33)	1 (5.88)	0	0	0	0	0
Blood cholesterol increased	0	0	0	6 (50.00)	3 (17.65)	1 (33.33)	0	0	0	1 (25.00)
Blood creatine phosphokinase increased	0	0	0	0	1 (5.88)	0	0	0	1 (33.33)	0
Blood creatinine increased	1 (33.33)	0	0	1 (8.33)	0	2 (66.67)	0	0	0	0
Blood phosphorus decreased	0	0	0	0	0	0	0	1 (33.33)	0	0
Blood triglycerides increased	0	1 (33.33)	0	2 (16.67)	3 (17.65)	1 (33.33)	0	0	0	1 (25.00)
Candida test positive	0	0	0	0	0	1 (33.33)	0	0	0	0
Ejection fraction decreased	1 (33.33)	0	0	0	0	2 (66.67)	0	0	0	1 (25.00)
Electrocardiogram QT prolonged	2 (66.67)	0	0	0	0	1 (33.33)	0	0	0	1 (25.00)
Gamma-glutamyltransferase increased	0	0	0	1 (8.33)	0	0	0	1 (33.33)	0	2 (50.00)
Glucose urine present	0	0	0	0	1 (5.88)	0	0	0	0	0
International normalized ratio increased	0	0	0	0	1 (5.88)	0	0	0	0	0
Lipase increased	2 (66.67)	0	0	2 (16.67)	5 (29.41)	0	1 (33.33)	0	0	1 (25.00)
Lipids increased	0	0	0	0	1 (5.88)	0	0	0	0	1 (25.00)
Liver function test increased	0	0	0	0	1 (5.88)	0	0	0	0	0
Transaminases increased	0	0	0	0	1 (5.88)	0	0	0	0	0
Weight decreased	0	0	0	0	0	1 (33.33)	0	0	0	0
Weight increased	0	1 (33.33)	1 (33.33)	3 (25.00)	3 (17.65)	1 (33.33)	1 (33.33)	0	0	2 (50.00)
Metabolism and Nutrition Disorders	**2 (66.67)**	**3 (100.00)**	**2 (66.67)**	**11 (91.67)**	**13 (76.47)**	**3 (100.00)**	**3 (100.00)**	**3 (100.00)**	**1 (33.33)**	**3 (75.00)**
Decreased appetite	0	0	0	0	0	0	0	0	0	2 (50.00)
Dehydration	0	0	0	1 (8.33)	1 (5.88)	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Fluid retention	0	0	0	2 (16.67)	0	0	0	1 (33.33)	0	0
Hypercalcemia	0	0	0	0	0	0	0	1 (33.33)	0	0
Hypercholesterolemia	1 (33.33)	2 (66.67)	1 (33.33)	7 (58.33)	12 (70.59)	2 (66.67)	3 (100.00)	1 (33.33)	1 (33.33)	1 (25.00)
Hyperglycemia	0	1 (33.33)	0	0	1 (5.88)	0	0	0	0	0
Hyperlipidemia	0	0	0	0	2 (11.76)	0	0	0	0	0
Hypertriglyceridemia	0	1 (33.33)	1 (33.33)	4 (33.33)	6 (35.29)	1 (33.33)	2 (66.67)	0	1 (33.33)	1 (25.00)
Hyperuricemia	0	0	0	0	0	1 (33.33)	0	0	0	1 (25.00)
Hypocalcaemia	0	0	0	0	0	1 (33.33)	0	0	0	0
Hypocholesterolemia	0	0	0	0	1 (5.88)	0	0	0	0	0
Hypokalemia	0	0	1 (33.33)	0	1 (5.88)	2 (66.67)	1 (33.33)	1 (33.33)	0	0
Hypomagnesaemia	0	1 (33.33)	1 (33.33)	0	0	3 (100.00)	0	1 (33.33)	0	0
Hypophosphatemia	1 (33.33)	2 (66.67)	0	0	0	1 (33.33)	1 (33.33)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**1 (33.33)**	**1 (33.33)**	**1 (33.33)**	**8 (66.67)**	**12 (70.59)**	**1 (33.33)**	**2 (66.67)**	**0**	**1 (33.33)**	**2 (50.00)**
Arthralgia	1 (33.33)	1 (33.33)	0	2 (16.67)	4 (23.53)	0	1 (33.33)	0	1 (33.33)	1 (25.00)
Arthritis	0	1 (33.33)	0	1 (8.33)	0	0	0	0	0	0
Back pain	0	1 (33.33)	0	2 (16.67)	6 (35.29)	0	2 (66.67)	0	1 (33.33)	2 (50.00)
Bone lesion	0	0	0	0	1 (5.88)	0	0	0	0	0
Bone pain	0	0	0	1 (8.33)	1 (5.88)	0	0	0	0	0
Flank pain	0	0	0	0	2 (11.76)	0	0	0	0	0
Joint swelling	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	0
Limb discomfort	0	0	0	1 (8.33)	0	0	0	0	0	0
Muscle spasms	0	0	0	0	0	0	0	0	1 (33.33)	1 (25.00)
Muscular weakness	1 (33.33)	1 (33.33)	0	1 (8.33)	0	0	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	1 (5.88)	0	0	0	0	0
Musculoskeletal discomfort	0	0	0	0	1 (5.88)	0	0	0	0	0
Musculoskeletal pain	1 (33.33)	0	1 (33.33)	0	2 (11.76)	0	0	0	0	0
Myalgia	0	0	0	1 (8.33)	2 (11.76)	0	0	0	0	1 (25.00)
Neck pain	0	0	0	1 (8.33)	2 (11.76)	0	0	0	0	0
Osteoarthritis	0	0	0	1 (8.33)	0	0	0	0	0	0
Osteoporosis	0	0	0	0	0	0	0	0	0	1 (25.00)
Pain in extremity	0	0	0	1 (8.33)	1 (5.88)	1 (33.33)	0	0	1 (33.33)	0
Pain in jaw	0	0	0	0	2 (11.76)	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Plantar fasciitis	0	0	0	0	1 (5.88)	0	0	0	0	0
Torticollis	0	0	0	0	0	0	0	0	1 (33.33)	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**0**	**0**	**0**	**0**	**1 (5.88)**	**0**	**0**	**0**	**0**	**0**
Melanocytic nevus	0	0	0	0	1 (5.88)	0	0	0	0	0
Nervous System Disorders	**2 (66.67)**	**3 (100.00)**	**1 (33.33)**	**9 (75.00)**	**12 (70.59)**	**3 (100.00)**	**3 (100.00)**	**1 (33.33)**	**3 (100.00)**	**4 (100.00)**
Amnesia	0	0	0	0	0	0	1 (33.33)	0	1 (33.33)	0
Aphasia	2 (66.67)	0	0	0	0	0	1 (33.33)	0	1 (33.33)	0
Ataxia	0	0	0	0	0	0	0	0	1 (33.33)	0
Balance disorder	0	0	0	0	0	0	0	0	0	1 (25.00)
Carpal tunnel syndrome	0	0	0	1 (8.33)	0	0	0	0	1 (33.33)	0
Cognitive disorder	1 (33.33)	1 (33.33)	0	2 (16.67)	0	2 (66.67)	1 (33.33)	0	0	1 (25.00)
Disturbance in attention	0	0	0	2 (16.67)	0	0	1 (33.33)	0	0	0
Dizziness	1 (33.33)	1 (33.33)	0	1 (8.33)	2 (11.76)	0	0	0	0	1 (25.00)
Dysesthesia	0	0	0	0	1 (5.88)	0	0	0	0	0
Dysarthria	0	1 (33.33)	0	1 (8.33)	0	0	0	0	1 (33.33)	0
Dysgeusia	0	0	0	2 (16.67)	0	0	0	0	0	1 (25.00)
Formication	0	0	0	0	0	0	1 (33.33)	0	0	0
Headache	1 (33.33)	0	0	3 (25.00)	1 (5.88)	1 (33.33)	1 (33.33)	1 (33.33)	1 (33.33)	2 (50.00)
Hemiparesis	0	0	0	0	0	1 (33.33)	0	0	0	0
Hypoesthesia	0	1 (33.33)	0	3 (25.00)	1 (5.88)	0	0	0	1 (33.33)	0
Memory impairment	0	1 (33.33)	0	1 (8.33)	2 (11.76)	0	0	0	0	1 (25.00)
Mental impairment	0	0	0	0	0	0	1 (33.33)	0	0	0
Migraine	0	0	0	1 (8.33)	0	0	0	0	0	0
Nervous system disorder	0	0	0	0	1 (5.88)	0	0	0	0	0
Neuralgia	0	1 (33.33)	0	0	0	0	0	0	0	0
Neuropathy peripheral	2 (66.67)	0	1 (33.33)	5 (41.67)	2 (11.76)	1 (33.33)	2 (66.67)	0	1 (33.33)	0
Neurotoxicity	0	0	0	0	1 (5.88)	0	0	0	0	0
Paresthesia	0	2 (66.67)	0	1 (8.33)	2 (11.76)	0	1 (33.33)	1 (33.33)	1 (33.33)	2 (50.00)
Partial seizures	0	0	0	0	0	1 (33.33)	0	0	0	0
Peripheral sensory neuropathy	0	0	0	1 (8.33)	1 (5.88)	0		0	0	0
Peroneal nerve palsy	1 (33.33)	0	0	0	0	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Presyncope	1 (33.33)	0	0	0	0	0	0	0	0	1 (25.00)
Psychomotor hyperactivity	0	0	0	0	1 (5.88)	0	0	0	0	0
Seizure	0	1 (33.33)	0	0	0	0	0	0	0	0
Sensory disturbance	0	0	0	0	0	1 (33.33)	0	0	0	0
Slow speech	0	0	1 (33.33)	1 (8.33)	3 (17.65)	0	1 (33.33)	0	0	0
Speech disorder	0	0	0	2 (16.67)	1 (5.88)	0	1 (33.33)	0	1 (33.33)	0
Tremor	0	0	0	1 (8.33)	0	0	0	0	0	0
Psychiatric Disorders	**2 (66.67)**	**0**	**0**	**5 (41.67)**	**5 (29.41)**	**1 (33.33)**	**3 (100.00)**	**1 (33.33)**	**3 (100.00)**	**1 (25.00)**
Abnormal dreams	0	0	0	0	0	1 (33.33)	1 (33.33)	0	0	0
Affect lability	1 (33.33)	0	0	3 (25.00)	0	0	1 (33.33)	0	0	0
Agitation	0	0	0	0	0	0	0	1 (33.33)	0	0
Anxiety	0	0	0	2 (16.67)	0	0	0	1 (33.33)	0	1 (25.00)
Attention deficit/hyperactivity disorder	0	0	0	0	1 (5.88)	0	0	0	0	0
Bradyphrenia	0	0	0	1 (8.33)	0	0	0	0	0	0
Confusional state	0	0	0	0	2 (11.76)	1 (33.33)	0	0	1 (33.33)	0
Depressed mood	0	0	0	1 (8.33)	0	0	0	0	1 (33.33)	0
Hallucination	0	0	0	0	0	1 (33.33)	0	0	0	0
Insomnia	0	0	0	1 (8.33)	0	1 (33.33)	0	0	0	0
Irritability	0	0	0	0	2 (11.76)	0	1 (33.33)	0	0	0
Mental status changes	1 (33.33)	0	0	0	0	0	0	0	0	0
Nightmare	0	0	0	0	0	0	1 (33.33)	0	0	0
Reading disorder	0	0	0	0	1 (5.88)	0	0	0	0	0
Sleep disorder	0	0	0	0	0	0	0	0	1 (33.33)	0
Renal and Urinary Disorders	**1 (33.33)**	**0**	**0**	**0**	**3 (17.65)**	**1 (33.33)**	**0**	**0**	**0**	**1 (25.00)**
Chronic kidney disease	0	0	0	0	0	1 (33.33)	0	0	0	0
Hematuria	0	0	0	0	2 (11.76)	0	0	0	0	0
Hydronephrosis	0	0	0	0	1 (5.88)	0	0	0	0	0
Micturition urgency	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	0
Pollakiuria	1 (33.33)	0	0	0	1 (5.88)	0	0	0	0	0
Proteinuria	0	0	0	0	1 (5.88)	1 (33.33)	0	0	0	0
Urinary incontinence	0	0	0	0	1 (5.88)	1 (33.33)	0	0	0	1 (25.00)

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	25 mg QD n (%)	50 mg QD n (%)	75 mg QD n (%)	100 mg QD n (%)	150 mg QD n (%)	200 mg QD n (%)	35 mg BID n (%)	75 mg BID n (%)	100 mg BID n (%)
Reproductive System and Breast Disorders	**0**	**0**	**0**	**1 (8.33)**	**1 (5.88)**	**0**	**0**	**0**	**0**	**0**
Menstruation irregular	0	0	0	0	1 (5.88)	0	0	0	0	0
Vaginal hemorrhage	0	0	0	1 (8.33)	0	0	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**3 (100.00)**	**3 (100.00)**	**1 (33.33)**	**1 (8.33)**	**7 (41.18)**	**2 (66.67)**	**3 (100.00)**	**2 (66.67)**	**1 (33.33)**	**4 (100.00)**
Acute respiratory failure	0	0	0	0	0	1 (33.33)	0	0	0	0
Bronchitis chronic	0	0	0	0	1 (5.88)	0	0	0	0	0
Cough	1 (33.33)	2 (66.67)	1 (33.33)	1 (8.33)	1 (5.88)	0	1 (33.33)	0	0	2 (50.00)
Dysphonia	1 (33.33)	0	0	0	0	0	0	0	0	1 (25.00)
Dyspnea	1 (33.33)	1 (33.33)	1 (33.33)	0	3 (17.65)	0	0	2 (66.67)	1 (33.33)	2 (50.00)
Dyspnea exertional	0	1 (33.33)	0	0	1 (5.88)	0	0	0	0	0
Epistaxis	0	0	0	0	1 (5.88)	1 (33.33)	0	1 (33.33)	0	0
Hemoptysis	0	0	0	0	0	0	2 (66.67)	0	0	0
Hypoxia	1 (33.33)	0	0	0	0	0	0	0	0	0
Laryngeal inflammation	0	0	1 (33.33)	0	0	0	0	0	0	0
Nasal congestion	0	0	0	1 (8.33)	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	1 (5.88)	0	0	0	0	1 (25.00)
Pleural effusion	0	0	0	0	0	0	0	1 (33.33)	0	0
Pleuritic pain	0	0	0	0	1 (5.88)	0	0	0	1 (33.33)	0
Productive cough	0	0	0	0	0	1 (33.33)	0	0	0	0
Pulmonary embolism	1 (33.33)	0	0	0	0	0	0	0	0	0
Pulmonary hypertension	0	0	0	0	0	0	0	0	0	1 (25.00)
Pulmonary edema	0	0	0	0	0	0	0	1 (33.33)	0	0
Rales	0	0	1 (33.33)	0	0	0	0	0	0	0
Respiratory tract congestion	0	0	0	0	0	1 (33.33)	0	0	0	0
Rhinorrhea	0	0	0	0	0	0	0	0	0	1 (25.00)
Sinus congestion	0	0	0	0	0	1 (33.33)	0	0	0	0
Wheezing	0	0	1 (33.33)	0	0	0	0	1 (33.33)	0	0
Skin and Subcutaneous Tissue Disorders	2 (66.67)	2 (66.67)	0	6 (50.00)	4 (23.53)	2 (66.67)	2 (66.67)	0	1 (33.33)	2 (50.00)
Alopecia	0	0	0	1 (8.33)	0	0	1 (33.33)	0	0	1 (25.00)
Dermatitis acneiform	0	1 (33.33)	0	0	0	0	0	0	0	0

Table 11. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 1 (Continued)

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	PF-06463922									
	10 mg QD n (%)	25 mg QD n (%)	50 mg QD n (%)	75 mg QD n (%)	100 mg QD n (%)	150 mg QD n (%)	200 mg QD n (%)	35 mg BID n (%)	75 mg BID n (%)	100 mg BID n (%)
Dermatitis contact	0	0	0	0	1 (5.88)	0	0	0	0	0
Dermatomyositis	0	0	0	0	0	1 (33.33)	0	0	0	0
Dry skin	0	0	0	0	1 (5.88)	0	0	0	1 (33.33)	1 (25.00)
Hyperhidrosis	0	0	0	2 (16.67)	0	0	0	0	0	0
Night sweats	0	0	0	1 (8.33)	0	0	0	0	0	0
Photosensitivity reaction	0	0	0	0	0	0	1 (33.33)	0	0	0
Pruritus	1 (33.33)	0	0	0	0	0	0	0	0	0
Rash	1 (33.33)	1 (33.33)	0	3 (25.00)	1 (5.88)	0	0	0	0	0
Rash erythematous	0	0	0	0	0	0	1 (33.33)	0	0	0
Rash maculo-papular	0	0	0	0	1 (5.88)	0	0	0	0	0
Rash pruritic	0	0	0	1 (8.33)	0	0	0	0	0	0
Rosacea	0	0	0	0	0	0	0	0	0	1 (25.00)
Seborrheic dermatitis	0	0	0	1 (8.33)	0	0	0	0	0	0
Skin lesion	0	0	0	0	0	1 (33.33)	0	0	0	0
Swelling face	0	0	0	0	0	0	0	0	0	1 (25.00)
Vascular Disorders	**2 (66.67)**	**0**	**0**	**3 (25.00)**	**1 (5.88)**	**2 (66.67)**	**0**	**1 (33.33)**	**1 (33.33)**	**2 (50.00)**
Deep vein thrombosis	1 (33.33)	0	0	0	0	0	0	0	0	1 (25.00)
Hematoma	0	0	0	0	0	0	0	0	0	1 (25.00)
Hemorrhage	0	0	0	1 (8.33)	0	0	0	0	0	0
Hot flush	0	0	0	0	0	0	0	0	1 (33.33)	1 (25.00)
Hypertension	0	0	0	2 (16.67)	1 (5.88)	1 (33.33)	0	1 (33.33)	0	0
Hypotension	1 (33.33)	0	0	0	0	1 (33.33)	0	0	0	0
Shock	0	0	0	0	0	0	0	1 (33.33)	0	0

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; QD = once daily.

Phase 2

Incidence of treatment-emergent all-causality non-SAEs in >5% of patients (Phase 2) was summarized in Table 12. Overall, in Phase 2, 273 out of 275 patients had treatment-emergent all-causality non-SAEs.

Table 12. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 2

Page 1 of 5

	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Number (%) of Patients:						
Evaluable for AEs	30	27	60	65	46	47
With AEs	30 (100.00)	27 (100.00)	59 (98.33)	65 (100.00)	45 (97.83)	47 (100.00)
Number (%) of Patients with AEs by: System Organ Class and MedDRA (version 20.0) Preferred Term						
Blood and Lymphatic System Disorders	**5 (16.67)**	**2 (7.41)**	**3 (5.00)**	**12 (18.46)**	**7 (15.22)**	**5 (10.64)**
Anemia	5 (16.67)	1 (3.70)	3 (5.00)	12 (18.46)	7 (15.22)	3 (6.38)
Thrombocytopenia	0	1 (3.70)	1 (1.67)	1 (1.54)	0	3 (6.38)
Cardiac Disorders	**2 (6.67)**	**1 (3.70)**	**0**	**5 (7.69)**	**4 (8.70)**	**3 (6.38)**
Pericardial effusion	2 (6.67)	0	0	0	3 (6.52)	0
Tachycardia	0	1 (3.70)	0	5 (7.69)	2 (4.35)	3 (6.38)
Ear and Labyrinth Disorders	**2 (6.67)**	**2 (7.41)**	**3 (5.00)**	**7 (10.77)**	**4 (8.70)**	**1 (2.13)**
Tinnitus	2 (6.67)	2 (7.41)	3 (5.00)	7 (10.77)	4 (8.70)	1 (2.13)
Eye Disorders	**5 (16.67)**	**3 (11.11)**	**1 (1.67)**	**6 (9.23)**	**6 (13.04)**	**4 (8.51)**
Eye irritation	2 (6.67)	0	0	0	0	0
Vision blurred	3 (10.00)	2 (7.41)	0	3 (4.62)	3 (6.52)	2 (4.26)
Visual impairment	0	1 (3.70)	1 (1.67)	3 (4.62)	3 (6.52)	2 (4.26)
Gastrointestinal Disorders	**17 (56.67)**	**11 (40.74)**	**24 (40.00)**	**37 (56.92)**	**21 (45.65)**	**22 (46.81)**
Abdominal distension	2 (6.67)	1 (3.70)	0	4 (6.15)	3 (6.52)	5 (10.64)
Abdominal pain	0	1 (3.70)	2 (3.33)	4 (6.15)	3 (6.52)	1 (2.13)
Constipation	8 (26.67)	5 (18.52)	8 (13.33)	8 (12.31)	5 (10.87)	5 (10.64)
Diarrhea	7 (23.33)	4 (14.81)	7 (11.67)	16 (24.62)	8 (17.39)	7 (14.89)
Dyspepsia	1 (3.33)	1 (3.70)	2 (3.33)	5 (7.69)	0	1 (2.13)
Dysphagia	0	1 (3.70)	3 (5.00)	4 (6.15)	2 (4.35)	0
Gastroesophageal reflux disease	1 (3.33)	0	4 (6.67)	1 (1.54)	2 (4.35)	3 (6.38)
Nausea	4 (13.33)	3 (11.11)	4 (6.67)	15 (23.08)	7 (15.22)	6 (12.77)
Odynophagia	0	2 (7.41)	1 (1.67)	0	1 (2.17)	0
Stomatitis	1 (3.33)	2 (7.41)	2 (3.33)	2 (3.08)	1 (2.17)	2 (4.26)
Toothache	2 (6.67)	0	1 (1.67)	0	1 (2.17)	1 (2.13)
Vomiting	4 (13.33)	0	5 (8.33)	7 (10.77)	3 (6.52)	5 (10.64)

Table 12. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
General Disorders and Administration Site Conditions	**22 (73.33)**	**15 (55.56)**	**39 (65.00)**	**39 (60.00)**	**30 (65.22)**	**33 (70.21)**
Asthenia	3 (10.00)	2 (7.41)	8 (13.33)	6 (9.23)	5 (10.87)	2 (4.26)
Chest pain	0	1 (3.70)	2 (3.33)	6 (9.23)	5 (10.87)	2 (4.26)
Face edema	2 (6.67)	0	2 (3.33)	1 (1.54)	1 (2.17)	1 (2.13)
Fatigue	8 (26.67)	4 (14.81)	3 (5.00)	11 (16.92)	4 (8.70)	7 (14.89)
Gait disturbance	0	0	0	5 (7.69)	3 (6.52)	0
Mucosal inflammation	3 (10.00)	0	1 (1.67)	2 (3.08)	1 (2.17)	0
Edema	4 (13.33)	1 (3.70)	4 (6.67)	6 (9.23)	4 (8.70)	3 (6.38)
Edema peripheral	12 (40.00)	12 (44.44)	29 (48.33)	21 (32.31)	15 (32.61)	24 (51.06)
Pain	2 (6.67)	0	1 (1.67)	4 (6.15)	2 (4.35)	2 (4.26)
Peripheral swelling	0	2 (7.41)	1 (1.67)	7 (10.77)	4 (8.70)	3 (6.38)
Pyrexia	2 (6.67)	1 (3.70)	5 (8.33)	7 (10.77)	1 (2.17)	5 (10.64)
Infections and Infestations	**9 (30.00)**	**9 (33.33)**	**12 (20.00)**	**21 (32.31)**	**4 (8.70)**	**11 (23.40)**
Bronchitis	1 (3.33)	2 (7.41)	1 (1.67)	3 (4.62)	0	1 (2.13)
Influenza	2 (6.67)	1 (3.70)	1 (1.67)	3 (4.62)	0	1 (2.13)
Lung infection	0	2 (7.41)	3 (5.00)	2 (3.08)	0	1 (2.13)
Pneumonia	0	1 (3.70)	0	8 (12.31)	1 (2.17)	0
Rhinitis	0	1 (3.70)	5 (8.33)	2 (3.08)	0	3 (6.38)
Sinusitis	0	0	2 (3.33)	0	1 (2.17)	3 (6.38)
Upper respiratory tract infection	5 (16.67)	2 (7.41)	2 (3.33)	6 (9.23)	1 (2.17)	3 (6.38)
Viral upper respiratory tract infection	1 (3.33)	3 (11.11)	2 (3.33)	2 (3.08)	2 (4.35)	3 (6.38)
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**6 (9.23)**	**2 (4.35)**	**5 (10.64)**
Fall	0	0	0	5 (7.69)	2 (4.35)	2 (4.26)
Procedural pain	0	0	0	1 (1.54)	0	3 (6.38)
Investigations	**20 (66.67)**	**18 (66.67)**	**37 (61.67)**	**42 (64.62)**	**30 (65.22)**	**32 (68.09)**
Alanine aminotransferase increased	5 (16.67)	1 (3.70)	6 (10.00)	5 (7.69)	5 (10.87)	7 (14.89)
Amylase increased	1 (3.33)	0	4 (6.67)	7 (10.77)	2 (4.35)	7 (14.89)
Aspartate aminotransferase increased	7 (23.33)	1 (3.70)	7 (11.67)	7 (10.77)	6 (13.04)	4 (8.51)
Blood cholesterol increased	13 (43.33)	13 (48.15)	18 (30.00)	17 (26.15)	16 (34.78)	18 (38.30)
Blood creatine phosphokinase increased	1 (3.33)	1 (3.70)	5 (8.33)	0	0	2 (4.26)
Blood triglycerides increased	2 (6.67)	2 (7.41)	4 (6.67)	3 (4.62)	3 (6.52)	3 (6.38)

Table 12. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Electrocardiogram QT prolonged	0	1 (3.70)	3 (5.00)	4 (6.15)	9 (19.57)	2 (4.26)
Lipase increased	3 (10.00)	4 (14.81)	1 (1.67)	7 (10.77)	5 (10.87)	6 (12.77)
Weight increased	4 (13.33)	4 (14.81)	11 (18.33)	18 (27.69)	10 (21.74)	10 (21.28)
Metabolism and Nutrition Disorders	**25 (83.33)**	**18 (66.67)**	**44 (73.33)**	**55 (84.62)**	**38 (82.61)**	**36 (76.60)**
Decreased appetite	4 (13.33)	1 (3.70)	0	5 (7.69)	2 (4.35)	2 (4.26)
Hypercholesterolemia	14 (46.67)	11 (40.74)	33 (55.00)	37 (56.92)	25 (54.35)	25 (53.19)
Hyperglycemia	3 (10.00)	1 (3.70)	2 (3.33)	3 (4.62)	6 (13.04)	5 (10.64)
Hyperlipidemia	2 (6.67)	0	0	0	2 (4.35)	0
Hypertriglyceridemia	20 (66.67)	12 (44.44)	27 (45.00)	44 (67.69)	29 (63.04)	23 (48.94)
Hyperuricemia	2 (6.67)	1 (3.70)	2 (3.33)	1 (1.54)	3 (6.52)	3 (6.38)
Hypoalbuminemia	3 (10.00)	0	3 (5.00)	4 (6.15)	4 (8.70)	2 (4.26)
Hypokalemia	2 (6.67)	0	4 (6.67)	4 (6.15)	2 (4.35)	3 (6.38)
Hypomagnesaemia	2 (6.67)	0	2 (3.33)	1 (1.54)	3 (6.52)	3 (6.38)
Hypophosphatemia	0	2 (7.41)	2 (3.33)	1 (1.54)	3 (6.52)	3 (6.38)
Musculoskeletal and Connective Tissue Disorders	**12 (40.00)**	**14 (51.85)**	**23 (38.33)**	**27 (41.54)**	**22 (47.83)**	**26 (55.32)**
Arthralgia	5 (16.67)	4 (14.81)	9 (15.00)	11 (16.92)	11 (23.91)	14 (29.79)
Back pain	2 (6.67)	5 (18.52)	2 (3.33)	10 (15.38)	5 (10.87)	3 (6.38)
Bone pain	1 (3.33)	0	1 (1.67)	0	3 (6.52)	0
Joint swelling	0	1 (3.70)	0	2 (3.08)	0	3 (6.38)
Muscle spasms	0	0	3 (5.00)	1 (1.54)	3 (6.52)	5 (10.64)
Muscular weakness	2 (6.67)	0	6 (10.00)	3 (4.62)	1 (2.17)	3 (6.38)
Musculoskeletal chest pain	0	0	3 (5.00)	0	1 (2.17)	4 (8.51)
Musculoskeletal pain	4 (13.33)	2 (7.41)	3 (5.00)	3 (4.62)	2 (4.35)	2 (4.26)
Musculoskeletal stiffness	1 (3.33)	0	0	3 (4.62)	1 (2.17)	4 (8.51)
Myalgia	3 (10.00)	2 (7.41)	5 (8.33)	6 (9.23)	5 (10.87)	6 (12.77)
Pain in extremity	2 (6.67)	8 (29.63)	4 (6.67)	6 (9.23)	4 (8.70)	8 (17.02)
Nervous System Disorders	**17 (56.67)**	**16 (59.26)**	**37 (61.67)**	**39 (60.00)**	**27 (58.70)**	**24 (51.06)**
Amnesia	0	0	6 (10.00)	6 (9.23)	2 (4.35)	2 (4.26)
Aphasia	0	2 (7.41)	0	2 (3.08)	2 (4.35)	1 (2.13)
Cognitive disorder	1 (3.33)	1 (3.70)	5 (8.33)	6 (9.23)	2 (4.35)	3 (6.38)
Disturbance in attention	0	0	1 (1.67)	2 (3.08)	1 (2.17)	3 (6.38)

Table 12. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Dizziness	6 (20.00)	4 (14.81)	5 (8.33)	9 (13.85)	7 (15.22)	11 (23.40)
Dysgeusia	2 (6.67)	0	1 (1.67)	6 (9.23)	2 (4.35)	1 (2.13)
Headache	5 (16.67)	6 (22.22)	8 (13.33)	11 (16.92)	10 (21.74)	2 (4.26)
Memory impairment	2 (6.67)	3 (11.11)	4 (6.67)	6 (9.23)	2 (4.35)	7 (14.89)
Neuropathy peripheral	5 (16.67)	3 (11.11)	6 (10.00)	7 (10.77)	5 (10.87)	5 (10.64)
Paraesthesia	3 (10.00)	4 (14.81)	11 (18.33)	9 (13.85)	5 (10.87)	5 (10.64)
Peripheral sensory neuropathy	3 (10.00)	3 (11.11)	7 (11.67)	3 (4.62)	4 (8.70)	2 (4.26)
Presyncope	0	0	1 (1.67)	0	0	3 (6.38)
Slow speech	0	0	5 (8.33)	2 (3.08)	0	0
Psychiatric Disorders	**8 (26.67)**	**7 (25.93)**	**12 (20.00)**	**15 (23.08)**	**10 (21.74)**	**9 (19.15)**
Affect lability	0	0	2 (3.33)	2 (3.08)	0	3 (6.38)
Anxiety	0	2 (7.41)	1 (1.67)	7 (10.77)	1 (2.17)	4 (8.51)
Depression	1 (3.33)	2 (7.41)	6 (10.00)	1 (1.54)	1 (2.17)	1 (2.13)
Insomnia	4 (13.33)	3 (11.11)	5 (8.33)	3 (4.62)	3 (6.52)	4 (8.51)
Irritability	3 (10.00)	1 (3.70)	3 (5.00)	2 (3.08)	6 (13.04)	1 (2.13)
Mood swings	2 (6.67)	1 (3.70)	0	0	0	0
Renal and Urinary Disorders	**2 (6.67)**	**0**	**1 (1.67)**	**1 (1.54)**	**0**	**2 (4.26)**
Hematuria	2 (6.67)	0	1 (1.67)	1 (1.54)	0	2 (4.26)
Respiratory, Thoracic and Mediastinal Disorders	**12 (40.00)**	**9 (33.33)**	**23 (38.33)**	**30 (46.15)**	**19 (41.30)**	**21 (44.68)**
Cough	9 (30.00)	3 (11.11)	7 (11.67)	11 (16.92)	8 (17.39)	9 (19.15)
Dysphonia	1 (3.33)	0	4 (6.67)	2 (3.08)	2 (4.35)	0
Dyspnea	7 (23.33)	3 (11.11)	14 (23.33)	13 (20.00)	9 (19.57)	14 (29.79)
Dyspnea exertional	1 (3.33)	1 (3.70)	3 (5.00)	6 (9.23)	3 (6.52)	1 (2.13)
Epistaxis	0	2 (7.41)	3 (5.00)	3 (4.62)	0	1 (2.13)
Hemoptysis	2 (6.67)	0	2 (3.33)	5 (7.69)	1 (2.17)	0
Hypoxia	0	0	0	1 (1.54)	5 (10.87)	1 (2.13)
Pleural effusion	1 (3.33)	0	0	5 (7.69)	1 (2.17)	4 (8.51)
Wheezing	1 (3.33)	0	1 (1.67)	2 (3.08)	3 (6.52)	2 (4.26)
Skin and Subcutaneous Tissue Disorders	**9 (30.00)**	**8 (29.63)**	**8 (13.33)**	**15 (23.08)**	**9 (19.57)**	**11 (23.40)**
Alopecia	2 (6.67)	2 (7.41)	2 (3.33)	2 (3.08)	3 (6.52)	2 (4.26)
Dry skin	3 (10.00)	1 (3.70)	2 (3.33)	0	0	1 (2.13)

Table 12. All Causalities Treatment-Emergent Non Serious Adverse Events in >5% of Patients by System Organ Class and Preferred Term – Phase 2 (Continued)

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	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Erythema	0	2 (7.41)	1 (1.67)	1 (1.54)	0	0
Hyperhidrosis	0	1 (3.70)	2 (3.33)	5 (7.69)	1 (2.17)	4 (8.51)
Pruritus	0	0	0	1 (1.54)	4 (8.70)	1 (2.13)
Rash	5 (16.67)	3 (11.11)	2 (3.33)	7 (10.77)	2 (4.35)	4 (8.51)
Vascular Disorders	**2 (6.67)**	**1 (3.70)**	**2 (3.33)**	**8 (12.31)**	**4 (8.70)**	**3 (6.38)**
Hypertension	2 (6.67)	1 (3.70)	2 (3.33)	8 (12.31)	4 (8.70)	3 (6.38)

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; EXP = expansion cohort; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients.

Withdrawals Due to Adverse Events

Phase 1

The incidence of patients permanently discontinuing from treatment due to AEs (Phase 1) was summarized in Table 13. Lorlatinib was permanently discontinued for 5 patients, which was associated with AEs. Each of the AEs was associated with no more than 1 patient. None of these AEs were considered treatment-related, except the AEs of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that were reported for a same patient.

Table 13. Discontinuations from Treatment Due To AEs – Phase 1

	PF-06463922									
	10 mg QD n (%)	**25 mg QD n (%)**	**50 mg QD n (%)**	**75 mg QD n (%)**	**100 mg QD n (%)**	**150 mg QD n (%)**	**200 mg QD n (%)**	**35 mg BID n (%)**	**75 mg BID n (%)**	**100 mg BID n (%)**
Number (%) of Patients	3	3	3	12	17	3	3	3	3	4
Discontinuations from Treatment										
Related to Study Drug	0	0	0	0	0	0	0	0	0	1 (25.0)
AEs	0	0	0	0	0	0	0	0	0	1 (25.0)
Not Related to Study Drug	1 (33.3)	0	0	0	0	2 (66.7)	0	0	0	1 (25.0)
AEs	1 (33.3)	0	0	0	0	2 (66.7)	0	0	0	1 (25.0)

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; QD = once daily.

Phase 2

The incidence of patients permanently discontinuing from treatment due to AEs was summarized in Table 14. Lorlatinib was permanently discontinued due to AEs for 20 patients (7 of them were treatment-related). Most of the AEs were associated with no more than 1 patient.

Table 14. Discontinuations from Treatment Due To AEs – Phase 2

	EXP-1 n (%)	EXP-2 n (%)	EXP-3 n (%)	EXP-4 n (%)	EXP-5 n (%)	EXP-6 n (%)
Number (%) of Patients	30	27	60	66	46	47
Discontinuations from Treatment						
Related to Study Drug	1 (3.3)	2 (7.4)	2 (3.3)	2 (3.0)	0	0
AEs	1 (3.3)	2 (7.4)	2 (3.3)	2 (3.0)	0	0
Not Related to Study Drug	0	0	2 (3.3)	1 (1.5)	5 (10.9)	5 (10.6)
AEs	0	0	2 (3.3)	1 (1.5)	5 (10.9)	5 (10.6)

Patients were only counted once per treatment for each row.
Included all data collected since the first dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AEs = adverse events; EXP = expansion cohort; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients.

Death

Phase 1

No deaths or Grade 5 (death-related) AEs were considered treatment-related. A total of 7 (13%) of 54 patients died on study treatment or within 28 days of their last dose of lorlatinib, and 20 (37.0%) patients died after 28 days of their last dose of lorlatinib (Table 15). Among the 27 deaths, the majority (24) died due to the disease under study, 1 patient died due to "other" causes specified as hypertension, supplemental oxygen dependency, morbid obesity and diabetes, and other 2 patients died due to an unknown cause.

Table 15. Summary of Deaths (Phase 1) - Safety Analysis Set

	Total (N=54)
	n (%)
Deaths from start of treatment to ≤28 days after last dose	7 (13.0)
Deaths during follow-up period >28 days after last dose	20 (37.0)
Cause of death	
Disease under study	24 (44.4)
Study treatment toxicity	0
Unknown	2 (3.7)
Other	1 (1.9)[a]

Abbreviations: N = number of evaluable patients; n = number of patients that died.
a. Specified as hypertension, supplemental oxygen dependency, morbid obesity and diabetes.

Phase 2

No deaths or Grade 5 (death-related) AEs were considered treatment-related. Out of 275 patients in Phase 2, 26 (9.5%) died on study treatment or within 28 days of their last dose of study drug, and 38 (13.8%) patients died after 28 days of their last dose (Table 16). For the 64 patients that died, the most common reason was Disease progression (59 [21.5%] patients), 4 were due to "other" causes, and 1 was due to unknown cause.

Table 16. Summary of Deaths (Phase 2) - Safety Analysis Set

	Total (N=275)
	n(%)
Deaths from start of treatment to ≤28 days after last dose	26 (9.5)
Deaths during follow-up period >28 days after last dose	38 (13.8)
Cause of death	
Disease under study	59 (21.5)
Study treatment toxicity	0
Unknown	1 (0.4)
Other	4 (1.5)[a]

Abbreviations: N = number of patients evaluable for death; n = number of patients that died.
a. Specified as pneumonia for 2 patients; Probable lung infection and suspected thrombus embolism for 1 patient each.

Clinical Laboratory Evaluations

Hematology

Phase 1

Most patients had hematology baseline values of Grade 0 or Grade 1. No Grade 4 hematology shifts and minor Grade 3 shifts were observed in Phase 1.

Phase 2

Most patients had hematology baseline values of Grade 0 or Grade 1. No Grade 4 hematology shifts and minor Grade 3 shifts were observed in Phase 2.

Chemistry

Phase 1

Most of the patients had the laboratory values at Grade 0 or Grade 1 at baseline. Very few of shifts to Grade 3 or Grade 4 were observed. No elevations of lipase and amylase transferred to the AE of Pancreatitis. One (1) patient had abnormal liver test values meeting the criteria of potential Hy's Law case.

Phase 2

Most of the patients had the laboratory values at Grade 0 or Grade 1 at baseline. Very few of shifts to Grade 3 or Grade 4 were observed. One (1) patient had abnormal liver test values meeting the criteria of potential Hy's Law case.

Lipids

Phase 1

In Phase 1, all of the non-missing lipid values were Grade 0 or Grade 1 at baseline. For cholesterol (excluding patients with missing values at baseline), shifts to Grade 3 post-baseline occurred for 2 patients and shifts to Grade 4 post-baseline occurred for another 2 patients. For triglycerides (excluding patients with missing values at baseline), shifts to Grade 3 post-baseline occurred for 6 patients, and no shifts to Grade 4 post-baseline occurred.

Phase 2

In Phase 2, the majority of the cholesterol and triglycerides values were Grade 0 or Grade 1 at baseline. For cholesterol, shifts to Grade 3 post-baseline occurred for 42 patients and shifts to Grade 4 post-baseline occurred for 5 patients. For triglycerides, shifts to Grade 3 post-baseline occurred for 39 patients and shifts to Grade 4 post-baseline occurred for 8 patients.

Other Safety Evaluations

Vital Signs and Body Weight

Phase 1

A few patients had vital signs data meeting categorical values, 9 (16.7%) patients had body weight increase >20%.

Phase 2

A few patients had vital signs data meeting categorical values, 33 (12.6%) patients had body weight increase >20%.

Electrocardiograms

Phase 1

Fifty-two (52) (96.3%) patients had QTcF <450 msec at baseline, and no patients had a QTcF ≥500 msec post-baseline. ECG QT prolonged was reported as an associated AE for 4 (7.4%) patients.

Most (52/54) patients had PR interval <200 msec at baseline. Four (4) patients had a PR interval ≥200 msec (shifts to 200 - <220 msec post-baseline occurred in 3 patients and shifts to 220 - <240 msec post-baseline occurred in 1 patient). No patients had AEs of PR prolongation or AV block in Phase 1.

Phase 2

Most (95.3%) patients had QTcF of <450 msec at baseline. Shifts to 480-<500 msec post-baseline occurred in 7 patients, and shifts to QTcF ≥500 msec occurred in 1 patient. ECG QT prolonged was reported as an associated AE for 19 patients (16 were treatment-related).

For PR prolongation, shifts to 200-<220 msec post-baseline occurred for 28 patients, shifts to 220 - <240 msec post-baseline occurred for 8 patients, shifts to 240 - <260 msec post-baseline occurred for 5 patients, and shifts to ≥260 msec post-baseline occurred for 5 patients. AEs associated with prolonged PR interval included AV block first degree (2 patients), and AV block complete (1 patient).

Left Ventricular Ejection Fraction

Phase 1

A total of 14 (25.9%) patients had a maximum decrease of ≥20% from baseline in LVEF, among whom 4 (23.5%) patients were in the 100 mg QD dosing cohort. Four (4) (7.4%) patients had the AE of Ejection fraction decreased and 1 of them was treatment-related.

Phase 2

Thirty-one (31) (11.3%) patients had a maximum decrease from baseline in LVEF ≥20%. Seven (7) (2.5%) patients had AEs of Ejection fraction decreased and 6 of them were treatment-related.

ECOG Performance Status

Phase 1

Most of the patients had ECOG performance score of 0 (37.7%) or 1 (58.5%) at baseline. Three (3) patients shifted to performance score of 3 (<5%). No patients shifted to scores of 4 or 5.

Phase 2

Most patients had Grade 0 or Grade 1 ECOG performance at baseline. Six (6) patients shifted to ECOG status of Grade 3 and 1 patient shifted to Grade 4. No Grade 5 ECOG was observed.

Cogstate Analyses of Mood, Suicidal Ideation and Behavior, and Cognitive Function (Phase 2 Only)

The results from this substudy can be summarized as follows:

- There is little evidence of any systematic decline in cognition associated with treatment with lorlatinib. There was evidence of systematic decline in attention observed for the EXP-1, EXP-3, EXP-4, and EXP-5 subpopulations. However, true drug-related cognitive decline would manifest on more than 1 aspect of cognition in the same subpopulation. For example, performance on the Detection Test and the One Back Memory Test are correlated highly with performance on the Identification Test, although not strongly with one another. Thus, true treatment related attentional decline should have been accompanied by decline in psychomotor function (Detection Test) or decline in working memory (One Back Test). Similarly, when abnormal decline on multiple tests at the same cycle was required for classification of clinically important decline, rates of cognitive decline were very low across all study subpopulations. Therefore, there is no strong evidence that lorlatinib was associated with cognitive decline.

- Overall, there were no trends in the Beck Depression Inventory II (BDI-II) summary data to suggest worsening of symptoms during treatment with lorlatinib.

- Overall, there were no trends in the Columbia Suicide Severity Rating Scale (C-SSRS) group summary data to suggest a notable shift in suicidal ideation or behavior during treatment with lorlatinib.

CONCLUSIONS:

Efficacy

- Lorlatinib treatment provided a clinically meaningful benefit in patients with advanced ALK-positive or ROS1-positive NSCLC as evidenced by rapid, deep, and durable systemic and intracranial responses.

- Across expansion cohorts, in ALK-positive NSCLC patients who were treatment-naïve or had received up to 3 prior ALK inhibitors, ORRs as assessed by independent review ranged between 33.3% and 90.0%, which numerically exceeded historical controls in comparable segments.

    - The ORR in treatment-naïve patients was 90.0%, which was higher than any of the other approved second generation ALK TKIs in comparable patient populations (EXP-1).

    - In patients previously treated with one or more ALK inhibitors, the ORR was 47.2%. This ORR is notable considering that this broad segment not only comprises patients previously treated with crizotinib and chemotherapy, but also patients whose disease progressed on up to 3 ALK TKIs, including second-generation ALK TKIs (Pooled EXP-2 through EXP-5).

    - In patients previously treated with only crizotinib, lorlatinib treatment resulted in an ORR of 74.1%. Although a direct comparison to the ORR of other ALK TKIs in this segment is not possible due to lack of published data, the magnitude of this ORR highlights the robust activity of lorlatinib in this subset (EXP-2).

    - Patients pre-treated with crizotinib and 1-2 prior chemotherapy regimens had an ORR of 65.6%, which numerically exceeded ORRs reported for other approved ALK TKIs (EXP-3A).

    - Patients treated with lorlatinib had an ORR of 38.7% in this population, offering substantial improvement over standard-of-care single-agent chemotherapy (ORR 7%) (Pooled EXP-4 and EXP-5).

    - The ORR was 33.3% for lorlatinib in patients whose disease relapsed after treatment with a non-crizotinib ALK TKI with or without prior chemotherapy, where no standard of care is available and no published data exist (EXP-3B).

- Across expansion cohorts, lorlatinib produced rapid, deep, and durable intracranial responses consistent with its ability to cross the blood-brain barrier with ORRs as assessed by independent central review ranging from 39.5% to 75.0%, including complete intracranial responses, irrespective of prior lines of therapy, which numerically exceeded historical controls in comparable segments.

  - The reported IC-ORR (67.6%) in patients whose disease progressed on crizotinib with or without prior chemotherapy falls in the range of the reported IC-ORRs of the approved ALK TKIs (Pooled EXP-2 and EXP-3A).

  - While there is no benchmark in the literature, lorlatinib fills an important medical need in patients with brain metastasis whose disease progressed on 2 or more ALK TKIs (IC-ORR 48.2%) (Pooled EXP-4 and EXP-5).

- The ORR and the IC-ORR for lorlatinib in patients with advanced ROS1-positive NSCLC whose disease progressed on or after crizotinib with or without prior chemotherapy were 36.2% and 56.0%, respectively.

- Although a median DOR/IC-DOR was not yet reached in either ALK or ROS1-positive NSCLC patient population, the lower boundary of the 95% CI was 10 months for the treatment-naïve cohort and 11.1 months for the cohort of patients previously treated with at least 1 ALK TKI.

- Lorlatinib demonstrated antitumor activity across a variety of ALK kinase domain resistance mutations, including the difficult-to-treat G1202R/G1202del mutations. Lorlatinib also evoked tumor responses in tumors resistant to prior ALK TKIs that did not contain ALK resistance mutations.

- Lorlatinib treatment showed improvement from baseline in global quality of life that was maintained over time. In addition, there was improvement in physical, emotional, social, and role functioning, while cognitive functioning neither improved nor worsened. Improvements were shown in appetite loss and key lung cancer symptoms such as pain, dyspnea, cough, and fatigue. An increase in peripheral neuropathy was noted.

Safety

- Lorlatinib was generally tolerable and, when needed, AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy.

- Lorlatinib 100 mg QD was established as the RP2D in patients with advanced ALK-positive and ROS1-positive NSCLC.

- In Phase 2, main safety observations included:

  - The most frequent (reported in ≥30% of patients) all-causality AEs were HYPERCHOLESTEROLEMIA (81.8%), HYPERTRIGLYCERIDEMIA (60.7%), EDEMA (51.3%), and PERIPHERAL NEUROPATHY (43.3%).

  - The most frequent (reported in ≥2% of patients) all-causality Grade 3 or 4 AEs were HYPERCHOLESTEROLEMIA (16.0%) and HYPERTRIGLYCERIDEMIA (15.6%), Lipase increased (5.1%), Dyspnoea (4.4%) Hypertension (3.6%), Anaemia and Amylase increased (2.9% each), EDEMA and PERIPHERAL NEUROPATHY,

Pneumonia, and Pleural effusion, (2.5% each), Weight increased, Hypophosphataemia, and Hyperglycaemia (2.2% each).

- Hyperlipidemia was successfully managed with lipid-lowering agents.
- Cognitive effects were generally mild and reversible upon dose modification.
- The most frequent (≥2%) all-causality SAEs were Disease Progression (8.0%), Dyspnoea, and Pyrexia (2.2% each).
- Only 7.6% of patients permanently discontinued due to AEs.
- There were 26 (9.5%) deaths on treatment (including 28 days after the last dose), none of which were treatment related. There were no Grade 5 treatment-related AEs.

Overall

In summary, lorlatinib conferred a clinically meaningful benefit in patients with advanced ALK- and ROS1-positive NSCLC across a range of treatment with prior ALK inhibitors and/or chemotherapies, including in treatment settings with a high unmet medical need. Lorlatinib was generally tolerable, as AEs were primarily mild to moderate in severity, and manageable as rates of permanent discontinuations due to AEs were low and could be managed by dosing interruption, dose reduction, and/or standard supportive medical therapy.