16 December 2021
EMA/22356/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lorviqua

International non-proprietary name: lorlatinib

Procedure No. EMEA/H/C/004646/II/0015

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
(e)CRF	(electronic) case report form
(s)NDA	(supplemental) New Drug Application
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AV	atrioventricular
BICR	(blinded) Independent Central Review
BID	twice a day
BOR	best overall response
Cav	average or time-normalized drug concentration
CDx	companion diagnostic
cfDNA	circulating free deoxyribonucleic acid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	mean peak plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COVID-19	Corona virus disease 2019
CR	complete response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CYP	cytochrome P450
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
E-DMC	external data monitoring committee
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EML4	echinoderm microtubule associated protein like 4
EOP1	end of Phase 1
EORTC QLQ	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
E-R	exposure response
FA	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	hazard ratio
IA	interim analysis
iAP	integrated analysis plan
IC	intracranial

Term	Definition
ICH	International Council for Harmonisation
IF	information fraction
IHC	immunohistochemical
ISS	Integrated Summary of Safety
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
NSCLC	non-small-cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMAR	Pharmacokinetic Modeling Analysis Report
PMR	Post-marketing requirement
PR	partial response
PRO	patient reported outcome
PT	Preferred Term
QD	once daily
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QTcF	QT interval corrected for heart rate with Fridericia correction
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ROS oncogene-1
RTOR	Real-Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
TTP	time to tumour progression
TTR	time to tumour response
UGT	uridine diphosphate-glucuronosyltransferase

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 2 February 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from the phase III randomised CROWN (1006) study listed as a specific obligation (SOB) in the Annex II; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package leaflet is updated accordingly. Version 3.0 of the RMP has also been submitted. In addition, the Applicant proposes to downgrade the specific obligation to conduct a single arm study in patients who progressed after alectinib or ceritinib to a recommendation and convert the conditional MA to a full MA.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0006/2021 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific Advice on the development relevant for the sought indication from the CHMP on 28 April 2016 (EMEA/H/SA/3268/1/2016/II). The Scientific Advice pertained to the following clinical aspects of the dossier:

- A Phase 3 randomised, open label study of lorlatinib with standard of care (SOC) therapy as comparator: overall study design and objectives; proposed patient population (ALK-positive advanced NSCLC), eligibility criteria, and approach to identify ALK-positive patients; choice of SOC comparator; primary endpoint of progression-free survival, and key secondary endpoints;

statistical approach including sample size, power, statistical testing of primary endpoint including effect size and proposed interim analysis; use of proposed patient reported outcome data adequacy of the safety data to initiate the Phase 3 study.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Armando Genazzani

Timetable	Actual dates
Submission date	2 February 2021
Start of procedure:	20 February 2021
CHMP Rapporteur's preliminary assessment report circulated on:	16 April 2021
CHMP Co-Rapporteur's preliminary assessment report circulated on:	16 April 2021
PRAC Rapporteur's preliminary assessment report circulated on:	22 April 2021
PRAC Rapporteur's updated assessment report circulated on:	29 April 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	6 May 2021
CHMP Rapporteur(s) (Joint) updated assessment report circulated on:	12 May 2021
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 May 2021
MAH's responses submitted to the CHMP on:	7 July 2021
CHMP Rapporteur(s) (Joint) preliminary assessment report on the MAH's responses circulated on:	18 August 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	19 August 2021
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	26 August 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	2 September 2021
CHMP Rapporteur(s) (Joint) updated assessment report on the MAH's responses circulated on:	9 September 2021
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	16 September 2021
MAH's responses submitted to the CHMP on:	8 October 2021
CHMP Rapporteur(s) (Joint) preliminary assessment report on the MAH's responses circulated on:	16 November 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	16 November 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	2 December 2021
CHMP Rapporteur(s) (Joint) updated assessment report on the MAH's responses circulated on:	9 December 2021
CHMP opinion adopted on:	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This application is for treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Claimed therapeutic indication

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Epidemiology

The global incidence of lung cancer was estimated to be 2.1 million new cases in 2018 and non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancer cases[1] . Genetic alterations, such as the ALK rearrangements are typically found in 3-5% of all NSCLC cases. Patients with ALK-rearranged NSCLC have a median 50 years of age at diagnosis and mostly have non- or light-smoking history.

It is estimated that CNS metastases occur in 20-40% of patients with ALK-positive NSCLC who are ALK-TKI and treatment-naïve.

Biologic features, Aetiology and pathogenesis

ALK is a tyrosine kinase encoded on chromosome 2 and is primarily involved in developmental processes and expressed at low levels in adults[2]. The first genetic rearrangement of ALK seen in NSCLC involved a fusion between the echinoderm microtubule-associated protein-like 4 (EML4) gene and the ALK tyrosine kinase domain. EML4-ALK has the capacity to transform fibroblasts grown in culture and as subcutaneous xenografts to induce tumour formation[3]. A number of additional ALK fusion partners have been described in NSCLC that are believed to result in aberrant signalling and oncogenic transformation[4,5]. ALK rearrangements are more common among patients with adenocarcinoma histology, patients who have never smoked, and patients who have wild-type EGFR and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS)[6].

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
[2] Camidge D, Doebele RC. Treating ALK-positive lung cancer-early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77
[3] Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448(7153):561-6.
[4] Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell. 2007;131(6):1190-203.
[5] Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res.2009;15(9):3143-9.
[6] Camidge D, Doebele RC. Treating ALK-positive lung cancer-early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77.

Clinical presentation, diagnosis and prognosis

Approximately, one-third of the patients with Stage IIIA disease are considered operable. However, the majority of patients with Stage IIIA/B have inoperable (unresectable) disease and are amenable to receiving curative intention chemoradiation treatment. The biological characteristics of locally advanced, Stage III disease are poorly defined; the clinical characteristics associated with prognosis are nodal station involvement, size of primary tumour, baseline pulmonary function, gender, presence or absence of significant weight loss, and performance status (PS).

Pathological diagnosis based on tumour samples includes immunohistochemistry (IHC) to identify adenocarcinoma or squamous cell carcinoma and cytogenetic analysis by fluorescence in situ hybridisation (FISH) test to detect ALK rearrangements. Molecular testing should be carried out to determine genetic alterations, such as EGFR mutations and ALK rearrangements which determine choice of targeted treatment.

Management

Alectinib, ceritinib, and brigatinib are second-generation ALK-TKIs that prolong PFS and have CNS anti-tumour effects. These therapies are recommended for treating patients with previously untreated advanced ALK-positive NSCLC, with alectinib being the preferred treatment option in the first-line setting.

Most patients with ALK-positive NSCLC derive clinical benefit from first-line treatment with second-generation ALK TKIs. However, emergence of resistance mechanisms, including ALK mutations continues to be a treatment challenge. Therefore, there is an unmet medical need for additional ALK TKIs with broader mutational coverage and CNS penetration.

Lorlatinib is a third-generation, selective, ATP-competitive, brain-penetrant, small molecule inhibitor of the ALK tyrosine kinase that was designed to overcome or prevent major mechanisms of resistance that develop following previous ALK-inhibitor treatment. It was also designed to penetrate the blood-brain-barrier. In addition, lorlatinib' s ability to overcome most known resistance mutations might delay ALK-dependent mechanisms of resistance. These features indicate that lorlatinib has potential as therapy for previously untreated ALK-positive NSCLC.

2.1.2. About the product

Lorlatinib is a small molecule tyrosine kinase inhibitor (TKI) and works as a selective, adenosine triphosphate (ATP)-competitive, small molecule inhibitor of ALK and c-ros oncogene 1 (ROS1) receptor tyrosine kinases.

The CHMP adopted a positive opinion for Lorviqua in the following indications (new indication in bold):

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Lorviqua as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK TKI.

Treatment with lorlatinib should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Detection of ALK-positive NSCLC is necessary for selection of patients for treatment with lorlatinib because these are the only patients for whom benefit has been shown. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. Improper assay performance can lead to unreliable test results.

Posology

The recommended dose is 100 mg lorlatinib taken orally once daily.

Duration of treatment

Treatment with lorlatinib should be continued until disease progression or unacceptable toxicity.

Delayed or missed doses

If a dose of Lorviqua is missed, then it should be taken as soon as the patient remembers unless it is less than 4 hours before the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose modifications

Dosing interruption or dose reduction may be required based on individual safety and tolerability. Lorlatinib dose reduction levels are summarised below:

- First dose reduction: 75 mg taken orally once daily
- Second dose reduction: 50 mg taken orally once daily

Lorlatinib should be permanently discontinued if the patient is unable to tolerate the 50 mg dose taken orally once daily.

Dose modification recommendations for toxicities and for patients who develop atrioventricular (AV) block are provided in Table 1 of the SmPC.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant has generally followed the given advice from the CHMP.

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the Applicant.

2.2. Non-clinical aspects

No new non-clinical data besides updated ERA documentation have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

Lorlatinib, the active ingredient in Lorviqua, is a selective ATP-competitive small-molecule inhibitor of ALK and ROS1 receptor tyrosine kinases, that was specifically designed to address mechanisms of resistance. Lorlatinib has demonstrated potent and selective inhibitory activity against ALK translocations, most known acquired crizotinib-resistant ALK mutations, and the ALK mutation that was reported in patients with ALK-positive NSCLC who developed resistance to previous ALK-TKI treatment.

2.2.2. Pharmacology

Not applicable.

2.2.3. Pharmacokinetics

Not applicable.

2.2.4. Toxicology

Not applicable.

2.2.5. Ecotoxicity/environmental risk assessment

This Environmental Risk Assessment was submitted as part of the type II variation application dossier for Lorviqua (lorlatinib), 25 mg and 100 mg film-coated tablets and followed the CHMP guidance EMEA/CHMP/ SWP/4447/00 entitled; "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006.

Lorlatinib is an ionisable compound and log Dow values as a function of pH covering an environmentally relevant pH-range ranging from pH 5 to 9 were determined. Log Dow values were below 4.5 thus lorlatinib had no PBT potential and further PBT assessment was not required.

When estimating the PECSW, the Fpen was refined to 0.00013 by providing adequately justified market penetration data based on published epidemiological data. The PECSW was calculated to 0.0065 µg/L below the action limit of 0.01 µg/L.

Based on the presented data of lorlatinib, no other environmental concerns were apparent, and the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients with ALK-positive NSCLC. A Phase II environmental fate and effect analysis was not required since lorlatinib had no PBT potential and the PECSW was below the action limit of 0.01 µg/L.

Summary of main study results

Substance (INN/Invented Name): Lorlatinib/Lorviqua			
CAS-number (if available): 1454846-35-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH = 5 -> Log D = 2.23 pH = 7 -> Log D = 2.47 pH = 9 -> Log D = 2.45	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, ($Fpen_{refined}$)	0.0065, (0.00013)	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)	-	-	None

2.2.6. Discussion and conclusion on non-clinical aspects

Lorlatinib was not considered a PBT substance as log D values did not exceed 4.5 at environmentally relevant pHs. In addition, PECsurfacewater value was below the action limit of 0.01 µg/L.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of lorlatinib.

Considering the above data, lorlatinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Overview of clinical studies including participants who received lorlatinib and were evaluable for pharmacokinetics

Protocol No. Study Status	Study Design	Treatment Groups (Formulation)	Number of Participants	Sampling	PK Analysis	Demographics	Study start (FPFV)/ Study end (LPLV)
HEALTHY PARTICIPANT STUDIES							
Mass Balance Study							
B7461017 Completed	Phase 1, open-label, single-dose, single-center study to further the understanding of human metabolism of lorlatinib, specifically with respect to the metabolic pathway involving the formation of PF-06895751.	100 mg lorlatinib containing approximately 100 μCi of [^{14}C]lorlatinib (Bulk powder for preparation of an oral solution at the clinic)	6 healthy participants	Full PK profile	NCA	Sex: 6 Males Mean age (SD): 23.83 (4.17) years Age range: 19-29 years Race: 5 White/ 1 Black	05 July 2017/ 25 August 2017
B7461026 Completed	Phase 1, open-label, 2-period, 2-treatment, fixed-sequence DDI study	Cohort 1: Period 1 (Reference) - lorlatinib 50 mg single dose; Period 2 (Test) - modafinil 400 mg QD for 19 days and lorlatinib 50 mg single dose on Day 15 Cohort 2: Period 1 (Reference) - lorlatinib 75 mg single dose; Period 2 (Test) - modafinil 400 mg QD for 19 days and lorlatinib 75 mg single dose on Day 15 Cohort 3&4: Period 1 (Reference) - lorlatinib 100 mg single dose; Period 2 (Test) - modafinil 400 mg QD for 19 days and lorlatinib 100 mg single dose on Day 15 (Lorlatinib 25 mg tablets and Modafinil (Provigil®) 100 mg tablets)	16 healthy participants	Full PK profile	NCA	Sex: 16 Males Mean age (SD): 34.8 (10.57) years Age range: 23-56 years Race: 16 White	22 August 2019/ 09 December 2019
B7461001 DDI Sub-study Ongoing	To evaluate the potential of lorlatinib to inhibit/induce CYP2B6, CYP2C9, P-gp, and select UGT isoforms.	A single dose of a probe substrate alone was administered on Day -2. Lorlatinib 100 mg QD on Cycle 1 Day 1 and another single dose of the probe substrate was administered concurrently with lorlatinib on Cycle 1 Day 15. (Probe drugs bupropion, tolbutamide, acetaminophen and fexofenadine)	32 ALK-positive or ROS1-positive NSCLC patients	Full PK profiles	NCA	Part of ongoing larger Study B7461001	DDI sub-study FPFV: 30 January 2017 – ongoing
B7461006 Ongoing	Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study	Arm A: Lorlatinib monotherapy at the RP2D of 100 mg QD, administered as 4 × 25 mg oral tablets; Arm B: Crizotinib monotherapy at the registered starting dose of 250 mg BID, administered as 1 × 250 mg oral capsules, BID.	296 ALK-positive NSCLC patients.	Sparse sampling	popPK analysis	Sex: 175 Females/ 121 Males Mean age (SD): 57.4 (13.41) years Age range: 26-90 years Race: 1 Black/ 144 White/ 130 Asian/ 21 Missing	27 April 2017/ Data Cutoff Date: 20 March 2020
B7461010 Completed	Phase 1, open-label, multi-center, single treatment study in participants with normal renal function and varying degrees of renal impairment who were otherwise healthy to evaluate PK of lorlatinib.	Group A (Normal Function): lorlatinib 100 mg single dose, fasted. Group B (Mild Impairment): lorlatinib 100 mg single dose, fasted. Group C (Moderate Impairment): lorlatinib 100 mg single dose, fasted. Group D (Severe Impairment): lorlatinib 100 mg single dose, fasted. (Lorlatinib 25 mg free base tablets)	29 participants	Full PK profiles	NCA	Sex: 12 Females/ 17 Males Mean age (SD): 59.7 (6.81) years Age range: 43-71 years Race: 5 Black/ 23 White/ 1 Asian	23 August 2018/ 20 February 2020

2.3.2. Pharmacokinetics

Within this application, the Applicant has submitted 5 clinical pharmacology studies (Study B7461001, B7461010, B7461017, B7461026 and B7461006). However, study B7461006 is the most relevant study due to the population included that corresponds to the proposed new indication. According to this, the focus in the pharmacological part of the assessment report was on study B7461006.

Study B7461006 is a Phase 3, multinational, multicentre (at approximately 160 sites), randomized, open-label, parallel 2-arm study in which approximately 280 patients with previously untreated advanced ALK-positive NSCLC were randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy:

- Arm A: Lorlatinib single agent;
- Arm B: Crizotinib single agent.

The primary objective of this study was to demonstrate that lorlatinib as a single agent (Arm A) is superior to crizotinib alone (Arm B) in prolonging PFS in advanced ALK-positive NSCLC patients previously not treated with an ALK-inhibitor. Additional objectives included, comparing Arm A and Arm B in treatment-naive advanced ALK-positive NSCLC patients with respect to OS, evaluating the antitumor activity in each treatment arm, and evaluating the safety and tolerability in each treatment arm.

Evaluation and Qualification of Models

In Study B7461006, plasma concentrations of lorlatinib and its major metabolite PF-06895751 were determined by a validated LC-MS/MS method using a stable isotope labelled internal standard and liquid-liquid extraction for sample preparation. No new bioanalytical methods were applied.

In support of Study B7461006, 2135 samples were analysed for lorlatinib in 18 accepted runs within 605 days which is within documented storage stability at -20°C. Sample dilution applied, 10:1. Incurred sample reanalysis was conducted for 216 samples of which 207 were within acceptance criteria. 2121 samples were analysed for PF-06895751 (major human metabolite of lorlatinib) in 19 accepted runs within 628 days. 4 runs failed. Sample dilution applied, 20:1. ISR was conducted on 215 samples of which 199 passed the acceptance criteria.

Characterization of lorlatinib popPK in previously untreated patients with ALK-positive NSCLC (Study B7461006) and subsequent estimation of the post-hoc exposure parameters was performed using NONMEM version 7.4.3 (Icon Development Solutions, Dublin, Ireland). PKPD efficacy analyses were performed using NONMEM version 7.4.3, Perl-speaks-NONMEM (PsN) version 4.9.0, and R software version 3.6.1 or later. The safety analyses was performed using the glm(), clm() and polr() functions in R. Simcyp version 17.1 was utilised in the development and verification of a PBPK model for lorlatinib, with model extrapolation applied for prediction of metabolic DDIs.

Population PK model – Study 1006 + other studies

The previous popPK analysis of lorlatinib included ALK- positive NSCLC patients from one Phase 1/Phase 2 study (B7461001), and healthy participants from 6 clinical pharmacology studies (B7461004, B7461005, B7461007, B7461008, B7461011, and B7461016).

Table 2. Number of observed pharmacokinetic concentrations

Study	PK Observations	Percentage (%)
B7461006	1954	25.18
Studies from the Original NDA	5806	74.82

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Studies from the Original NDA=All of the studies included in the popPK analysis from the first submission: B7461001, B7461004, B7461005, B7461007, B7461008, B7461011, and B7461016.

The current popPK analysis is a pooled analysis which includes data from the Phase 3 study B7461006, which tested lorlatinib versus crizotinib in previously untreated advanced ALK-positive NSCLC patients. Plasma samples for determination of plasma concentrations of lorlatinib and its potential metabolite(s) were collected at time 0 (pre-dose), and at times between 1 to 4 hours after the lorlatinib dose on Days 1, 8, and 15 in Cycle 1; and Day 1 in Cycles 2, 3, 5, 7, and 9 from patients enrolled in Arm A receiving lorlatinib. In the previous popPK model, lorlatinib PK was characterized by a two-compartment model, with sequential zero-first order absorption and time-varying clearance. BWT was included a priori in the base model, using allometric scaling exponents of 0.75 and 1 on CL and V2 respectively. BALB, WNCL, and TDOSE were significant covariates for CL. PPI use was a significant covariate for ka. The current pooled popPK analysis applied the same structural model and covariates.

Due to the sparse data of Study B7461001, stochastic approximation expectation maximization (SAEM) was used to estimate parameters. An expectation only importance sampling (IMP) step, fixed at the SAEM estimated population parameters was done subsequently to obtain an objective function value. The covariate parameters were re-estimated with the expanded dataset. Outliers were identified in the final model using the following criteria: CWRES>6 and IWRES>6 and the impact of removing them evaluated.

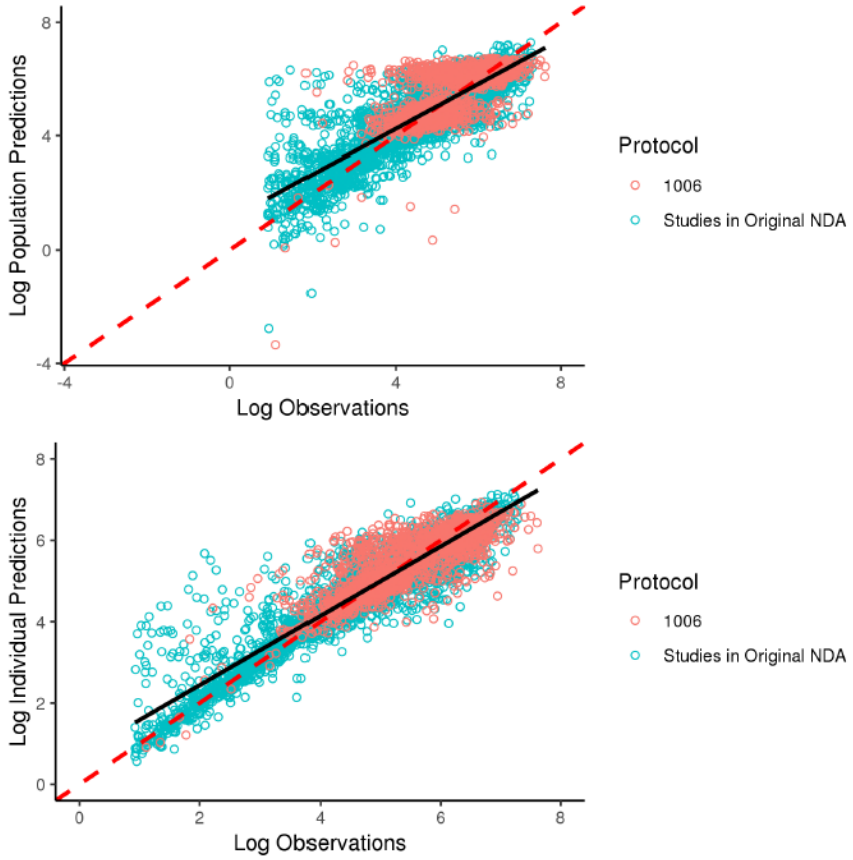
For the population PK dataset that included Study B7461006 data and reported in PMAR-1941, a listing of the excluded data was provided. The following data were excluded: *The pre-dose PK concentration, prior to the very first dose of lorlatinib.* This resulted in 143 PK samples that were excluded from the PMAR-1041 analysis, all of which were pre-dose PK samples collected prior to the very first dose of lorlatinib on the study.

Table 3. Final model parameter estimates

	Model Results			Bootstrap Results	
Parameter	Value	RSE(%)	Shrinkage(%)	Mean	95% Confidence Interval
$\theta_{CLI\ (L/h)}$	8.8154	3.9156	-	8.8731	(8.3022 - 9.6191)
$\theta_{V_2\ (L)}$	121.5150	4.9896	-	122.6822	(112.5878 - 135.4944)
$\theta_{ka\ (h^{-1})}$	2.2984	14.6816	-	2.3450	(1.6436 - 3.3238)
$\theta_{Q\ (L/h)}$	21.0745	3.2566	-	21.6974	(17.7496 - 26.2811)
$\theta_{V_3\ (L)}$	160.0420	6.5930	-	157.1280	(142.6466 - 187.2819)
θ_{IND}	0.0136	7.5348	-	0.0136	(0.0120 - 0.0161)
$\theta_{D1\ (h)}$	1.0853	3.0181	-	1.0881	(0.9888 - 1.2365)
	Model Results			Bootstrap Results	
Parameter	Value	RSE(%)	Shrinkage(%)	Mean	95% Confidence Interval
θ_F	0.7357	3.8286	-	0.7487	(0.6938 - 0.8012)
$\theta_{CLMX\ (L/h)}$	14.2653	3.6278	-	14.5191	(13.4027 - 15.6160)
$\theta_{Res.\ Error\ for\ IV}$	0.1148	4.7696	-	0.1102	(0.0852 - 0.1613)
$\theta_{Res.\ Error\ for\ PO}$	0.4543	0.3892	-	0.4544	(0.4348 - 0.4849)
$\theta_{BALB\ on\ CL}$	0.0582	30.5627	-	0.0585	(0.0242 - 0.1115)
$\theta_{TDOSE\ on\ CL}$	0.0020	14.8738	-	0.0021	(0.0012 - 0.0033)
$\theta_{WNCL\ on\ CL}$	0.2561	14.1924	-	0.2668	(0.1918 - 0.3567)
$\theta_{PPI\ on\ k_a}$	-0.6644	-2.2233	-	-0.6516	(-0.8074 - -0.4404)
IIV	Value	CV(%)	Shrinkage(%)	Mean	CI
ω^2_{CL}	0.0239	15.4683	35.0111	0.0281	(0.0141 - 0.0394)
$\omega_F\omega_{CLMX\ (L/h)}$	-0.0005	2.2858	-	0.0012	(-0.0078 - 0.0109)
ω^2_F	0.0346	18.5973	38.5645	0.0321	(0.0221 - 0.0541)
$\omega^2_{V_2}$	0.0633	25.1581	57.6675	0.0638	(0.0399 - 0.0999)
$\omega_{V_2}\omega_{V_3}$	-0.0034	5.8590	-	-0.0256	(-0.0525 - 0.0734)
$\omega^2_{V_3}$	0.2329	48.2573	49.6160	0.2307	(0.1168 - 0.4147)
ω^2_{ka}	2.8323	168.2932	35.0922	2.9432	(1.8891 - 4.3092)
OFV	-2717.3521	-	-	-2752.0631	(-3334.9648 - -1750.2132)

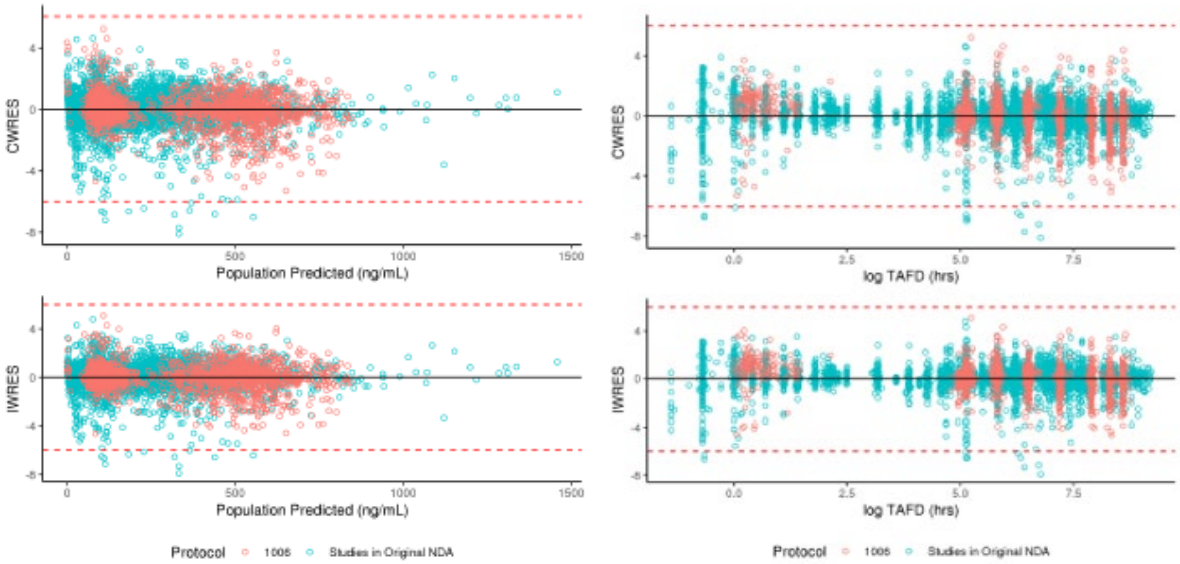
Repository artifact ID FI-9560256. Line 1 substituted.
The mean and 95% Confidence Intervals are generated from a bootstrap run of 1000 resampled datasets
BALB=baseline albumin; CI=confidence interval; CLI=initial clearance; CLMX=maximum clearance value after multiple dosing; CV=Coefficient of Variation; D1=zero order input duration; F=bioavailability; h=hour; IIV=inter-individual variability; IND=induction rate constant; IV=intravenous; ka=first order absorption rate constant; L=liter; OFV=objective function value; PPI=proton pump inhibitor use; PO=oral; Res. Err=Residual Error; RSE=relative standard error; TDOSE=total daily dose; V_2=central volume of distribution; V_3=peripheral volume of distribution; WNCL=weight normalized creatinine clearance

Figure 1. Log observed vs log population predictions/individual predictions



Repository artifact ID FI-9494114.
The x axis is the natural log of the observed concentrations while the y axis is the natural log of the population predicted concentration values or the individual predicted concentration values. The dashed red line is the line of unity. The black line is an overall trend line for all of the data. The red and blue circles represent data from the B7461006 study and other studies,respectively.
1006=Study B7461006

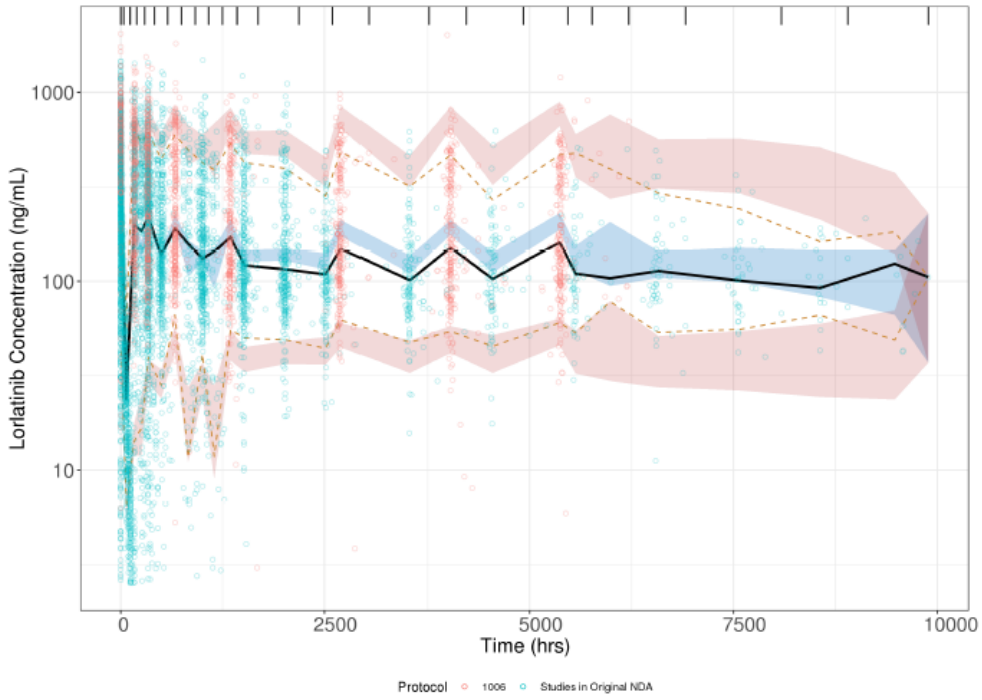
Figure 2. Residual error plots



(a) FI-9494123 **(b)** FI-9494124

Repository artifact IDs are shown in subfigure labels.
1006=Study B7461006; CWRES=conditional weighted residual error; IWRES=individual weighted residual error; TAFD=time after first dose

Figure 3. Visual predictive check



Repository artifact ID FI-9601200.
The solid black line represents the 50^{th} percentile of the observed data. The dashed red lines represent the 5^{th} and 95^{th} percentiles. The blue ribbon represents the 90% CI of the 50^{th} percentile of the simulated data. The red ribbons represent the 90% CI of the 5^{th} and 95^{th} percentiles of the simulated data.
1006=Study B7461006

PBPK model – CYP3A4 interactions

A minimal PBPK distribution model was developed in Simcyp to simulate the PK of lorlatinib IV. Vsac and Q were estimated in Simcyp based on the IV profile after 50 mg lorlatinib (B7461007) where CL was 9.7 L/h and Vss was 3.58 L/kg. Lorlatinib is an immediate release formulation hence a first order absorption model was used and the Fa value was assumed to be 1. The fraction unbound in the intestine (fu,gut) was assumed to be equal to the fraction unbound in plasma (fu,plasma),16 which was 0.34. Based on lorlatinib fm assignments intrinsic clearance values were calculated (Table 4). Due to the enzyme inhibition and induction properties of lorlatinib (both a time dependent inhibitor and an inducer of CYP3A4, with a net induction observed in vivo), the CYP3A fm value is non-stationary. A sensitivity analysis of CYP3A4 revealed that a Simcyp input of 0.275 for fm,CYP3A was able to yield a dynamic (time-variant) fm,CYP3A of 0.37 and approximates the fm,CYP3A estimated in both Study B74610177 (fm,CYP3A = 0.288) and B74610046 (fm,CYP3A = 0.268). Inhibition and induction parameters determined from human hepatocytes were used as Simcyp input parameters for lorlatinib (Table 4).

Table 4. Simcyp® input parameters for lorlatinib (PF-06463922)

Parameter	Value[a]	Method
Compound	PF-06463922	-
Molecular Weight	406.4	-
LogP	2.45	-
Compound type	Monoprotic Base	-
pKa	4.92	-
B/P ratio	1.05	Experimental
$f_{u,plasma}$	0.34	Experimental
F_a	1	Assumed
K_a (h^{-1})	1	Fitted based on clinical data
$f_{u,gut}$	0.34	Assumed
MDCK-LE (10^{-6} cm/s)	22	Exploratory experimental data
Q_{gut} (L/h)	12.0	Simcyp® predicted using MDCK-LE data
V_{ss} (L/kg)	3.58	Clinical data (B7461007)[6]
Q (L/h)	23.5	Simcyp® parameter estimate
V_{sac} (L/kg)	2.37	Simcyp® parameter estimate
CYP1A2 CL_{int} (µL/min/mg)	0.12	CL_{int} retrospectively predicted based on CL_{IV} following subtraction of CL_R and f_m assignment
CYP2C8 CL_{int} (µL/min/mg)	0.35	
CYP2C19 CL_{int} (µL/min/mg)	0.51	
CYP3A4 CL_{int} (µL/min/mg)	2.45	CL_{int} retrospectively predicted based on clinical data; input $f_{m,CYP3A4}$ = 0.275
UGT1A4 CL_{int} (µL/min/mg)	2.11	CL_{int} retrospectively predicted based on CL_{IV} following subtraction of CL_R and f_m assignment
HLM CL_{int} (µL/min/mg)	3.37	Remaining unassigned contributions based on clinical data
CYP3A4 K_i (µM)	5	Experimental
CYP3A4 K_I (µM)	7.92	Experimental
CYP3A4 k_{inact} (h^{-1})	1.2	Fitted based on clinical data (Experimental value was 4.86)
CYP3A4 Ind_{slope} (1/µM)	33.9	Calibrated using slope of rifampicin[b]
CL_R(L/h)	0.1	Clinical data, rounded up (B7461004)[7]

B/P ratio = Blood to plasma ratio; CL_{int} = Intrinsic clearance; CL_{IV} = Intravenous clearance; CL_R = Renal clearance; CYP = Cytochrome P450 enzyme; F_a = Fraction of dose absorbed from the gut; f_m = Fraction metabolized; $f_{u,gut}$ = Fraction unbound in the gut; $f_{u,plasma}$ = Fraction unbound in plasma; HLM = Human liver microsomes; Ind_{slope} = Induction slope; K_a = Absorption rate constant; K_i = Concentration at half maximum inhibition rate (reversible inhibition rate constant); K_I = Concentration at half maximum inactivation rate (inactivation rate constant); k_{inact} = Inactivation rate; LogP = Partition coefficient; MDCK-LE = Madin-Darby canine kidney-low efflux cells; mRNA = Messenger ribonucleic acid; pKa =Acid dissociation constant; Q = Intercompartmental clearance; Q_{gut} = Hybrid term including both villous blood flow and permeability through the enterocyte membrane; Simcyp® = Physiologically-based pharmacokinetic modeling software; UGT = Uridine diphosphate-glucuronosyltransferase; V_{sac} = Volume of single adjusting compartment; V_{ss} = Volume of distribution at steady state; - = Data not available or not applicable.

a. Lorlatinib input parameters are described in detail in Study PF-06463922_22Jun18_115307[2].

b. Induction for lorlatinib was calibrated against rifampin using the same lot of human hepatocytes. The linear model was used to fit the in vitro induction data for lorlatinib and rifampin. The measured slope (based on mRNA) for lorlatinib and rifampin were 72.1 μM^{-1} and 46.5 μM^{-1}, respectively.[8] The calibrated slope (based on enzyme activity) for lorlatinib was predicted to be 33.9 μM^{-1} using the Simcyp® induction calibrator.

The lorlatinib PBPK model was verified using observed PK data obtained from the single and multiple ascending dose PK studies after oral administration of lorlatinib (Study B74610013) and from clinical DDI studies after oral administration of lorlatinib (Studies B74610013, B74610114, and B74610125).

Table 5. Stimulated vs observed geometric mean pharmacokinetic parameters of lorlatinib after select single and multiple oral doses – Method verification data reported in study PF-06463922_22Jun18_115307

Dose (mg)	Predicted C_{max} (ng/mL)	Observed C_{max} (ng/mL)	C_{max} Ratio (Predicted/ Observed)	Predicted AUC_{inf} or AUC_{tau} (ng•h/mL)	Observed AUC_{inf} or AUC_{tau} (ng•h/mL)	AUC_{inf} or AUC_{tau} Ratio (Predicted/ Observed)
Single Dose[a]						
75	412	489.1	0.84	5930	7663	0.77
100	547	595.5	0.92	7640	8236	0.93
Multiple Doses[b]						
75	488	429.6	1.14	4930	4107	1.20
100	639	550.2	1.16	6350	5121	1.24

Notes: Data Reported in Study PF-06463922_22Jun18_115307[2]. Observed data from Study B7461001[3]. Simulations conducted in a simulated healthy volunteer population. AUC_{inf} reported for single dose data and AUC_{tau} reported for multiple dose data.
AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; AUC_{tau} = Area under the concentration-time curve over the dosing interval tau (tau = 24 hours); C_{max} = Maximum plasma concentration; n = Number of patients where parameter was determined.
a. Observed n = 11 for 75 mg dose and 15 for 100 mg dose.
b. Observed n = 12 for 75 mg dose and 16 for 100 mg dose.

The predicted impact matched well the clinically observed PK results after coadministration of a single dose of 100 mg lorlatinib on Day 5 with multiple 200 mg QD doses of the strong CYP3A4 inhibitor itraconazole for 11 days. The model predicted an AUC ratio of 1.49 and Cmax ratio of 1.08, which were 105% and 87% of observed values.

The PBPK model was used for prediction of metabolic DDIs with 1) itraconazole following single and multiple dose administration of lorlatinib (75 mg) with multiple doses of itraconazole (200 mg once daily [QD]); 2) diltiazem following single and multiple dose administration of lorlatinib (100 mg) with multiple doses of diltiazem (60 mg three times a day [TID]); 3) verapamil following single and multiple dose administration of lorlatinib (100 mg) with multiple doses of verapamil (80 mg TID); 4) erythromycin following single and multiple dose administration of lorlatinib (100 mg) with multiple doses of erythromycin (500 mg twice a day [BID]); 5) fluconazole following single and multiple dose administration of lorlatinib (100 mg) with multiple doses of fluconazole (200 mg QD); 6) fluvoxamine following single and multiple dose administration of (100 mg) with multiple doses of fluvoxamine (100 mg BID); and 7) fluoxetine following single and multiple dose administration of lorlatinib (100 mg) with multiple doses of fluoxetine (20 mg QD).

All simulations were conducted using a design of 10 trials with 10 subjects using the age range of 20 to 50 years and 50:50 male to female ratio. Simulations were performed in a virtual population library of healthy volunteers supplied by Simcyp® (Sim-Healthy Volunteers).

Absorption

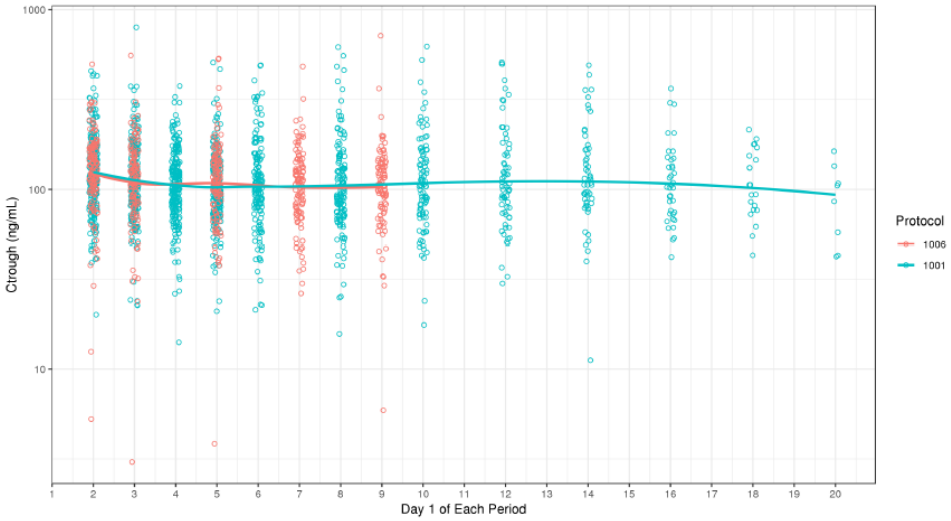
Lorlatinib oral bioavailability (F) was estimated to be 0.74 and D1 (zero order input duration) was estimated to be 1.09 hrs. The IND (induction rate constant) was estimated to be 0.0136 hr-1, or 0.326 days-1.

Exposure

Figure 4 presents a plot of the observed pre-dose Ctrough concentrations for both the B7461001 and B7461006 100 mg once daily (QD), cancer patients to provide a general comparison of the observed PK data between these two groups. As shown, the observed Ctrough concentrations are highly similar

between the previously untreated patients from Study B7461006 and the predominantly previously treated ALK-positive advanced NSCLC patients from Study B7461001 taking 100 mg QD. A trend line was plotted and the line for the B7461006 patients completely overlap with the line for the patients from the B7461001, further supporting this similarity.

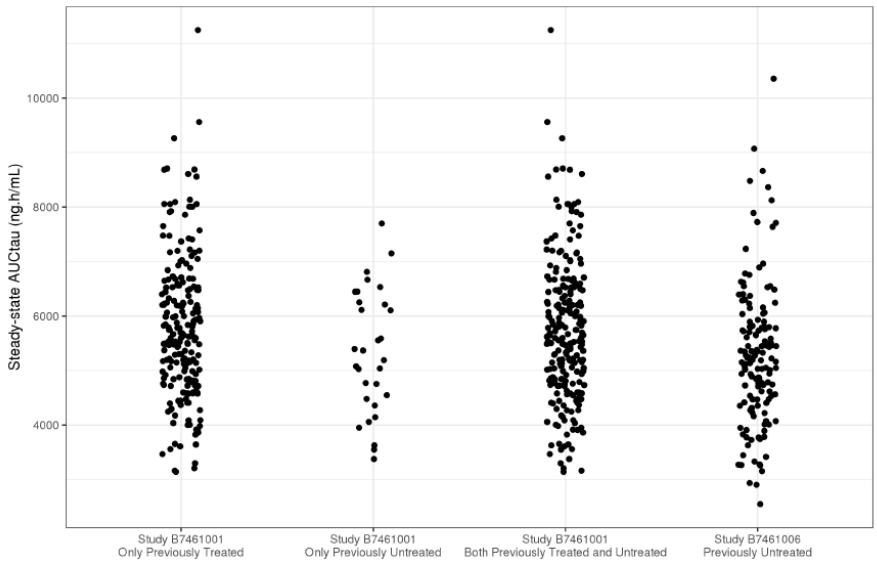
Figure 4. Observed Ctrough concentrations



Repository artifact ID FI-9494118.
The y axis is the lorlatinib C_{trough} in ng/mL. The x axis represents the first day for each period. The red and blue dots represent the observed C_{trough} values from the B7461006 and B7461001 100 mg QD patients, respectively. The locally estimated scatterplot smoothing (LOESS) line is a non-parametric local regression line, plotted using the "loess" method within geom_smooth as part of the ggplot R package. The span was set to 0.75. The red and blue lines are LOESS lines for the B7461006 and B7461001 patients, respectively.
1001=Study B7461001; 1006=Study B7461006; CI=confidence interval; QD=once daily dosing.

Figure 5 presents the individual post-hoc estimates for steady-state AUCtau, for patients taking lorlatinib 100 mg QD for Study B7461006 and Study B7461001. The patients from B7461001 are also further subdivided into previously treated and previously untreated patients. As shown, the steady-state AUCtau is similar across all groups, demonstrating that steady-state AUCtau is comparable between previously treated and previously untreated advanced ALK-positive NSCLC patients.

Figure 5. Comparison of steady-state AUCtau between study B741006 and study B7461001 100 mg QD patients



Repository artifact ID FI-10168932.
The "Study B7461001 Both Previously Treated and Untreated" group is comprised of the "Study B7461001 Only Previously Treated" and "Study B7461001 Only Previously Untreated" groups.

Table 6. Comparison of Lorlatinib Plasma Exposures in B7461001 and B7461006 Patients Receiving 100 mg QD Dosing

	Study B7461001	Study B7461006	Total
Single Dose Cmax (ng/mL)			
N (%)	294 (66)	149 (34)	443 (100)
Median	472.16	428.2	454.9
Range (Min; Max)	(179.51; 1302.92)	(143.49; 882.88)	(143.49; 1302.92)
Mean (Std. Dev.)	482.700 (127.861)	440.471 (138.636)	468.496 (132.936)
GeoMean	466.348	418.768	449.770
GeoCV (%)	27.1	33.4	29.8
Missing (%)	0 (0)	0 (0)	0 (0)
Single Dose 24 hour AUC (ng.h/mL)			
N (%)	294 (66)	149 (34)	443 (100)
Median	4673.64	5077.89	4744.53
Range (Min; Max)	(2777.37; 9956.96)	(1978.21; 8667.85)	(1978.21; 9956.96)
Mean (Std. Dev.)	4707.849 (793.419)	5037.654 (1150.955)	4818.777 (940.851)
GeoMean	4644.225	4897.577	4727.941
GeoCV (%)	16.6	25.0	19.9
Missing (%)	0 (0)	0 (0)	0 (0)
Steady State Cmax (ng/mL)			
N (%)	294 (66)	149 (34)	443 (100)
Median	601.93	647.08	621.34
Range (Min; Max)	(286.23; 1129.52)	(277.95; 1286.34)	(277.95; 1286.34)
Mean (Std. Dev.)	613.857 (143.349)	659.211 (171.784)	629.364 (154.966)
GeoMean	597.243	637.223	610.622
GeoCV (%)	24.0	26.9	25.2
Missing (%)	13 (4)	3 (2)	16 (4)
Steady State AUCtau (ng.h/mL)			
N (%)	294 (66)	149 (34)	443 (100)
Median	5595.47	5233.47	5464.74
Range (Min; Max)	(2445.38; 11247.60)	(2547.02; 10354.23)	(2445.38; 11247.60)
Mean (Std. Dev.)	5736.894 (1313.140)	5317.200 (1298.081)	5593.392 (1321.602)
GeoMean	5590.336	5165.261	5441.197
GeoCV (%)	23.2	24.6	24.0
Missing (%)	13 (4)	3 (2)	16 (4)

Analysis results archived at Pfizer Proprietary software Improve version 2.5.0-101, Artifact CP1:FI-19096560
GeoCV=geometric coefficient of variation; GeoMean=geometric mean; GeoSD=geometric standard deviation; Std. Dev.=standard deviation.

Distribution and Elimination

Clearance:

In the popPK analysis, CL after single dose is the clearance prior to auto-induction (CLI=initial clearance after single dose), which was estimated to be 8.82 L/hr.

Lorlatinib clearance after multiple doses increases with time until reaching its maximum value when the auto-induction effect is complete, CLMX=maximum clearance value after multiple dosing. Lorlatinib CLMX was estimated to be 14.3 L/hr.

In the initial MAA submission, the typical values of the final model parameter estimates and the bootstrap estimated 95%CI for CLI and CLMX were 9.04 (8.01-10.1) and 14.5 L/h (12.7-16.2), respectively.

The difference between the initial clearance estimates (predominantly previously treated ALK-positive NSCLC patients) and the clearance estimates from the current analysis is less than 10%. This indicates that lorlatinib PK in the pooled population which includes patients from B7461006, is comparable in terms of clearance to the population from the initial MAA submission dataset. Table 7 presents the post-hoc estimated single dose and steady state lorlatinib CL from the original popPK analysis as well as the current analysis, for all NSCLC patients (including data from both B7461001 and B7461006 studies) who were receiving the 100 mg QD dosing.

The typical value for V2 was estimated to be 122 L. The typical value for ka (first-order absorption rate constant) was estimated to be 2.30 hr^{-1}.

In addition, V3 (peripheral volume of distribution) was estimated to be 160 L, Q (inter compartment clearance) was estimated to be 21.1 L/hr.

Table 7. Comparison of post-hoc clearance estimates

	Protocol	Geometric Mean	Geometric SD	Geometric CV	n
Single Dose Lorlatinib Clearance					
Original PopPK	1001	8.456	1.203	0.186	291
Current PopPK	1001	8.420	1.187	0.173	291
Current PopPK	1006	8.091	1.170	0.158	149
Steady State Lorlatinib Clearance					
Original PopPK	1001	13.564	1.204	0.187	278
Current PopPK	1001	13.458	1.189	0.174	278
Current PopPK	1006	13.008	1.164	0.153	146

Repository artifact ID FI-9583992.
1001=Study B7461001; 1006=Study B7461006; CV=coefficient of variation; n=number of individuals; popPK=population PK; SD=standard deviation

Lorlatinib plasma elimination half-life at steady state was determined using the population PK data. The lorlatinib population PK post-hoc values for individual clearance and volume of distribution were used to estimate the steady state plasma elimination half-life (see Table 8) based on the following equations:

Elimination rate constant (k_{el}) = Clearance/Volume of distribution
Half-life = $ln(2)/k_{el}$

Table 8. Elimination Half-life

	Arithmetic Mean (± SD)
Lorlatinib Steady State Elimination Half-life (h)	6.17±1.316

Analysis results archived at Pfizer Proprietary software Improve version 2.5.0-101, Artifact CP1:FI-19096508
h=hours

The plasma half-life of lorlatinib after a single 100 mg dose was 23.6 hours, as stated in the SmPC for Lorviqua.

The shorter estimated steady-state population PK-based elimination half-life of 6.17 hours is likely due to net lorlatinib auto-induction following multiple dosing.

In order to provide the most appropriate estimate of the lorlatinib plasma elimination half-life at steady-state (post auto-induction), the Applicant has calculated the steady-state effective half-life of 14.83 hours based on steady-state clearance (CL) and terminal volume of distribution (Vz) estimates.

Dose proportionality and time dependencies

In this application, only the 100 mg QD dose was investigated. Due to auto-induction (of P-gp and CYP3A4), the elimination of lorlatinib increases with time as described above.

Special populations

Renal impairment

Table 9 presents the post-hoc estimated single dose and steady-state clearance, as well as steady-state Cmax and AUCt, for cancer patients receiving 100 mg QD in the B7461001 and B7461006 studies, stratified by baseline renal function as defined by the K/DOQI staging. Although there were no patients with severe baseline renal impairment, there is a trend of decreasing single and steady state lorlatinib CL with worsening impairment at baseline. Correspondingly, there is a trend of increasing lorlatinib steady-state Cmax and AUCt with worsening baseline renal impairment.

Table 9. Evaluation of lorlatinib pharmacokinetics based on baseline renal impairment

Renal Function	Normal	Mild	Moderate	Total
Single Dose Lorlatinib Clearance (L/h)				
N (%)	379 (85)	63 (14)	4 (1)	446 (100)
Median	8.39	7.59	7.19	8.21
Range (Min; Max)	(5.46; 12.99)	(4.88; 11.51)	(6.35; 8.85)	(4.88; 12.99)
Mean (Std. Dev.)	8.577 (1.435)	7.659 (1.203)	7.392 (1.058)	8.437 (1.439)
GeoMean (GeoSD)	8.460 (1.181)	7.567 (1.170)	7.338 (1.149)	8.317 (1.185)
GeoCV	0.167	0.158	0.140	0.171
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)
Steady State Lorlatinib Clearance (L/h)				
N (%)	379 (85)	63 (14)	4 (1)	446 (100)
Median	13.38	12.13	11.46	13.10
Range (Min; Max)	(8.20; 19.79)	(8.49; 18.35)	(10.12; 14.17)	(8.20; 19.79)
Mean (Std. Dev.)	13.657 (2.279)	12.328 (1.902)	11.802 (1.718)	13.463 (2.275)
GeoMean (GeoSD)	13.469 (1.182)	12.188 (1.164)	11.712 (1.152)	13.274 (1.183)
GeoCV	0.168	0.153	0.142	0.170
Missing (%)	11 (3)	6 (10)	0 (0)	17 (4)
Steady State Lorlatinib Cmax (ng/mL)				
N (%)	379 (85)	63 (14)	4 (1)	446 (100)
Median	602.60	700.44	734.74	621.34
Range (Min; Max)	(277.95; 1182.63)	(324.35; 1286.34)	(716.89; 848.67)	(277.95; 1286.34)
Mean (Std. Dev.)	616.654 (149.177)	698.854 (176.378)	758.759 (61.871)	628.901 (155.298)
GeoMean (GeoSD)	599.065 (1.274)	675.449 (1.313)	756.946 (1.082)	610.023 (1.283)
GeoCV	0.246	0.277	0.079	0.253
Missing (%)	11 (3)	6 (10)	0 (0)	17 (4)
Steady State Lorlatinib AUCtau (ng.h/mL)				
N (%)	379 (85)	63 (14)	4 (1)	446 (100)
Median	5444.53	5781.85	6604.41	5474.73
Range (Min; Max)	(2445.38; 11247.60)	(2903.27; 8948.56)	(5135.38; 7857.04)	(2445.38; 11247.60)
Mean (Std. Dev.)	5561.424 (1330.303)	5802.674 (1291.505)	6550.308 (1291.073)	5602.699 (1327.625)
GeoMean (GeoSD)	5408.394 (1.268)	5654.094 (1.265)	6453.025 (1.223)	5449.379 (1.268)
GeoCV	0.241	0.238	0.203	0.241
Missing (%)	11 (3)	6 (10)	0 (0)	17 (4)

Repository artifact ID FI-9519579. Line 1 substituted.
Renal function as described by K/DOQI staging.
AUC_{τ}=area under the curve over the dosing interval; C_{max}=maximum observed concentration; GeoMean=geometric mean; GeoSD=geometric standard deviation; GeoCV=geometric coefficient of variation; K/DOQI=Kidney Disease Outcomes Quality Initiative; L/h=liters per hour; Max=maximum; Min=minimum; ng/mL=nanograms per milliliter; N=number of individuals.

Table 10 presents the post-hoc estimated single dose and steady- state lorlatinib clearance estimates, as well as steady-state Cmax and AUCt, for cancer patients receiving 100 mg QD lorlatinib in the B7461001 and B7461006 studies, stratified by each patient's worst renal impairment while on study as defined by the K/DOQI staging.

Table 10. Evaluation of lorlatinib pharmacokinetics based on worst renal impairment

Renal Function	Normal	Mild	Moderate	Severe	Total
Single Dose Lorlatinib Clearance (L/h)					
N (%)	330 (74)	95 (21)	20 (4)	1 (0)	446 (100)
Median	8.55	7.71	7.66	6.49	8.21
Range (Min; Max)	(5.46; 12.99)	(4.88; 11.51)	(5.72; 8.92)	-	(4.88; 12.99)
Mean (Std. Dev.)	8.694 (1.451)	7.758 (1.156)	7.522 (0.941)	-	8.437 (1.439)
GeoMean (GeoSD)	8.575 (1.181)	7.673 (1.163)	7.464 (1.138)	-	8.317 (1.185)
GeoCV	0.167	0.152	0.130	-	0.171
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Steady State Lorlatinib Clearance (L/h)					
N (%)	330 (74)	95 (21)	20 (4)	1 (0)	446 (100)
Median	13.63	12.46	12.06	10.35	13.10
Range (Min; Max)	(8.20; 19.79)	(8.49; 18.35)	(9.13; 14.17)	-	(8.20; 19.79)
Mean (Std. Dev.)	13.837 (2.304)	12.471 (1.827)	11.896 (1.456)	-	13.463 (2.275)
GeoMean (GeoSD)	13.647 (1.182)	12.340 (1.158)	11.809 (1.135)	-	13.274 (1.183)
GeoCV	0.168	0.147	0.127	-	0.170
Missing (%)	9 (3)	7 (7)	1 (5)	0 (0)	17 (4)
Steady State Lorlatinib Cmax (ng/mL)					
N (%)	330 (74)	95 (21)	20 (4)	1 (0)	446 (100)
Median	598.21	684.46	716.89	796.54	621.34
Range (Min; Max)	(286.23; 1129.52)	(277.95; 1286.34)	(411.24; 939.96)	-	(277.95; 1286.34)
Mean (Std. Dev.)	606.125 (141.022)	691.689 (184.259)	714.058 (134.417)	-	628.901 (155.298)
GeoMean (GeoSD)	589.998 (1.264)	666.649 (1.323)	700.798 (1.228)	-	610.023 (1.283)
GeoCV	0.237	0.285	0.208	-	0.253
Missing (%)	9 (3)	7 (7)	1 (5)	0 (0)	17 (4)
Steady State Lorlatinib AUCtau (ng.h/mL)					
N (%)	330 (74)	95 (21)	20 (4)	1 (0)	446 (100)
Median	5375.58	5742.49	6178.57	7325.57	5474.73
Range (Min; Max)	(2445.38; 9558.97)	(2903.27; 11247.60)	(4578.69; 8948.56)	-	(2445.38; 11247.60)
Mean (Std. Dev.)	5473.490 (1271.824)	5890.436 (1437.672)	6362.301 (1299.146)	-	5602.699 (1327.625)
GeoMean (GeoSD)	5328.122 (1.264)	5725.408 (1.271)	6241.714 (1.221)	-	5449.379 (1.268)
GeoCV	0.237	0.244	0.202	-	0.241
Missing (%)	9 (3)	7 (7)	1 (5)	0 (0)	17 (4)

Repository artifact ID FI-9519581. Line 1 substituted.
Renal function as described by K/DOQI staging. Worst renal impairment defined as the highest renal impairment grade experienced while on study.
AUC_τ=area under the curve over the dosing interval; C_{max}=maximum observed concentration; GeoMean=geometric mean; GeoSD=geometric standard deviation; GeoCV=geometric coefficient of variation; K/DOQI=Kidney Disease Outcomes Quality Initiative; L/h=liters per hour; Max=maximum; Min=minimum; ng/mL=nanograms per milliliter; N=number of individuals.

Hepatic impairment

Table 11 presents the post-hoc estimated single dose and steady-state clearance, as well as steady-state Cmax and AUCt , for cancer patients receiving 100 mg QD lorlatinib in the B7461001 and B7461006 studies, stratified by baseline hepatic function as defined by the NCI (national cancer institute) and ODGW (Organ dysfunction working group) developed criteria for hepatic dysfunction.

Table 11. Evaluation of lorlatinib pharmacokinetics based on baseline hepatic impairment

Hepatic Function	Normal (A)	Mild (B1)	Mild (B2)	Moderate (C)	Total
Single Dose Lorlatinib Clearance (L/h)					
N (%)	392 (88)	46 (10)	7 (2)	1 (0)	446 (100)
Median	8.22	8.10	7.53	9.96	8.21
Range (Min; Max)	(4.88; 12.99)	(5.84; 11.97)	(6.62; 10.85)	-	(4.88; 12.99)
Mean (Std. Dev.)	8.441 (1.440)	8.400 (1.432)	8.232 (1.639)	-	8.437 (1.439)
GeoMean (GeoSD)	8.321 (1.185)	8.283 (1.184)	8.102 (1.209)	-	8.317 (1.185)
GeoCV	0.171	0.170	0.191	-	0.171
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Steady State Lorlatinib Clearance (L/h)					
N (%)	392 (88)	46 (10)	7 (2)	1 (0)	446 (100)
Median	13.11	12.94	12.33	15.95	13.10
Range (Min; Max)	(8.20; 19.79)	(9.30; 19.12)	(10.56; 17.29)	-	(8.20; 19.79)
Mean (Std. Dev.)	13.462 (2.265)	13.435 (2.342)	13.318 (2.818)	-	13.463 (2.275)
GeoMean (GeoSD)	13.275 (1.182)	13.239 (1.189)	13.082 (1.228)	-	13.274 (1.183)
GeoCV	0.169	0.175	0.207	-	0.170
Missing (%)	13 (3)	3 (7)	1 (14)	0 (0)	17 (4)
Steady State Lorlatinib Cmax (ng/mL)					
N (%)	392 (88)	46 (10)	7 (2)	1 (0)	446 (100)
Median	622.27	612.97	572.23	528.16	621.34
Range (Min; Max)	(277.95; 1286.34)	(358.89; 1091.40)	(460.11; 788.81)	-	(277.95; 1286.34)
Mean (Std. Dev.)	629.687 (155.400)	627.727 (160.345)	604.414 (141.412)	-	628.901 (155.298)
GeoMean (GeoSD)	610.687 (1.285)	608.916 (1.281)	590.967 (1.260)	-	610.023 (1.283)
GeoCV	0.255	0.252	0.235	-	0.253
Missing (%)	13 (3)	3 (7)	1 (14)	0 (0)	17 (4)
Steady State Lorlatinib AUCtau (ng.h/mL)					
N (%)	392 (88)	46 (10)	7 (2)	1 (0)	446 (100)
Median	5479.48	5394.74	5844.56	4353.43	5474.73
Range (Min; Max)	(2445.38; 11247.60)	(3259.36; 9262.34)	(4576.22; 7218.97)	-	(2445.38; 11247.60)
Mean (Std. Dev.)	5590.562 (1319.181)	5701.315 (1452.114)	5870.813 (1053.469)	-	5602.699 (1327.625)
GeoMean (GeoSD)	5437.834 (1.268)	5534.061 (1.276)	5791.427 (1.199)	-	5449.379 (1.268)
GeoCV	0.241	0.248	0.183	-	0.241
Missing (%)	13 (3)	3 (7)	1 (14)	0 (0)	17 (4)

Repository artifact ID FI-9519578. Line 1 substituted.
Hepatic function as defined by the NCI ODGW developed criteria for hepatic dysfunction.
AUC_{τ}=area under the curve over the dosing interval; C_{max}=maximum observed concentration; GeoMean=geometric mean; GeoSD=geometric standard deviation; GeoCV=geometric coefficient of variation; L/h=liters per hour; Max=maximum; Min=minimum; ng/mL=nanograms per milliliter; N=number of individuals; NCI=National Cancer Institute; ODGW=Organ Dysfunction Working Group.

Table 12 presents the post-hoc estimated single dose and steady-state lorlatinib clearance, as well as steady-state Cmax and AUCt, for cancer patients receiving 100 mg QD lorlatinib in the B7461001 and B7461006 studies, stratified by each patient's worst hepatic function while on study as defined by the NCI (national cancer institute) and ODGW (organ dysfunction working group) developed criteria for hepatic dysfunction.

Table 12. Evaluation of lorlatinib pharmacokinetics based on worst hepatic impairment

Hepatic Function	Normal (A)	Mild (B1)	Mild (B2)	Moderate (C)	Severe (D)	Total
Single Dose Lorlatinib Clearance (L/h)						
N (%)	216 (48)	210 (47)	15 (3)	3 (1)	2 (0)	446 (100)
Median	8.31	8.08	7.79	9.96	8.32	8.21
Range (Min; Max)	(4.88; 12.99)	(5.72; 12.25)	(6.62; 10.85)	(8.79; 10.17)	(7.59; 9.05)	(4.88; 12.99)
Mean (Std. Dev.)	8.492 (1.479)	8.376 (1.411)	8.260 (1.393)	9.637 (0.744)	8.316 (1.032)	8.437 (1.439)
GeoMean (GeoSD)	8.366 (1.190)	8.261 (1.181)	8.156 (1.176)	9.617 (1.082)	8.284 (1.133)	8.317 (1.185)
GeoCV	0.175	0.167	0.163	0.079	0.125	0.171
Missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Steady State Lorlatinib Clearance (L/h)						
N (%)	216 (48)	210 (47)	15 (3)	3 (1)	2 (0)	446 (100)
Median	13.38	12.83	12.72	15.95	14.42	13.10
Range (Min; Max)	(8.20; 19.79)	(9.13; 19.61)	(10.56; 17.29)	(14.06; 16.26)	-	(8.20; 19.79)
Mean (Std. Dev.)	13.604 (2.314)	13.304 (2.242)	13.259 (2.287)	15.424 (1.190)	-	13.463 (2.275)
GeoMean (GeoSD)	13.409 (1.187)	13.122 (1.180)	13.085 (1.182)	15.392 (1.082)	-	13.274 (1.183)
GeoCV	0.173	0.167	0.168	0.079	-	0.170
Missing (%)	12 (6)	3 (1)	1 (7)	0 (0)	1 (50)	17 (4)
Steady State Lorlatinib Cmax (ng/mL)						
N (%)	216 (48)	210 (47)	15 (3)	3 (1)	2 (0)	446 (100)
Median	619.43	624.42	644.32	515.92	552.08	621.34
Range (Min; Max)	(277.95; 1286.34)	(286.23; 1182.63)	(438.77; 832.32)	(480.73; 528.16)	-	(277.95; 1286.34)
Mean (Std. Dev.)	628.804 (160.141)	631.109 (152.982)	628.991 (136.835)	508.270 (24.620)	-	628.901 (155.298)
GeoMean (GeoSD)	609.254 (1.288)	612.374 (1.284)	614.857 (1.250)	507.866 (1.050)	-	610.023 (1.283)
GeoCV	0.257	0.254	0.226	0.049	-	0.253
Missing (%)	12 (6)	3 (1)	1 (7)	0 (0)	1 (50)	17 (4)
Steady State Lorlatinib AUCtau (ng.h/mL)						
N (%)	216 (48)	210 (47)	15 (3)	3 (1)	2 (0)	446 (100)
Median	5504.70	5453.92	5618.45	5054.92	5171.48	5474.73
Range (Min; Max)	(2445.38; 9558.97)	(2547.02; 11247.60)	(4576.22; 7571.05)	(4353.43; 5324.54)	-	(2445.38; 11247.60)
Mean (Std. Dev.)	5564.791 (1257.312)	5630.596 (1417.581)	5921.621 (1092.353)	4910.962 (501.308)	-	5602.699 (1327.625)
GeoMean (GeoSD)	5424.984 (1.256)	5458.533 (1.285)	5829.110 (1.202)	4893.383 (1.110)	-	5449.379 (1.268)
GeoCV	0.231	0.255	0.186	0.105	-	0.241
Missing (%)	12 (6)	3 (1)	1 (7)	0 (0)	1 (50)	17 (4)

Repository artifact ID FI-9519580. Line 1 substituted.
Hepatic function as defined by the NCI ODGW developed criteria for hepatic dysfunction. Worst hepatic impairment defined as the highest hepatic impairment grade experienced while on study.
AUC_τ=area under the curve over the dosing interval; C_{max}=maximum observed concentration; GeoMean=geometric mean; GeoSD=geometric standard deviation; GeoCV=geometric coefficient of variation; L/h=liters per hour; Max=maximum; Min=minimum; ng/mL=nanograms per milliliter; N=number of individuals; NCI=National Cancer Institute; ODGW=Organ Dysfunction Working Group.

Table 13. Summary Comparison of Lorlatinib Post-hoc PK Parameters Categorized by Hepatic Function

	Normal Hepatic Function		Mild (B1) Hepatic Impairment		Mild (B2) Hepatic Impairment		Moderate Hepatic Impairment	
	1001	1006	1001	1006	1001	1006	1001	1006
Single Dose Lorlatinib C_{max} (ng/mL)								
n	252	140	38	8	7	0	0	1
GeoMean	462.212	420.913	481.771	397.885	474.706	-	-	308.43
GeoCV (%)	27.9	33.6	26.8	33.1	25.6	-	-	-
Single Dose Lorlatinib 24-hour AUC (ng.h/mL)								
n	252	140	38	8	7	0	0	1
GeoMean	4623.135	4927.440	4725.026	4941.482	4728.666	-	-	3250.19
GeoCV (%)	16.9	25.2	15.8	22.5	13.8	-	-	-
Steady State Lorlatinib C_{max} (ng/mL)								
n	252	140	38	8	7	0	0	1
GeoMean	594.945	639.520	607.904	613.360	590.967	-	-	528.16
GeoCV (%)	24.1	27.1	25.3	26.6	23.5	-	-	-
Steady State Lorlatinib AUC_{tau} (ng.h/mL)								
n	252	140	38	8	7	0	0	1
GeoMean	5584.897	5187.458	5689.285	4903.246	5791.427	-	-	4353.43
GeoCV (%)	23.2	24.9	25.0	20.6	18.3	-	-	-

Analysis results archived at Pfizer Proprietary software Improve version 2.5.0-101, Artifacts CP1:FI-19105560 and CP1:FI-19105561
If only one value is available, then the one value will be reported.
Hepatic function as defined by the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG).
1001=Study B7461001; 1006=Study B7461006; GeoCV=geometric CV; GeoMean=geometric mean; n=number of patients.

Pharmacokinetic interaction studies

Results of PBPK model used for prediction of metabolic DDIs are shown in Table 14, Table 15 and Table 16.

Table 14. Stimulated geometric mean (90%CI) pharmacokinetic parameters of lorlatinib following coadministration of lorlatinib and 200 mg QD itraconazole

Lorlatinib Dose	C_{max} (ng/mL)	AUC_{inf} or AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	AUC_{inf} or AUC_{tau} (ng•h/mL)	C_{maxR}	AUC_R
	w/o Itraconazole		w/ Itraconazole			
Single Dose of Lorlatinib (on Day 5) and Multiple Doses of 200 mg QD Itraconazole (11 Days)						
75 mg	405 (391, 420)	6100 (5700, 6530)	435 (421, 450)	8980 (8330, 9690)	1.07 (1.07, 1.08)	1.47 (1.45, 1.50)
100 mg[a]	538 (519, 557)	7880 (7370, 8440)	580 (561, 600)	11700 (10900, 12700)	1.08 (1.07, 1.08)	1.49 (1.46, 1.51)
Multiple Doses of Lorlatinib and 200 mg QD Itraconazole						
75 mg QD[b]	486 (464, 508)	5020 (4680, 5380)	626 (595, 658)	7600 (7030, 8220)	1.29 (1.27, 1.30)	1.52 (1.49, 1.54)
100 mg QD[a,c]	636 (608, 666)	6470 (6021, 6940)	825 (785, 867)	9870 (9110, 10700)	1.30 (1.28, 1.31)	1.53 (1.50, 1.55)

Notes: Simulations conducted in a simulated healthy volunteer population. AUC_{inf} reported for single dose data and AUC_{tau} reported for multiple dose data.
AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; AUC_{tau} = Area under the concentration-time curve over the dosing interval tau (tau = 24 hours); AUC_R = Ratio of AUC of substrate drug with coadministration of the interacting drug to AUC of substrate drug alone; CI = Confidence interval; C_{max} = Maximum plasma concentration; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; QD = Once daily; w/ = With; w/o = Without.
a. Data reported previously in Study PF-06463922_22Jun18_115307[2].
b. Dosed for 15 Days.
c. Dosed for 14 Days.

Table 15. Stimulated geometric mean (90%CI) pharmacokinetic parameters of lorlatinib following coadministration of a single dose of 100 mg lorlatinib (on day 5 or 7) and multiple doses of moderate or weak CYP3A4 inhibitors (11 to 13 Days)

Inhibitor Dose	C_{max} (ng/mL) w/o Inhibitor	AUC_{inf} (ng•h/mL) w/o Inhibitor	C_{max} (ng/mL) w/ Inhibitor	AUC_{inf} (ng•h/mL) w/ Inhibitor	C_{maxR}	AUC_R
Moderate CYP3A4 Inhibitors						
Diltiazem (60 mg TID[a])	538 (519, 557)	7850 (7350, 8380)	555 (536, 575)	9100 (8480, 9770)	1.15 (1.14, 1.16)	1.16 (1.15, 1.17)
Verapamil (80 mg TID[a])	543 (526, 561)	7850 (7350, 8390)	566 (548, 584)	9230 (8950, 10400)	1.04 (1.04, 1.05)	1.23 (1.21, 1.24)
Erythromycin (500 mg BID[a])	550 (532, 569)	8010 (7500, 8560)	572 (553, 591)	9830 (9190, 10500)	1.04 (1.04, 1.04)	1.23 (1.21, 1.24)
Fluconazole (200 mg QD[b])	539 (521, 557)	7840 (7340, 8380)	576 (558, 595)	11200 (10500, 12000)	1.07 (1.06, 1.07)	1.43 (1.41, 1.46)
Weak CYP3A4 Inhibitors						
Fluvoxamine (100 mg BID[b])	550 (532, 569)	8010 (7500, 8560)	570 (551, 589)	9060 (8480, 9670)	1.04 (1.03, 1.04)	1.13 (1.12, 1.14)
Fluoxetine (20 mg QD[b])	538 (519, 557)	7870 (7350, 8430)	545 (527, 565)	8370 (7820, 8960)	1.01 (1.01, 1.02)	1.06 (1.06, 1.07)

Notes: Simulations conducted in a simulated healthy volunteer population.
AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; AUC_R = Ratio of AUC of substrate drug with coadministration of the interacting drug to AUC of substrate drug alone; BID = Twice a day; CI = Confidence interval; C_{max} = Maximum plasma concentration; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; QD = Once daily; TID = Three times a day; w/ = With; w/o = Without.
a. 100 mg lorlatinib dosed on Day 5 with multiple doses of inhibitor (11 days).
b. 100 mg lorlatinib dosed on Day 7 with multiple doses of inhibitor (13 days).

Table 16. Stimulated geometric mean (90%CI) pharmacokinetic parameters of lorlatinib following coadministration of multiple doses of 100 mg lorlatinib and multiple doses of moderate or weak CYP3A4 inhibitors (15 Days)

Inhibitor Dose	C_{max} (ng/mL) w/o Inhibitor	AUC_{tau} (ng•h/mL) w/o Inhibitor	C_{max} (ng/mL) w/ Inhibitor	AUC_{tau} (ng•h/mL) w/ Inhibitor	C_{maxR}	AUC_R
Moderate CYP3A4 Inhibitors						
Diltiazem (60 mg TID)	632 (605, 661)	6400 (5980, 6860)	677 (648, 708)	7190 (6700, 7700)	1.07 (1.07, 1.07)	1.12 (1.12, 1.13)
Verapamil (80 mg TID)	640 (614, 667)	6420 (5990, 6880)	687 (658, 717)	7260 (6760, 7790)	1.07 (1.07, 1.08)	1.13 (1.12, 1.14)
Erythromycin (500 mg BID)	652 (623, 681)	6560 (6110, 7040)	728 (697, 759)	8030 (7520, 8570)	1.12 (1.11, 1.13)	1.22 (1.20, 1.24)
Fluconazole (200 mg QD)	637 (609, 666)	6440 (6000, 6910)	818 (782, 856)	10100 (9430, 10800)	1.28 (1.27, 1.30)	1.57 (1.53, 1.60)
Weak CYP3A4 Inhibitors						
Fluvoxamine (100 mg BID)	652 (623, 681)	6560 (6110, 7040)	708 (678, 740)	7500 (7000, 8040)	1.09 (1.08, 1.09)	1.14 (1.13, 1.15)
Fluoxetine (20 mg QD)	634 (605, 664)	6420 (5970, 6900)	657 (627, 689)	6850 (6380, 7360)	1.04 (1.03, 1.04)	1.07 (1.06, 1.07)

Notes: Simulations conducted in a simulated healthy volunteer population.
AUC_{tau} = Area under the concentration-time curve over the dosing interval tau (tau = 24 hours); AUC_R = Ratio of AUC of substrate drug with coadministration of the interacting drug to AUC of substrate drug alone; BID = Twice a day; CI = Confidence interval; C_{max} = Maximum plasma concentration; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; QD = Once daily; TID = Three times a day; w/ = With; w/o = Without.

2.3.4. Pharmacodynamics

Primary and secondary pharmacology

Exposure-efficacy models – Study 1006

E-R results for efficacy endpoints were originally included in the initial MAA submission and were based on data from **Study 1001**, with predominantly pre-treated ALK+ advanced NSCLC patients. The objective of the such analysis was to assess the potential relationship between lorlatinib PK exposure (mainly as cumulative AUC) and the objective response rate (ORR) and intracranial objective response rate (IC-ORR); moreover, the analysis had the scope to evaluate the effect of covariates in the E-R relationship for the efficacy endpoints ORR and IC-ORR as assessed by independent central review (ICR).

A brief summary of the main findings of the original final model is shown below for the three populations considered for the initial analysis:

1. *Patients who received prior treatment with any number of ALK-inhibitors (ORR, N=268; IC-ORR, N=174).*
   - ORR: the variables that were statistically significant predictors of achieving ORR were Asian race, baseline haemoglobin (BHGB), number of prior systemic treatments (NTHER) and maximum hypercholesterolemia adverse event Grade ≥2 (CHLGR). The odds of achieving ORR were 2.090 times higher in Asian patients vs non-Asian, 3.343 times higher for patients with CHLGR ≥2 and 1.215 times higher for every unit of increase on BHGB.
   - IC-ORR: prior CNS radiation (PRAD), log of BAP (baseline alkaline phosphatise) and BAMY (baseline amylase) were statistically predictor of ORR. The odds of achieving ORR were 0.286 times higher for patients receiving PRAD vs patients that did not, 0.340 times higher for every 1 unit increase in BAP and 1.014 times higher for every unit increase in BAMY.
2. *Patients who received prior treatment with ≥1 ALK-inhibitors (ORR, N=197; IC-ORR, N=123).*
   - ORR: none of the tested predictors, including lorlatinib exposure metric Cmax, P1, were statistically significant predictors of achieving ORR. This was not surprising given the homogeneity of the data (i.e. all the patients had at least 1 prior ALK inhibitor and were treated with a starting dose of 100 mg QD lorlatinib).
   - IC-ORR: BAP and BAMY were statistically significant predictors of ORR. The odds of achieving IC-ORR were 1.015 times higher for every 1 unit increase of BAMY and 0.363 times higher for every 1 unit increase in BAP.
3. *Patients who received prior treatment with ≥2 ALK-inhibitors (ORR, N=111; IC-ORR, N=74).*
   - ORR: BAMY was a significant predictor of ORR. The odds of achieving ORR were 1.02 times higher for every 1 unit increase in BAMY.
   - IC-ORR: This analysis was not conducted due to the low number of patients with evaluable data.

The original E/R analysis did not show a correlation between lorlatinib exposure and efficacy response in terms of ORR and IC-ORR. The reason could be the high homogeneity in the population analysed in particular in terms of dose. Also, it was not possible to conclude that the covariates considered significant in the analysis are effectively useful to predict the response. The potential relationship between lorlatinib exposure and PFS was not characterized due to the small number of events at time of the initial MAA submission.

An updated E-R analysis for efficacy endpoints, including previously untreated patients from **Study 1006**, has been provided within the current application and is hereinafter discussed.

The dataset included all patients in the intention-to-treat (ITT) population in Study B7461006 (N=149 from the lorlatinib arm and N=147 from the crizotinib arm). The E-R analyses were performed using PFS, ORR, and IC-ORR as the efficacy endpoints. Only patients from the lorlatinib arm who had baseline CNS metastasis were included in the E-R analysis for IC-ORR (N=38). Time-to-event data was summarized using median, low, and high percentiles.

The PFS analysis was conducted using parametric time-to-event (TTE) models. Several survival distribution functions were evaluated including Weibull and exponential models where a log-normal hazard distribution best described the PFS data.

Table 17. Run log for tested hazard distributions in patients randomized to the lorlatinib arm

Base Model Distribution	AIC	OFV	Δ OFV
Log-Normal*	687.46	683.46	Reference
Gompertz	688.85	684.85	1.39
Log-Logistic	690.57	686.57	3.11
Exponential	691.64	689.64	6.17
Weibull	691.92	687.92	4.46

Repository Artifact ID FI-10481188.
The * indicates the model that was selected going forward.
OFV=objective function value; ΔOFV=change in OFV relative to reference base model.

Lorlatinib steady-state exposure metrics were evaluated in the PFS base model using a univariate approach and it was determined that the best exposure metric was predicted maximum concentration up to Cycle 1 Day 15 (Cmax ss). However, for the exposure-PFS analysis for patients in the lorlatinib arm, lorlatinib Cmax ss was not significantly associated with PFS in both univariate and multivariate regression models. In the final PFS model, higher baseline albumin (BALB) and higher baseline body weight (BWT) were associated with higher probability of longer PFS. Model evaluation was based on the likelihood ratio test, condition number and precision of the parameter estimates. TTE VPCs were used to compare simulated to observed Kaplan-Meier survival curves.

Table 18. Final model parameter estimates for PFS patients in the lorlatinib arm

Parameter	Value	RSE (%)	95% CI
θ_{σ}	1.7821	10.32	(1.422 - 2.143)
θ_{μ}	7.4419	3.70	(6.902 - 7.982)
$\theta_{\text{Baseline Albumin on } \mu}$	0.5279	33.57	(0.181 - 0.875)
$\theta_{\text{Baseline Body Weight on } \mu}$	0.3065	44.86	(0.037 - 0.576)
OFV	668.0861	-	-

Repository artifact ID FI-10394530. Line 1 substituted.
CI=confidence interval; θ=typical population value of model parameters; μ=location distribution parameter; σ=scale distribution parameter; OFV=objective function value; PFS=progression-free survival; RSE=relative standard error.

The modelling analyses for ORR and IC-ORR were performed using binomial logistic regression models. For each of the exploratory analyses for ORR and IC-ORR, Cmax ss was identified as the best exposure metric. In the final model for ORR, none of the tested covariates, including lorlatinib exposure metric Cmax ss, were statistically significant predictors of achieving ORR after backward covariate elimination. The c-index or area under the receiver operating characteristic (ROC) curve was calculated to assess the

model's ability to identify individuals with different risks of the target event and evaluate the model performance.

Table 19. ORR: Lorlatinib exposure metric selection

Parameter	AIC	ΔD	Pr(>|z|)
$Cmax_{SS}$	153.7353	149.7353	0.0995
$Ctrough_{SS}$	155.7946	151.7946	0.3833
$Cavg_{SS}$	156.1935	152.1935	0.5493

Repository artifact ID FI-11239074.

AIC=Akaike information criterion; $C_{avg\ ss}$=predicted average concentration calculated as the ratio of AUC_{Tau} over the dosing interval; $C_{trough\ ss}$=predicted concentration prior to Cycle 1 Day 15 lorlatinib dose; $C_{max\ ss}$=predicted maximum concentration up to Cycle 1 Day 15; ΔD=deviance difference between null and residual; ORR=objective response rate; Pr(>|z|)=it represents the tail area in a 2-tail test.

Table 20. IC-ORR: Lorlatinib exposure metric selection

Parameter	AIC	ΔD	Pr(>|z|)
$Cmax_{SS}$	46.7371	42.7371	0.0761
$Cavg_{SS}$	46.8384	42.8384	0.0737
$Ctrough_{SS}$	48.7974	44.7974	0.1887

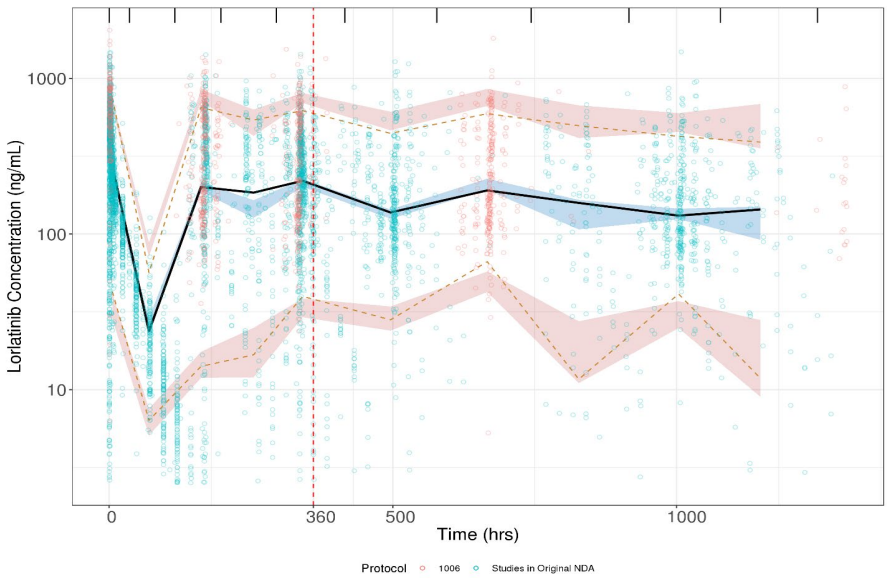
Repository artifact ID FI-11239073.

AIC=Akaike information criterion; $C_{avg\ ss}$=predicted average concentration calculated as the ratio of AUC_{Tau} over the dosing interval; $C_{trough\ ss}$=predicted concentration prior to Cycle 1 Day 15 lorlatinib dose; $C_{max\ ss}$=predicted maximum concentration up to Cycle 1 Day 15; ΔD=deviance difference between null and residual; IC-ORR=intracranial objective response rate; Pr(>|z|)=it represents the tail area in a 2-tail test.

In the final model for IC-ORR, only male sex was identified as a significant predictor for achieving IC-ORR. Due to the unequal distribution of sex (10 male, 28 female), low number of patients in this analysis set (N=38), and the overall high proportion of positive IC-ORR in the lorlatinib arm 66%, these analyses should be interpreted with caution.

The population PK model provided good predictive performance up to 360 hours after the start of lorlatinib treatment (Figure 6. Visual Predictive Check for the First 1300 hours).

Figure 6. Visual Predictive Check for the First 1300 hours



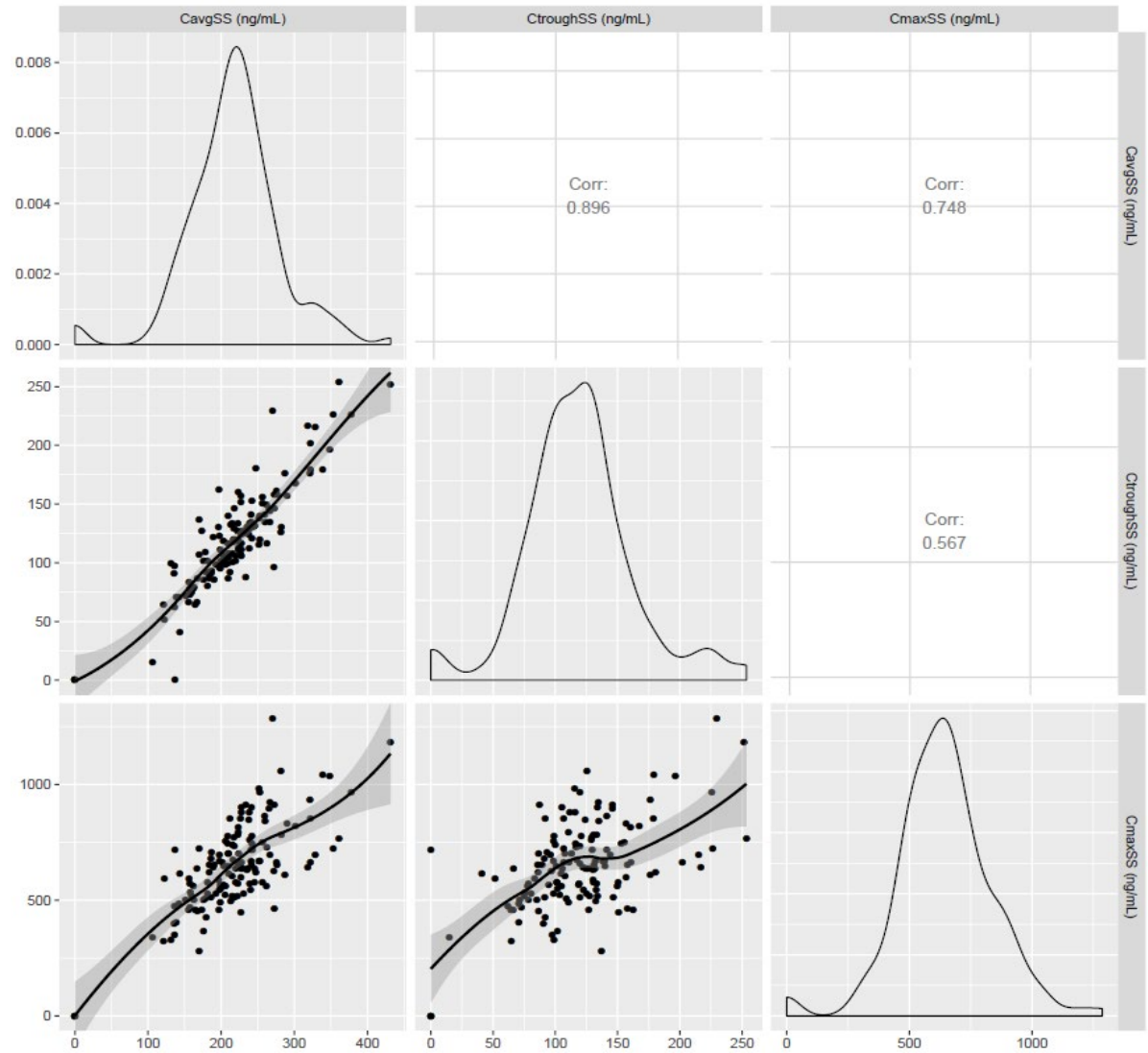
Analysis results archived at Pfizer Proprietary software Improve version 2.5.0-101, Artifact CP1:FI-19106201

The vertical dashed red line demarcates 360 hours post the first lorlatinib dose, which is equivalent to 24 hours post Cycle 1 Day 15 dose. The solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 90% CI of the 50th percentile of the simulated data. The red ribbons represent the 90% CI of the 5th and 95th percentiles of the simulated data.
1006=Study B7461006.

As pre-specified in the Population Modeling Analysis Plan, an agnostic approach was used to select the most appropriate Cycle 1, Day 15 (C1D15) lorlatinib exposure metrics to evaluate in the exposure-response (E-R) analyses for efficacy. For the purpose of the analyses in PMAR-EQDD-B746e-sNDA-1050, the exposure metrics considered were predicted maximum concentration up to Cycle 1 Day 15 ($C_{max\ ss}$), predicted concentration prior to Cycle 1 Day 16 lorlatinib dose ($C_{trough\ ss}$), and predicted average concentration calculated as the ratio of AUC_{tau} over 24 hours ($C_{avg\ ss}$).

Although $C_{max\ ss}$ was determined to be the most appropriate exposure metric, the difference in OFV was only slightly better for $C_{max,ss}$ compared to other metrics, e.g., $C_{trough,ss}$ and $C_{average,ss}$ since all of the lorlatinib exposure metrics evaluated were all correlated (>50%). (Figure 7). To confirm that the choice of the lorlatinib exposure metric would not change the results, the E-R analyses for efficacy (PFS, ORR, and ORR-IC) endpoints were re-run using the exposure metrics $C_{trough\ ss}$ and $C_{avg\ ss}$. The results are presented below in Table 21 and Table 22, which confirm that these results are consistent with those reported in PMAR-EQDD-B746e-sNDA-1050, which used the exposure metric $C_{max,ss}$.

Figure 7. Correlation of Lorlatinib Exposure Metrics



Analysis results archived at Pfizer Proprietary software *Improve M&S* version 2.5.0-101, Artifact number CP1:FI-19190517

Table 21. Results from Univariate Exposure-Response Analyses for Efficacy Endpoints Using Different Lorlatinib Plasma Exposure Metrics

Efficacy Endpoint	P-value for Exposure Metrics			
	Cmax ss	Ctrough ss	Cave ss	*Improve M&S* version 2.5.0-101, Artifact number
PFS, N=149				
mu	0.129700	0.270650	0.397390	FI-11168150
sigma	0.877300	0.894700	0.678440	
ORR, N=144	0.0995	0.3833	0.5493	FI-19190519
ORR-IC, N=37	0.0761	0.1887	0.0737	FI-19190518

Table 22. Results from Multivariate Exposure-Response Analyses for Efficacy Using Different Lorlatinib Exposure Metrics

	PFS, N=149	ORR, N=144	ORR-IC, N=37
Exposure Metric	Covariate Significance (*Improve M&S* version 2.5.0-101, Artifact number)		
$C_{max\ ss}$	Not significant (FI-11176705)	Not significant (FI-10481100; 168)	Not significant (FI-10481100; 310)
$C_{trough\ ss}$	Not significant (FI-19048242)	Not significant (FI-19190339; 189)	Not significant (FI-19190339; 436)
$C_{avg\ ss}$	Not significant (FI-19056088)	None (FI-19190339; 272)	Not significant (FI-19190339; 518)

Exposure-safety models – pooled analysis Study 1006 and Study 1001

Lorlatinib exposure metrics were derived from the final popPK model. Data from the Phase 3 B7461006 study in previously untreated ALK-positive advanced NSCLC patients (N=149), in combination with the data from the Phase 1/2 B7461001 study in patients with ALK-positive NSCLC (N=331) was used to evaluate the relations between lorlatinib exposure and a number of safety endpoints.

Studies' summary description

- Study 1006: phase 3, randomized, parallel 2-arms, open-label study. As a primary objective, it investigated the superiority of lorlatinib (Arm A: 100 mg QD as monotherapy) vs crizotinib (Arm B: 250 mg BID as monotherapy) in prolonging PFS in 296 previously untreated ALK+ NSCLC patients. It also investigated the safety and tolerability in each treatment arm.
- Study 1001: phase 1/2, open-label, multiple dose, dose escalation study. It investigated safety, PK, PD and efficacy of lorlatinib as monotherapy in patients with advanced ALK+ or ROS1+ NSCLC previously treated with other ALK-inhibitors.
  - Phase 1 part estimated the MTD for lorlatinib in dose escalation cohorts (10, 25, 50, 75, 100, 150 and 200 mg QD) and enrolled 55 patients. Although not initially planned, 25, 35, 50 and 75 mg BID dosing regimens were investigated due to the occurrence of (DLTs).
  - Phase 2 part evaluated the anti-cancer activity of lorlatinib in multiple subpopulations of patients and allowed a better definition of the safety, efficacy, PK and PD profiles of lorlatinib at 100 mg QD recommended dose.

For both studies, the safety endpoints were defined using standardized search criteria following the Standard MedDRA Query, HLGTs, HLTs and/or PTs. The safety outcomes of interest were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03 severity grade. TEAEs grade ≥3 were also analyzed.

E-R relationships were modelled for safety endpoints that occurred in at least 10% of patients, which included Hypercholesterolemia Grade ≥3, Hypertriglyceridemia Grade ≥3, Weight Gain Grade ≥2, and TEAE Grade ≥3 using binomial logistic regression. The same exposure-safety relationships were also investigated using ordinal logistic regression models to investigate the grade of a safety event.

Table 23. Potential predictors of response

Predictors	Description
Lorlatinib exposure metrics	$AUC_{24\ SD}$, $C_{ave\ SD}$, $C_{max\ SD}$, AUC_{360}, $AUC_{\tau\ SS}$, $C_{trough\ SS}$, $C_{ave\ 360}$, $C_{max\ 360}$
Demographic characteristics	Race, study, sex, baseline age, baseline body surface area, baseline body weight
Safety laboratory information at baseline	Albumin, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, hemoglobin, serum creatinine, creatinine clearance, lipase, amylase, LDL, HDL, triglycerides, total cholesterol, GGT
Treatments	Concomitant hepatoxic drugs (Y/N)[a], concomitant CYP inducers (Y/N)[b], concomitant steroids (Y/N), concomitant narcotics (Y/N), prior CNS radiation treatment (Y/N)
Disease characteristics	CNS metastasis (Y/N)

[a]Separately examined hepatotoxic drugs that have been associated with >100 cases of drug-induced liver injury and drugs that have been associated with >30 published case reports of drug induced liver injury [16].
[b]Included only potent CYP inducers defined by University of Washington Drug-Drug Interaction Database [17].
$AUC_{24\ SD}$=single dose 24-hour AUC; $C_{ave\ SD}$=single dose average concentration; $C_{max\ SD}$=single dose maximum concentration; AUC_{360}=AUC over first 360 hours; $AUC_{\tau\ SS}$=steady state AUC over the dosing interval; $C_{trough\ SS}$=steady state trough concentration; $C_{ave\ 360}$=average concentration over first 360 hours; $C_{max\ 360}$=maximum concentration over first 360 hours; LDL=low density lipoprotein; HDL=high density lipoprotein; GGT=gamma-glutamyl transferase; CNS=central nervous system; ALK=anaplastic lymphoma kinase; CYP=cytochrome P450; Y/N=Yes/No.

Covariates initially deemed clinically relevant or deemed potentially relevant after graphically inspection were initially included and excluded from the full model based on stepwise backwards elimination except for the exposure metric. The goodness-of-fit, c-index and ROC curves were used to assess the models. Below are the final model parameters of the binomial logistic regression analyses for the four modelled safety endpoints (Table 24, Table 25,Table 26, Table 27). The final parameters of the ordinal logistic regression models are not shown since the logistic regression models serve as the primary analysis.

Table 24. Final model hypercholesterolemia exposure-response analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
HCHOL ≥3	Intercept	-5.77	(-7.21; -4.44)	-8.2	<0.0001
	Cholesterol (mg/dL)	0.02	(0.0139; 0.0267)	6.19	<0.0001
	Odds ratio				
	Cholesterol (mg/dL)	1.02	(1.014; 1.027)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-43.79	374.2	1	<0.0001	-185.1

Repository artifact ID FI-9750237. Line 1 substituted.
Abbreviations: HCHOL=hypercholesterolemia, mg=milligram, dL=deciliter, CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

Table 25. Final model hypertriglyceridemia exposure-response analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
HTG ≥3	Intercept	-18.1	(-22.6; -14)	-8.18	<0.0001
	Race: Asian	1.03	(0.442; 1.64)	3.39	0.0007
	Baseline Albumin (g/dL)	0.812	(0.215; 1.45)	2.58	0.0098
	Log Baseline Triglycerides (mg/dL)	2.61	(1.91; 3.39)	6.92	<0.0001
	Odds ratio				
	Race: Asian	2.803	(1.557; 5.144)		
	Baseline Albumin (g/dL)	2.253	(1.24; 4.263)		
	Log Baseline Triglycerides (mg/dL)	13.64	(6.724; 29.69)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-92.26	297.5	3	<0.0001	-144.7

Repository artifact ID FI-9752809. Line 1 substituted.

Abbreviations: HTG=hypertriglyceridemia, g=gram, mg=milligram, dL=deciliter, CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

Table 26. Final model weight gain exposure-response analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
Weight Gain ≥2	Intercept	-0.074	(-1.19; 1.04)	-0.129	0.8970
	Age (years)	-0.045	(-0.0661; -0.0244)	-4.23	<0.0001
	Concomitant Narcotics	0.715	(0.199; 1.24)	2.7	0.0070
	Study B7461006	1.65	(1.11; 2.21)	5.91	<0.0001
	Odds ratio				
	Age (years)	0.9562	(0.9361; 0.9759)		
	Concomitant Narcotics	2.043	(1.221; 3.459)		
	Study B7461006	5.213	(3.041; 9.121)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-50.32	403	3	<0.0001	-197.5

Repository artifact ID FI-9753203. Line 1 substituted.

Abbreviations: CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

Table 27. Final model treatment-emergent adverse event exposure-response analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
TEAE ≥3	Intercept	-5.05	(-7.37; -2.82)	-4.37	<0.0001
	Single Dose C_{ave} (ng/mL)	0.007	(0.0031; 0.0103)	3.63	0.0003
	Log Baseline Triglyceride (mg/dL)	0.84	(0.396; 1.3)	3.64	0.0003
	Concomitant Steroids	0.695	(0.26; 1.14)	3.1	0.0020
	Concomitant Narcotics	0.556	(0.138; 0.982)	2.58	0.0098
	Odds ratio				
	Single Dose C_{ave} (ng/mL)	1.007	(1.003; 1.01)		
	Log Baseline Triglyceride (mg/dL)	2.317	(1.485; 3.676)		
	Concomitant Steroids	2.004	(1.297; 3.134)		
	Concomitant Narcotics	1.744	(1.147; 2.671)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-46.89	564	4	1.0000	-277

Repository artifact ID FI-9753351. Line 1 substituted.

Abbreviations: TEAE=treatment-emergent adverse event, ng=nanogram, mL=milliliter, CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, C_{ave}=average concentration, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

Exposure-response-relationship

Efficacy E-R relationship results

The observed efficacy results in terms of PFS and ORR for patients in the overall population and IC-ORR for patients with intracranial metastases at baseline for Study 1006 are shown in the following table.

Study B7461006: Summary of PFS Efficacy Outcomes

Variable	Category	Lorlatinib	Crizotinib
N (%)		149	147
PFS in all randomized patients	Total number censored	108 (72%)	61 (41%)
	Number with event	41 (28%)	86 (59%)

Repository artifact ID FI-10375867.
N=number of patients; PFS=progression-free survival.

Study B7461006: Summary of ORR Efficacy Outcome

Variable	Category	Lorlatinib	Crizotinib
N (%)		149	147
ORR	Number Positive ORR	113 (76%)	85 (58%)
	Number Negative ORR	36 (24%)	62 (42%)
N		38	40
Intracranial ORR	Number Positive ORR-IC	25 (66%)	8 (20%)
	Number Negative ORR-IC	13 (34%)	32 (80%)

Repository artifact ID FI-10375866.
ORR=objective response; N=number of patients.

The following table summarizes the exposure metrics derived for patients in Study 1006 who received at least 1 dose of lorlatinib and had PK information available.

Study B7461006: Summary of Lorlatinib Exposure Metrics

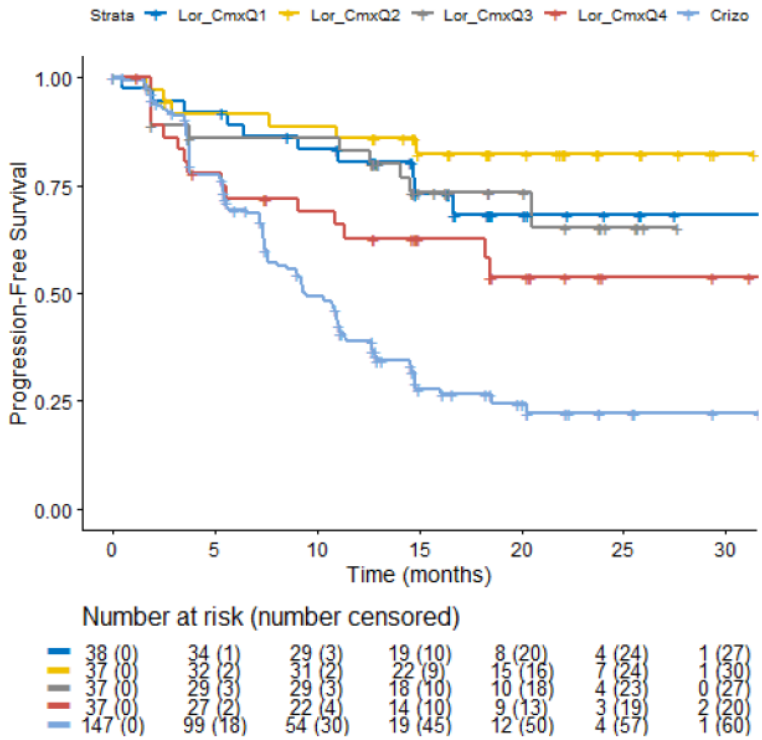
Variable	N	Nm	Mean (Stdev)	Median (Min-Max)
Ctrough ss (ng/mL)	149	3	120.361 (40.656)	116.997 (0.132-253.466)
cCaverage ss (ng/mL)	149	3	282.652 (64.831)	284.394 (107.874-506.595)
Caverage ss (ng/mL)	149	3	221.550 (54.087)	218.061 (106.126-431.426)
Cmax ss (ng/mL)	149	3	659.211 (171.784)	647.084 (277.952-1286.343)
Ctrough p1 (ng/mL)	149	5	111.965 (38.370)	109.301 (0.027-244.076)

Repository artifact ID FI-10375869.
Only patients who received at least one dose of lorlatinib and had PK information available are summarized in this table.
$C_{average\ ss}$=predicted average concentration calculated as the ratio of AUC_{Tau} over the dosing interval; $cC_{average\ ss}$=predicted average concentration calculated as the ratio of the cummulative AUC_{ss} over the time frame for the cumulative exposure; $C_{trough\ ss}$=predicted concentration prior to Cycle 1 Day 15 lorlatinib dose; $C_{trough\ p1}$=predicted concentration prior to Cycle 2 Day 1 lorlatinib dose; $C_{max\ ss}$=predicted maximum concentration up to Cycle 1 Day 15; Max=maximum; Min=minimum value; N=number of patients; Nm=number of patients with missing observations; Stdev=standard deviation.

Below figure shows the observed PFS for patients in Study 1006. The blue, yellow, grey and red lines represent patients in the lorlatinib arm stratified by exposure quartiles (Cycle 1 Day 15 average concentration) and the light blue line represents patients in the crizotinib arm. The median PFS in the crizotinib arm was 9.3 months (95% CI: 7.6, 11.1 months) and the median PFS was not reached in any of the lorlatinib exposure quartiles. Lorlatinib exposure quartiles, in terms of $C_{max\ ss}$, mostly overlap and

the highest exposure quartile 4 (median 853 ng/mL [range 752-1286 ng/mL]) may be associated with slightly shorter PFS compared to quartiles 1-3 (median 465 ng/mL [range 0-528 ng/mL], 591 ng/mL [range 530-644 ng/mL], and 696 ng/mL [range 647-746 ng/mL]. Similar trends were observed for other lorlatinib steady-state exposure metrics (i.e. $C_{trough\ ss}$ and $C_{avg\ ss}$). Therefore, the analyses intended to quantify any potential relationships between PFS and possible covariates, including lorlatinib exposure.

Figure 8. PFS for patients in study B7461006



Repository artifact ID FI-10481199.
PFS for patients in Study B7461006 Stratified by treatment arm and lorlatinib exposure quartiles (Cycle 1 Day 15 average concentration).

Safety E-R relationship - results

Results from the assessment of exposure-response relationship for safety endpoints were included in the submission of the initial MAA and were based on data from Study 1001 with predominantly pretreated ALK-positive advanced NSCLC patients. An updated E-R analysis for safety, pooling the individuals from Studies 1001 and 1006 was conducted. E-R relationships were analysed using binomial logistic regression for safety endpoints that occurred in at least 10% of patients, which included:

- Hypercholesterolemia Grade ≥3
- Hypertriglyceridemia Grade ≥3
- Weight gain Grade ≥2 (defined as the PT Weight increased)
- TEAE Grade ≥3

The same E-R relationships were also analysed using ordinal logistic regression. These same endpoints were modelled in the previously submitted lorlatinib E-R safety analysis.

The E-R analysis included 480 patients treated with lorlatinib from Study B7461006 (N=149) and Study B7461001 (N=331).

Tables below summarize the incidence and rate of safety events and the events graded by severity according to the NCI CTCAE v.4.03 severity grade.

Table 28. Summary of safety endpoints for binomial logistic regression analysis

AE Category	N	Missing	No Event	Incidence[a]	Model
CNS Mood Grade ≥2	480	0	456	24 (5.0)	
CNS Speech Grade ≥2	480	0	476	4 (0.8)	
CNS Cognition Grade ≥2	480	0	445	35 (7.3)	
Elevated AST Grade ≥2	480	3	466	11 (2.3)	
Elevated ALT Grade ≥2	480	3	461	16 (3.4)	
Hypercholesterolemia Grade ≥3	480	6	399	75 (15.8)	Yes
Hypertriglyceridemia Grade ≥3	480	8	393	79 (16.7)	Yes
Weight Gain Grade ≥2	480	15	379	86 (18.5)	Yes
Elevated Serum Lipase Grade ≥3	480	5	443	32 (6.7)	
Elevated Serum Amylase Grade ≥3	480	16	454	10 (2.2)	
AV Block Grade ≥1	480	0	475	5 (1.0)	
Seizures Grade ≥2	480	0	475	5 (1.0)	
Peripheral Neuropathy Grade ≥2	480	0	434	46 (9.6)	
Peripheral Edema Grade ≥3	480	0	467	13 (2.7)	
TEAE Grade ≥3	480	0	153	327 (68.1)	Yes
Psychosis Grade ≥2	149	0	148	1 (0.7)	

Repository artifact ID FI-9511736. Line 1 substituted.
Grades were based on NCI CTCAE v.4.03 definitions.
[a]Incidence is presented as n (%), where n represents the number of patients experiencing a safety event and (%) is calculated as n/(N-Missing).
Abbreviations: AE=adverse event, N=number of patients included in data file, Missing=number of patients in data file with missing data for the safety endpoint, CNS=central nervous system, AST=aspartate aminotransferase, ALT=alanine aminotransferase, AV=atrioventricular, TEAE=treatment-emergent adverse event.

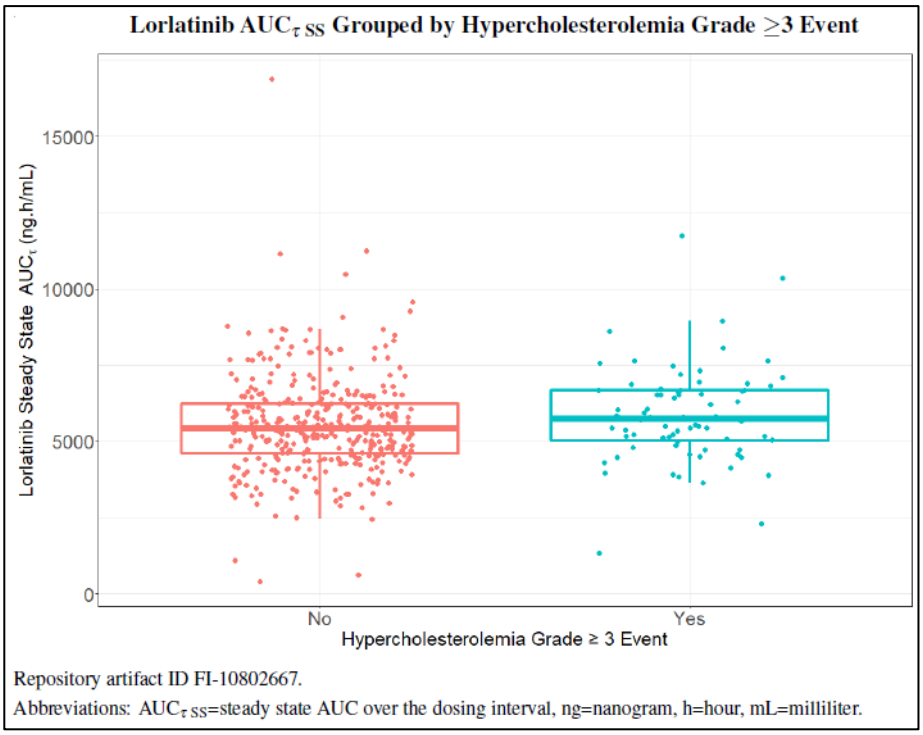
Table 29. Summary of safety endpoints by grade for ordinal logistic regression analysis

AE Category	N	Missing	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CNS Mood	480	0	385 (80)	71 (15)	18 (4)	5 (1)	1 (0)	0 (0)
CNS Speech	480	0	435 (91)	41 (9)	2 (0)	2 (0)	0 (0)	0 (0)
CNS Cognition	480	0	365 (76)	80 (17)	26 (5)	9 (2)	0 (0)	0 (0)
Elevated AST	480	3	359 (75)	107 (22)	4 (1)	5 (1)	2 (0)	0 (0)
Elevated ALT	480	3	366 (77)	95 (20)	8 (2)	7 (1)	1 (0)	0 (0)
Hypercholesterolemia	480	6	101 (21)	82 (17)	216 (46)	67 (14)	8 (2)	0 (0)
Hypertriglyceridemia	480	8	184 (39)	110 (23)	99 (21)	60 (13)	19 (4)	0 (0)
Weight Gain	480	15	338 (73)	41 (9)	51 (11)	35 (8)	0 (0)	0 (0)
Elevated Serum Lipase	480	5	390 (82)	40 (8)	13 (3)	25 (5)	7 (1)	0 (0)
Elevated Serum Amylase	480	16	391 (84)	49 (11)	14 (3)	8 (2)	2 (0)	0 (0)
AV Block	480	0	475 (99)	4 (1)	0 (0)	1 (0)	0 (0)	0 (0)
Seizures	480	0	471 (98)	4 (1)	4 (1)	1 (0)	0 (0)	0 (0)
Peripheral Neuropathy	480	0	278 (58)	156 (32)	34 (7)	12 (2)	0 (0)	0 (0)
Peripheral Edema	480	0	222 (46)	187 (39)	58 (12)	13 (3)	0 (0)	0 (0)
TEAE	480	0	1 (0)	22 (5)	130 (27)	228 (48)	53 (11)	46 (10)
Psychosis	149	0	144 (97)	4 (3)	1 (1)	0 (0)	0 (0)	0 (0)

Repository artifact ID FI-9511737. Line 1 substituted.
Grades were based on NCI CTCAE v.4.03 definitions. Grade 0-5 are summarized as n (%), where n represents the number of patients experiencing a safety event at the specified Grade and (%) is calculated as n/(N-Missing). Some percentages do not add up to 100% due to rounding.
Abbreviations: AE=adverse event, N=number of patients included in data file, Missing=number of patients in data file with missing data for the safety endpoint, CNS=central nervous system, AST=aspartate aminotransferase, ALT=alanine aminotransferase, AV=atrioventricular, TEAE=treatment-emergent adverse event.

Hypercholesterolemia

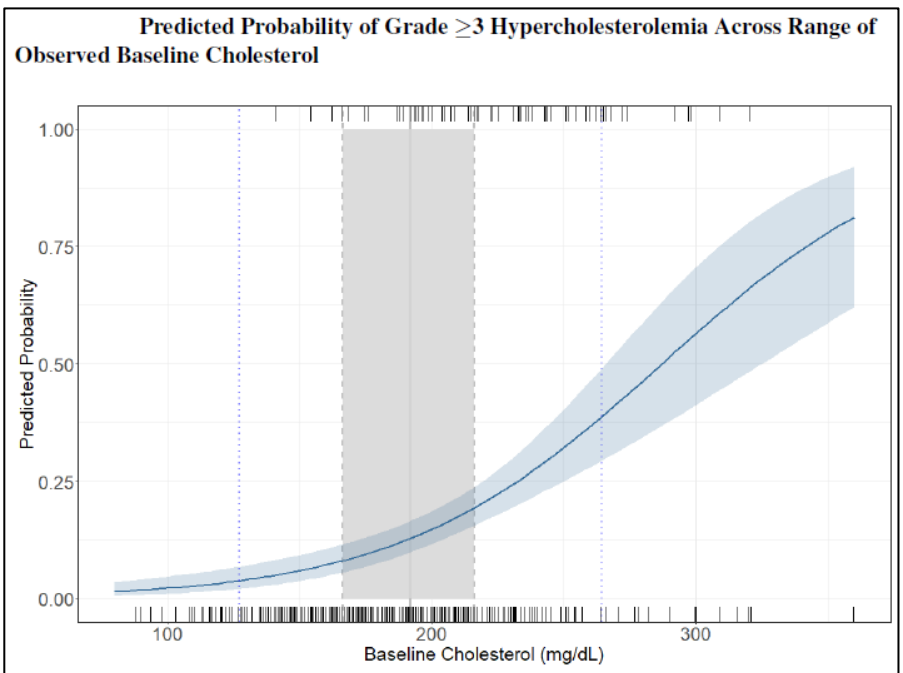
No E-R relationship was identified for Hypercholesterolemia Grade ≥3 with lorlatinib plasma exposure metrics. None of the PK exposure metrics met significance indeed.



Repository artifact ID FI-10802667.

Abbreviations: $AUC_{\tau SS}$=steady state AUC over the dosing interval, ng=nanogram, h=hour, mL=milliliter.

The binomial logistic regression results indicated that patients with higher baseline cholesterol were more likely to experience Grade ≥3 Hypercholesterolemia.



Repository artifact ID FI-9750241.

Blue line and shaded region represent median and 95% CI predicted probability of the event. Vertical grey shaded rectangular region represent the observed 25th and 75th percentiles of baseline cholesterol. Blue dotted vertical lines represent the observed 5th and 95th percentiles of baseline cholesterol. Rug lines on the top and bottom of the plot indicate the baseline cholesterol levels for patients who did (top) and did not (bottom) experience this safety event.

Abbreviations: mg=milligram, dL=deciliter.

The ordinal logistic regression results found the same directional relationship with baseline cholesterol, and also found female patients or patients who have had prior radiation treatment were more likely to experience higher grades of hypercholesterolemia.

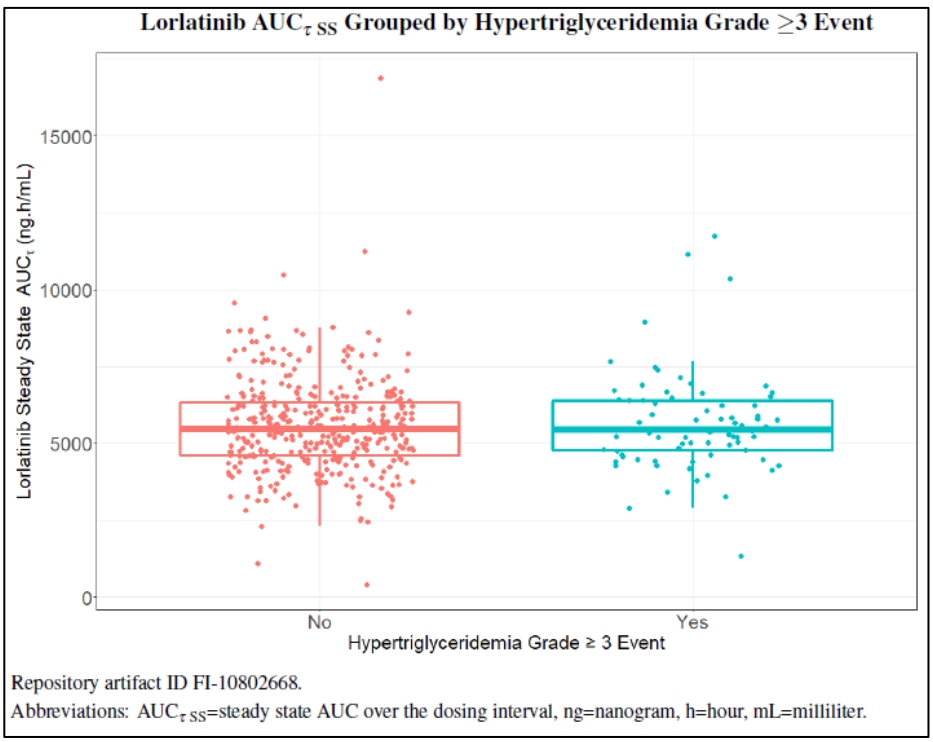
Final Model Hypercholesterolemia Exposure-Response Analysis

Endpoint	Variable	Estimate	95% CI	z Value	Pr> |z|
HCHOL	Intercept-Grade 0 to 1	1.7972		4.2392	<0.0001
	Intercept-Grade 1 to 2	2.7222		6.3178	<0.0001
	Intercept-Grade 2 to ≥ 3	5.1133		10.6107	<0.0001
	Cholesterol (mg/dL)	0.0148	(0.0105; 0.0193)	6.5897	<0.0001
	Prior Radiation Treatment	0.5055	(0.1203; 0.8942)	2.5625	0.0104
	Sex (Female)	0.5045	(0.1622; 0.8489)	2.8814	0.0040
	Odds Ratio				
	Cholesterol (mg/dL)	1.015	(1.011; 1.019)		
	Prior Radiation Treatment	1.658	(1.128; 2.445)		
	Sex (Female)	1.656	(1.176; 2.337)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-573.09	1158.17	6(0)	<0.001	3000000.0

Repository artifact ID FI-9856263.
Abbreviations: HCHOL=hypercholesterolemia, mg=milligram, dL=deciliter, CI=confidence interval, z value=level of marginal significance within a statistical hypothesis test, Pr>|z|=tail area in a 2-tail test, AIC=akaike information criterion, LogLik=log-likelihood, Iter(Convergence)=number of model iterations and whether or not convergence was achieved (0), Cond.number=condition number of the Hessian matrix.

Hypertriglyceridemia

No E-R relationship was identified for Hypertriglyceridemia Grade ≥3 with lorlatinib plasma exposure metrics:



Repository artifact ID FI-10802668.
Abbreviations: $AUC_{\tau SS}$=steady state AUC over the dosing interval, ng=nanogram, h=hour, mL=milliliter.

The binomial logistic regression results indicate patients with higher log-transformed baseline triglycerides, higher baseline albumin, or were of Asian race were more likely to experience Grade ≥3 hypertriglyceridemia.

Final Model Hypertriglyceridemia Exposure-Response Analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
HTG ≥3	Intercept	-18.1	(-22.6; -14)	-8.18	<0.0001
	Race: Asian	1.03	(0.442; 1.64)	3.39	0.0007
	Baseline Albumin (g/dL)	0.812	(0.215; 1.45)	2.58	0.0098
	Log Baseline Triglycerides (mg/dL)	2.61	(1.91; 3.39)	6.92	<0.0001
	Odds ratio				
	Race: Asian	2.803	(1.557; 5.144)		
	Baseline Albumin (g/dL)	2.253	(1.24; 4.263)		
	Log Baseline Triglycerides (mg/dL)	13.64	(6.724; 29.69)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-92.26	297.5	3	<0.0001	-144.7

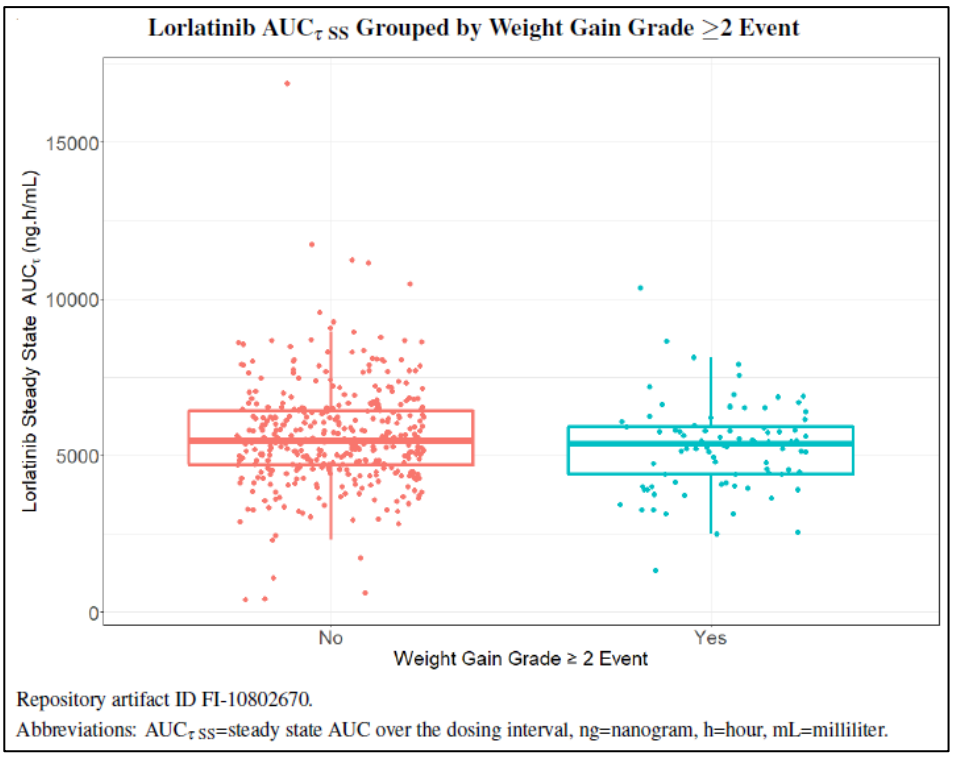
Repository artifact ID FI-9752809. Line 1 substituted.

Abbreviations: HTG=hypertriglyceridemia, g=gram, mg=milligram, dL=deciliter, CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

The ordinal logistic regression results found the same directional relationships, indicating patients with the aforementioned factors were more likely to experience higher grades of hypertriglyceridemia.

Weight Gain

No clinically meaningful E-R relationship was identified for weight gain Grade ≥2 with lorlatinib plasma exposure metrics:



Repository artifact ID FI-10802670.

Abbreviations: $AUC_{\tau\ SS}$=steady state AUC over the dosing interval, ng=nanogram, h=hour, mL=milliliter.

The binomial logistic regression results indicate patients who were younger, were from Study 1006, or had taken concomitant narcotics were more likely to experience Grade ≥2 weight gain. The ordinal logistic regression results found the same directional relationships for age and Study, indicating younger patients or patients from Study 1006 were more likely to experience higher grades of weight gain.

Final Model Weight Gain Exposure-Response Analysis

Endpoint	Variables	Estimate	95% CI	z-value	Probability >|z|
Weight Gain ≥2	Intercept	-0.074	(-1.19; 1.04)	-0.129	0.8970
	Age (years)	-0.045	(-0.0661; -0.0244)	-4.23	<0.0001
	Concomitant Narcotics	0.715	(0.199; 1.24)	2.7	0.0070
	Study B7461006	1.65	(1.11; 2.21)	5.91	<0.0001
	Odds ratio				
	Age (years)	0.9562	(0.9361; 0.9759)		
	Concomitant Narcotics	2.043	(1.221; 3.459)		
	Study B7461006	5.213	(3.041; 9.121)		
	ΔD	**AIC**	**df**	**1-p-Value**	**Log-Lik**
	-50.32	403	3	<0.0001	-197.5

Repository artifact ID FI-9753203. Line 1 substituted.
Abbreviations: CI=confidence interval, z-value=level of marginal significance within a statistical hypothesis test, Probability>|z|=tail area in a 2-tail test, ΔD=change in deviance, AIC=akaike information criterion, df=degrees of freedom, 1-p-value=one-tailed p-value, Log-Lik=log-likelihood.

The retained Study covariate in both binomial and ordinal logistic regression weight gain analyses are consistent with the observed data, as a higher percentage of patients in Study 1006 experienced weight gain Grade ≥2 than patients in Study 1001.

An E-R relationship was identified for Grade ≥3 TEAE:

The binomial logistic regression results indicated patients with higher $C_{ave\ SD}$, were older, took concomitant narcotics, took concomitant steroids, or were from Study 1006 were more likely to experience Grade ≥3 TEAE.

The ordinal logistic regression results found the same directional relationships, indicated patients with the aforementioned factors were more likely to experience higher grades of TEAE.

Final Model Weight Gain Exposure-Response Analysis

Endpoint	Coefficients	Estimate	95% CI	z Value	Pr> |z|
Weight Gain	Intercept-Grade 0 to 1	-0.5173		-1.1226	0.2616
	Intercept-Grade 1 to 2	0.0209		0.0453	0.9639
	Intercept-Grade 2 to 3	1.1164		2.3686	0.0179
	Age (years)	-0.0350	(-0.0522; -0.0181)	-4.0287	0.0001
	Study B7461006	1.1971	(0.7557; 1.6421)	5.3019	<0.0001
	Odds Ratio				
	Age (years)	0.966	(0.949; 0.982)		
	Study B7461006	3.310	(2.129; 5.166)		
	Loglik	AIC	Iter(Convergence)	Gradient	Cond.number
	-392.31	794.62	6(1)	<0.001	170000.0

Repository artifact ID FI-10034846.
Abbreviations: CI=confidence interval, z value=level of marginal significance within a statistical hypothesis test, Pr>|z|=tail area in a 2-tail test, AIC=akaike information criterion, LogLik=log-likelihood, Iter(Convergence)=number of model iterations and whether or not convergence was achieved (0), Cond.number=condition number of the Hessian matrix.

The positive relationship between lorlatinib plasma $C_{ave\ SD}$ and Grade ≥3 TEAE observed in the current analysis is consistent with the previously submitted lorlatinib E-R safety analysis, where a positive relationship was identified with lorlatinib plasma exposure. This is consistent with the current lorlatinib label, which has instructions for handling drug-related Grade ≥3 TEAE.

Finally, as seen with the weight gain safety endpoint, the retained study covariate in both binomial and ordinal logistic regression TEAE analyses were consistent with the observed data, as a higher percentage of patients in Study 1006 experienced Grade ≥3 TEAE than patients in Study 1001.

2.3.5. Discussion on clinical pharmacology

Within this application, the MAH has submitted 5 clinical pharmacology studies (Study B7461001, B7461010, B7461017, B7461026 and B7461006). However, only the new study, study B7461006, is the most relevant study due to the population included that corresponds to the proposed new indication: "Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor." According to this, the focus in the pharmacological part of the assessment report was on study B7461006.

Plasma concentrations of lorlatinib and its major metabolite PF-06895751 were determined by a validated LC-MS/MS method in study B7461006. The overall accuracy and precision of the method performance was acceptable. The in-study validation of bioanalysis conducted in Study B7461006 is endorsed. A previous 2-compartment model with time-varying clearance and a sequential zero-first order absorption which included lorlatinib data from several studies with dense sampling was pooled with the sparse data from study B7461006 in patients that received lorlatinib (Arm A). The goodness-of fit plots, visual predictive checks (VPC) and parameter estimates were acceptable and did not indicate any major misspecifications. None of the confidence intervals (bootstrap n=1000) for the structural parameter estimates or covariate effects contained the null. The inter-individual variability (IIV) was less well described, especially for volumes and ka.

The final popPK model included data from the previously untreated ALK-positive advanced NSCLC patients (Study 1006), in addition to data presented in the final popPK model of the initial MAA submission from previously treated ALK-positive advanced NSCLC patients (Study 1001), and healthy participants (Studies 1004, 1005, 1007, 1008, 1011 and 1016). No additional covariate screening was done as the distribution of patient demographics as well as the observed concentrations were similar between the populations considered. However, the covariate parameters were re-estimated with the expanded dataset. The typical values differed by less than 10%, so the estimates were deemed sufficiently similar. Lorlatinib exposure estimates were used in the subsequent E-R and E-S analyses.

In a post hoc analysis, performed by the MAH, the Applicant has determined the lorlatinib plasma elimination half-life at steady state, using the PK data. It was estimated to be 6.17 hours. In current SmPC section 5.2, the reported elimination half-life of 23.6 hours represents the half-life after a single dose 100 mg. As lorlatinib is both a substrate and a net inducer of CYP3A4, and is supposed to be administered at 100 mg daily, it is found relevant to report the estimated elimination half-life at steady state, in the updated SmPC. The MAH has additionally reported the more appropriate estimate of the lorlatinib plasma elimination half-life at steady state (post auto-induction) of 14.83 hours within the SmPC section 5.2, which is considered acceptable.

The PK parameters estimates in the current popPK differ less than 10% of those estimated in the original popPK model and this can suggest that the inclusion of the previously untreated ALK-positive advanced NSCLC patients in Study 1006 does not have a significant impact on PK parameters estimation. However, as already noted in the original popPK model, the shrinkage for some of the estimated lorlatinib PK parameters is higher than recommended and parameters were estimated with high variability. The MAH claimed that the sparse PK data collection in study 1006 contributed to the high shrinkage, but in this case, the shrinkage in CL is higher than in the previous model (35% vs 23%). The higher shrinkage in CL could have contributed to the overprediction of simulated

concentrations as showed by the VPC, in particular at 50th and 95th percentiles. However, for estimation of the steady-state exposure (used for ER analysis), only data through Day 15 (360 hours) were used and did not include the model predictions at the later time points when overprediction was noted in the VPCs. In the VPC presented, predictions before 360 hours seem more in line with observed data, in particularly for the 50th percentile.

There is an observed trend of increasing lorlatinib steady-state Cmax and AUCt with worsening baseline renal impairment, which is in accordance with the performed clinical study B7461010. Therefore, it seems relevant to acknowledge this trend, and to mention this within the SmPC: *"Population pharmacokinetic analyses have shown that lorlatinib steady state plasma exposure and Cmax values slightly increase with worsening baseline renal function."*

Moreover, it was shown that lorlatinib plasma exposures, (i.e. AUC and Cmax), are comparable at both steady-state, and after single dose administration, across different levels of hepatic function (i.e. normal, mild, moderate hepatic function). Only the AUCtau, on the level of moderate hepatic impairment seems to decrease significantly, compared to normal hepatic function. However, only one individual was included in the moderate hepatic impairment group, so the results should be interpreted with caution.

A PBPK model was developed in Simcyp for simulation of lorlatinib CYP3A4 DDI. Lorlatinib is both a substrate and a net inducer of CYP3A4. Even the PBPK model seems to capture this complex effect, it was never verified by clinical data since the clinical DDI study with itraconazole was performed with a single dose of lorlatinib. Therefore, the PBPK model simulations are not acceptable for SmPC recommendations and should be interpreted with caution.

An updated E-R analysis for efficacy with previously untreated patients from Study 1006 was conducted to evaluate the relationship between lorlatinib exposure and the efficacy endpoint PFS, as this was the primary efficacy endpoint analyzed in Study 1006. Exploratory analyses for ORR and IC-ORR were also conducted. All patients randomized to lorlatinib in study 1006 were included in the analyses for PFS and ORR (N=149), while only patients from the lorlatinib arm who had baseline CNS metastasis were included in the E-R analysis for IC-ORR (N=38).

Baseline body weight and baseline albumin were the only significant covariates associated with PFS in the E-R efficacy time to event (TTE) analysis; higher baseline albumin and higher baseline body weight were associated with higher probability of longer PFS. It is known that low albumin levels and low body weight are in general poor prognostic factors for outcome in patients with cancer. The highest lorlatinib exposure quartile (Q4) had lower baseline body weight and baseline albumin compared to quartiles 1-3 (Q1, Q2, and Q3) (data not shown). Therefore, the apparent relationship observed in Figure 8 is likely confounded by the uneven distribution of established predictive variables across the exposure quartiles.

No E-R relationship was identified between lorlatinib plasma exposure and PFS, indeed both univariate and multivariate regression models did not point-out a significant association between Cmax ss and such efficacy endpoint. Following an exploratory analysis, no E-R relationship was found between lorlatinib exposure and ORR/IC-ORR and this is consistent with the original E-R analysis provided for ALK+ NSCLC patients who received lorlatinib after previous treatment with other ALK inhibitors. For characterization of ORR and IC-ORR binomial logistic regression models were used. For ORR, no covariates were significant. For IC-ORR, only male sex was identified as being significant but this result should be interpreted with caution due to limited and unbalanced data in patients with baseline CNS metastasis.

Finally, the MAH provided an updated E-R analysis for safety, pooling data derived from studies 1001, in which different lorlatinib doses were used, and 1006, where only the 100 mg dose was

administered. E-R relationships were analysed using both binomial and ordinal logistic regression for safety endpoints that occurred in at least 10% of patients, which included hypercholesterolemia Grade ≥3, hypertriglyceridemia Grade ≥3, weight gain Grade ≥2 (defined as the PT Weight increased) and TEAE Grade ≥3. Hypercholesterolemia, hypertriglyceridemia, and weight gain did not demonstrate clinically meaningful relationships with lorlatinib plasma exposures, while Grade ≥3 TEAE demonstrated a positive relationship with lorlatinib plasma exposure.

2.3.6. Conclusions on clinical pharmacology

In conclusion, the clinical pharmacology studies within this application overall support the use of the proposed dose in the treatment of adult patients with ALK-positive advanced non-small cell lung cancer previously not treated with an ALK inhibitor.

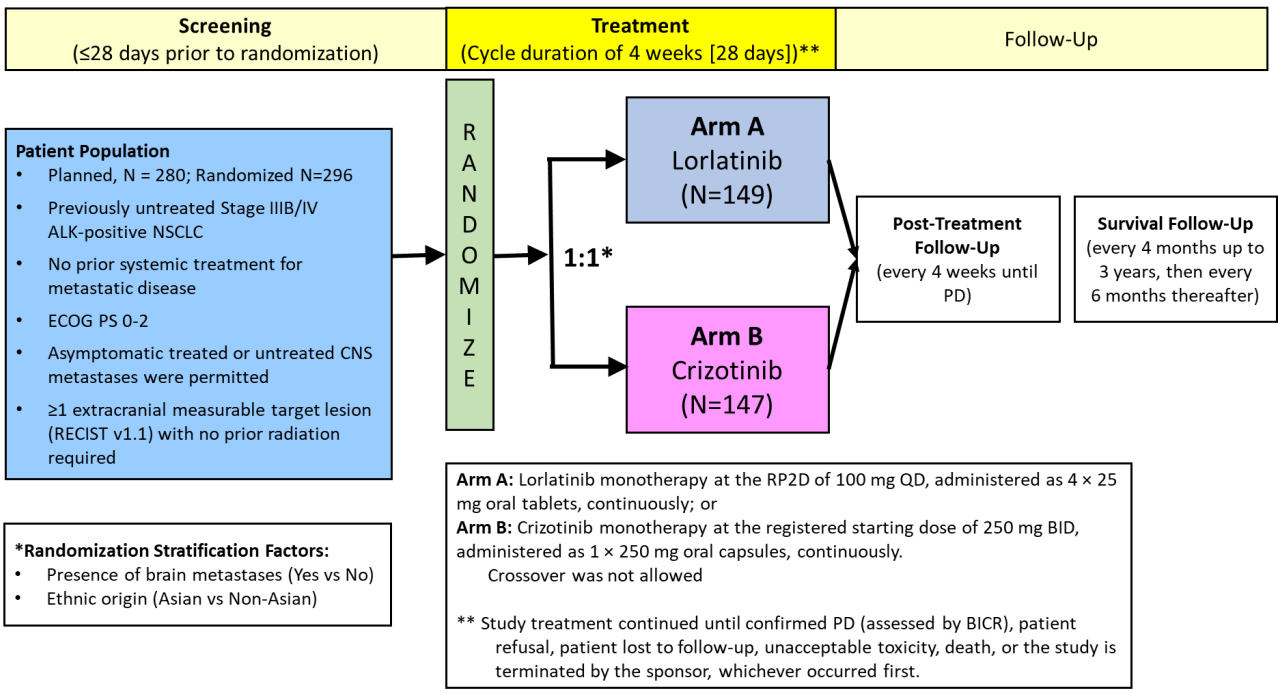
2.4. Clinical efficacy

2.4.1. Main study

Study B7461006 (CROWN)

The pivotal study B7461006 (also referred to as Study 1006 or CROWN) is a Phase 3, multinational, multicentre, open-label study. In total, 296 participants were randomised in a 1:1 ratio and no cross-over was allowed. Enrolment was closed on 28 February 2019.

Figure 9. Study B7461006 Design



Methods

Study participants

Previously untreated Stage IIIB/IV participants with ALK-positive NSCLC were randomized in this study. Key inclusion and exclusion criteria are listed below.

Key Inclusion Criteria

- Diagnosis:

  a. Study Population: Participants with histologically or cytologically confirmed diagnosis of locally advanced [(Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) by AJCC v 7.0] ALK-positive NSCLC where ALK status was determined by the FDA-approved (for use in US), CE marked (for EU and other countries that accept CE marking), and PMDA-approved (for use in Japan) Ventana ALK (D5F3) CDx IHC test performed on the Ventana ULTRA or XT platforms;

  b. Tumour Requirements: At least 1 extracranial measurable target lesion per RECIST v1.1 that had not been previously irradiated. CNS metastases were allowed if asymptomatic and:

  1. Either untreated and not currently requiring corticosteroid treatment, or on a stable or decreasing dose of ≤10 mg QD prednisone or equivalent; or

  2. Local treatment had been completed with full recovery from the acute effects of radiation therapy or surgery prior to randomization, and if corticosteroid treatment for these metastases had been withdrawn for at least 4 weeks with neurological stability; or

  3. In case of Leptomeningeal disease or CM if visualized on MRI, or if baseline CSF-positive cytology was available.

- No prior systemic NSCLC treatment for advanced (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) disease, including molecularly targeted agents (e.g., ALK TKIs), angiogenesis inhibitors, immunotherapy, or chemotherapy. Prior treatment for earlier Stages of the NSCLC was only allowed if completed more than 12 months prior to randomization.
- ECOG PS 0, 1, or 2.
- Age ≥18 years (or ≥20 years as required by local regulation).
- Acute effects of prior radiotherapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator's judgment did not constitute a safety risk for the participant.

Key Exclusion Criteria

- Spinal cord compression unless the participant had good pain control attained through therapy, and there was stabilization or recovery of neurological function for the 4 weeks prior to randomization.
- Major surgery within 4 weeks prior to randomization.
- Radiation therapy within 2 weeks prior to randomization, including stereotactic or partial brain irradiation. Participants who completed whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization were also not be included in the study.
- Clinically significant vascular (both arterial and venous) and non-vascular cardiac conditions, (active or within 3 months prior to enrolment).

- Participants with predisposing characteristics for acute pancreatitis according to investigator judgment (e.g., uncontrolled hyperglycaemia, current gallstone disease) in the last month prior to randomization.
- History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.
- Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behaviour.

Treatments

- Arm A: Lorlatinib 100 mg QD, administered as 4 x 25 mg oral tablets, continuously; or
- Arm B: Crizotinib at the registered starting dose of 250 mg BID, administered as 1 x 250 mg oral capsules, continuously.

Each cycle duration was 28 days, and study treatment was to be continued until confirmed progressive disease (PD) assessed by blinded Independent Central Review (BICR), participant refusal, unacceptable toxicity, participant lost to follow-up, study termination by the sponsor or death, whichever came first.

Objectives

Primary Objective

To demonstrate that lorlatinib as a single agent is superior to crizotinib alone in prolonging PFS in advanced ALK-positive NSCLC participants who are treatment naïve.

Secondary Objectives

- To compare lorlatinib and crizotinib in treatment naïve advanced ALK-positive NSCLC participants with respect to OS;
- To evaluate the antitumor activity in each treatment arm;
- To evaluate PROs of health-related quality of life, disease/treatment related symptoms of lung cancer, and general health status for each treatment arm;
- To evaluate candidate biomarkers of sensitivity or resistance to single agent crizotinib or lorlatinib in peripheral blood.

Outcomes/endpoints

Table 30. Summary of Endpoints and Statistical Methodology for the Interim Analysis (Protocol B7461006)

Endpoint	Definition	Statistical Method
Primary Endpoint		
PFS (BICR)	Time from date of randomization, to the date of the first documentation of PD per RECIST v1.1 based on BICR assessment; or death due to any cause, whichever occurs first.	HR (1-sided stratified log rank test)
Secondary Endpoints [d]		

Endpoint	Definition	Statistical Method
OS	Time from randomization to the date of death due to any cause. OS was hierarchically tested provided PFS (BICR) endpoint was statistically significant favoring lorlatinib.	HR (1-sided stratified log rank test)
PFS (Investigator)	Time from date of randomization, to the date of the first documentation of PD per RECIST v1.1 based on derived investigator assessment; or death due to any cause, whichever occurred first.	HR (1-sided stratified log rank test)
ORR	Percentage of participants with a confirmed BOR of CR or PR assessed by both BICR and investigator according to RECIST v1.1. Participants without documented CR or PR were considered as non-responders.	Odds ratio (1 sided stratified CMH test)
IC-ORR [a]	Aligned with definition of ORR (see above) using a modified version of RECIST v1.1 in participants with IC disease at baseline based on BICR IC assessment.	Odds ratio (1 sided stratified CMH test)
IC-TTP [b]	Time from date of randomization, to the date of the first documentation of PD per modified RECIST v1.1 based on BICR IC assessment.	HR (1-sided stratified log rank test)
DOR	For participants with a confirmed OR by BICR assessment per RECIST version 1.1, defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or death due to any cause, whichever occurs first.	Descriptive statistics only
IC-DOR [a]	Based on BICR IC assessment and as defined above for DOR, only in participants with a confirmed IC-OR	
TTR	Based on BICR assessment is defined, for participants with a confirmed OR, as the time from the date of randomization to the first documentation of OR (CR or PR) which is subsequently confirmed.	
IC-TTR [a]	Based on BICR IC assessment is defined as above for TTR, only in participants with a confirmed IC-OR.	
PRO	PROs were assessed using the EORTC QLQ-C30 and its corresponding module for lung cancer (QLQ-LC13) and the EQ-5D-5L questionnaire Lung symptoms Time to Deterioration (TTD) [c]	Longitudinal random intercept random slope mixed-effect model HR (1-sided stratified log rank test)
Biomarkers	Peripheral blood cfDNA biomarkers including, but not limited to, ALK gene rearrangement and/or ALK kinase domain mutations.	Descriptive statistics of ALK variants by treatment-arm. Analyses by ALK variants for PFS, ORR, and DOR

Source: Study 1006 SAP

[a] Analyzed for all participants with baseline brain metastases and the subset thereof with *measurable* baseline brain metastases.

[b] Analyzed separately for participants with and without baseline brain metastases.

[c] Pain in chest, dyspnea, or cough individually from the EORTC QLQ-LC13 and as a composite endpoint, defined as the time from randomization to the first time a participant's score increased 10 points or after baseline in any of the 3 symptoms.

[d] The secondary OS endpoint was analyzed using a hierarchical testing procedure. No other secondary endpoints were controlled by multiplicity.

Sample size

Approximately 280 participants (140 in each arm) were to be randomized using a 1:1 ratio stratified by presence of brain metastases and ethnic origin. A total of 177 PFS events were required to have at least 90% power to detect a HR of 0.611 using a one-sided stratified log-rank test at a significance level of

0.025 (one-sided), and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) alpha-spending function to determine the efficacy boundaries.

The planned sample size was determined based on the assumption of a HR of 0.611 under the alternative hypothesis (under an exponential model, assuming median PFS of 11 months in the crizotinib arm and 18 months in the lorlatinib arm). The sample size further assumed a 15% drop-out rate within each treatment arm at 30 months, a non-uniform participant accrual over approximately 15 months, and follow-up after the last participant was randomized of approximately 18 months.

The sample size also allowed comparison of OS between the 2 treatment arms, provided that superiority of lorlatinib over crizotinib with respect to PFS had been demonstrated. If the true HR was 0.70 under the alternative hypothesis (under an exponential model, assuming median OS of 48 months on the crizotinib arm and 68.6 months on the lorlatinib arm), a total of 198 deaths were required to have 70% power using a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and a 3-look group-sequential design with Lan-DeMets (O'Brien-Fleming) alpha-spending function to determine the efficacy boundaries. These calculations further assumed a 15% drop-out rate for OS on either treatment arm at 120 months, and a follow-up of approximately 110 months after the last participant was randomized.

Randomisation

Patients were to be randomized in a 1:1 fashion to receive lorlatinib or crizotinib. Randomization was to be stratified by presence of brain metastases (Yes vs. No) and ethnic origin (Asian vs. non-Asian). Presence of brain metastases at baseline is considered an important prognostic factor. Ethnic origin is not expected to be predictive or prognostic and this is best conformed by using this as a stratification factor. The stratified randomization was centrally allocated across all centres via the interactive response technology (IRT) system.

Blinding (masking)

This study was open-label and ongoing at the time of data cut-off. The BICR and the sponsor's study team were blinded to the randomized treatment.

Participants who developed radiological disease progression confirmed by BICR assessment but were otherwise continuing to derive clinical benefit from study treatment were eligible to continue with the treatment they were assigned to, provided that the treating physician determined that the benefit/risk for doing so was favourable.

Crossover between treatment arms was not permitted.

Statistical methods

Full Analysis Set

The full analysis (FA) set will include all patients who are randomized. Patients will be classified according to the treatment assigned at randomization. Randomized but not treated patients will be reported under their randomized treatment group for the full analysis set. The FA set will be the primary population for evaluating all efficacy endpoints and patient.

Primary Endpoint: Progression-free Survival as Assessed by BICR per RECIST v1.1

The primary efficacy analysis will compare PFS based on BICR assessment between the experimental arm and the control arm, and will be performed using a one-sided stratified log-rank test. The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by presence of brain metastases and ethnic origin at randomization to calculate the hazard ratio. Kaplan-Meier estimates will be presented by treatment arm together with a summary of associated statistics including the median PFS time with two-sided 95% confidence intervals (CI). The PFS rate at 12 months will be estimated with corresponding two-sided 95%CIs.

Table 31. Outcome and event dates for PFS analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of randomization	Censored [a]
Progression or death ≤126 days after last adequate tumor assessment or ≤126 days after date of randomization	Date of progression or death	Event
Progression or death >126 days after the last adequate tumor assessment [b]	Date of last adequate assessment [b] documenting no PD prior to anti-cancer therapy or missed assessments	Censored
No progression		
New anti-cancer therapy given prior to PD		

[a] if the patient dies ≤126 days after date of randomization the death is an event on the death date.

[b] if there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of randomization; if the criteria were met the censoring will be on the randomization date.

Sensitivity Analyses for PFS as Assessed by BICR

These analyses are regarded as purely exploratory. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) on the FA with the modifications below:

- PFS based on BICR assessment and counting all PDs and deaths as events regardless of missing assessments or timing of the event (ie, not censoring due to start of new anti-cancer therapy prior to event or due to missed assessments).
- PFS based on BICR assessment using an unstratified analysis.
- PFS based on BICR assessment analysed with stratified analysis using the two randomization stratification factors and baseline ECOG PS value from the CRF.
- Multivariable Cox proportional hazard models will also be used to explore the potential influences of baseline patient characteristics (such as age, gender, ethnic origin, presence of brain metastasis at baseline based on BICR intracranial assessment, smoking status, ECOG performance status, extent of disease, histology, etc.) on PFS.

Secondary endpoint: OS

The primary analysis of OS will compare the OS time between the experimental arm and the control arm, and will be performed using a one-sided stratified log-rank test. The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the hazard ratio.

OS time associated with each treatment arm will be summarized using the Kaplan- Meier method. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CIs.

Censoring reasons are as follows:

- Alive;
- Withdrawal of consent;
- Lost to follow-up (Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up >365 days prior to data cut off date).

Sensitivity Analyses for OS

These analyses are regarded as purely exploratory. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) on the FA with the modifications below:

- OS using an unstratified analysis.
- OS with stratified analysis using the two randomization stratification factors and baseline ECOG PS value from the CRF.
- Multivariable Cox proportional hazard models will also be used to explore the potential influences of baseline patient on OS. The same methodology described for PFS will be used for OS.

Secondary endpoint: Objective Response

Objective Response Rate (ORR) is defined as the percentage of patients with a best overall confirmed response of CR or PR according to RECIST v1.1. Patients without documented CR or PR will be considered as non-responders. The evaluation of ORR will be provided both based on BICR and Investigator and will be relative to the FA population.

The ORR on each treatment arm will be estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided. OR comparison between the 2 treatment arms will be assessed using Cochran-Mantel-Haenszel (CMH) test using the stratification factors and risk ratio and the corresponding 2-sided 95% CI will be provided as well.

Interim analyses and multiplicity considerations

The original study design has been revised to have a PFS interim analysis for efficacy and a PFS final analysis. The interim analysis will be performed after approximately 133 (75%) PFS events have been documented by BICR assessment. The final analysis for PFS will occur when 177 PFS events have been documented by BICR, if the efficacy boundary has not been crossed at the interim analysis. Follow-up for OS will continue and a final OS analysis is planned to be performed when 198 deaths have occurred.

The nominal significance levels for the interim and final efficacy analyses of PFS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The overall significance level will be preserved at 0.025 (one-sided).

As the observed number of events at the interim analysis may not be exactly equal to the planned number of events, the efficacy boundaries will be updated based on the actual number of observed events using the pre-specified α-spending functions.

The secondary OS endpoint will be analysed using a hierarchical testing procedure, provided the primary PFS endpoint is statistically significant favouring the experimental arm. An α-spending function according to Lan-DeMets (O'Brien-Fleming) will be used to preserve the 0.025 overall level of significance and the repeated testing of the OS hypotheses at the interim and final analyses. The trial allows for the stopping of the study for a superior OS result, provided the primary PFS endpoint has already been shown to be statistically significant.

A maximum of three analyses are planned for OS:

1. A first interim analysis at the time of the interim/final PFS analysis (at the one that exceeded the efficacy boundary);

2. A second interim analysis when 139 deaths (70% of the total events planned for final OS analysis) are observed;

3. A final analysis when 198 deaths are observed.

The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

Changes to the SAP and the planned analyses

This Statistical Analysis Plan (SAP) for study B7461006 is based on the protocol amendment 4 dated 04OCT2019.

Table 32. Summary of major changes in SAP amendments

SAP Version	Date	Change	Rationale
1	21-Dec-2016	Original SAP	Not Applicable
2	26-May-2020	The group-sequential design of the study based on the primary PFS endpoint as assessed by BICR has been modified by replacing the planned futility analysis, that was to be conducted at 60% information fraction (IF), with an interim efficacy analysis to be conducted at approximately 75% IF.	The rationale for this change is based on the observation that PFS events in study B7461006 are accumulating at a much slower rate than originally projected
		Added IC-DR and IC-TTR; Removed CBR.	The list of the secondary endpoints has been revised to focus on the relevant ones for the compound.
		Added clarifications on a few algorithms Removed secondary analyses deemed unnecessary Added sensitivity analyses to be conducted to mitigate COVID impact	

Sensitivity analyses of OS and analysis of PFS2 that were prespecified have not been performed at the current stage due to immaturity in these endpoints.

Results

Participant flow

Figure 10. Participant flow

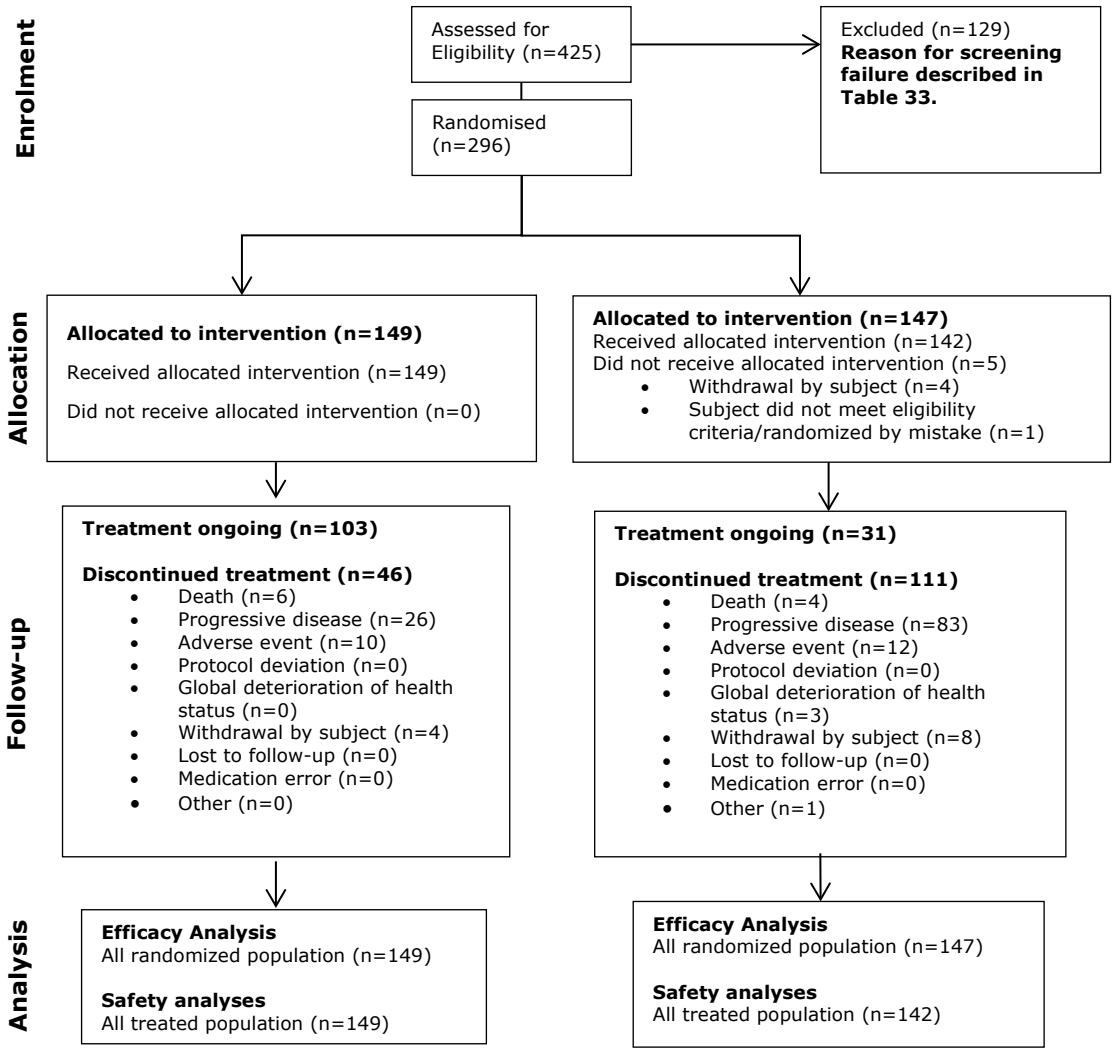


Table 33. Reasons for Screening Failure from Screening and Enrollment Forms.

Screening Failure Reason	participants N	participants %
Eligibility not met: Inclusion Criterion #1 (N=55) no confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC (N=48) Other IC#1 (N=7) Other inclusion/exclusion criteria (N=25)	80	62
Consent withdrawn	17	13
Clinical worsening / Disease progression	7	5
Exceeded screening/re-screening period	7	5
Urgent/other treatment	6	5

Death	5	4
Unknown	5	4
Investigator decision	1	1
Occurrence of SAE (unrelated to study drug)	1	1
TOTAL	129	100

Recruitment

A total of 296 participants were randomized in this study between 11 May 2017 and 28 February 2019 and they were recruited at 104 sites in 23 countries. The countries with the highest enrolment (≥10% of participants) were Japan (16.2%) and Italy (11.1%).

Conduct of the study

Changes in the Conduct of the Study

The original protocol dated 05 October 2016 was amended 4 times. As of the data cutoff date, COVID-19-related changes to study conduct are described in Table 34.

Table 34. COVID-19 impacted participants

Participant ID	Site	Country	COVID-19 Impact Description
11291004	1129	Italy	At Cycle 18, urine analysis not performed.
11551002	1155	Singapore	At Cycle 19, 3 cycles of study drugs were shipped to participant's home.
11971002	1197	Hong Kong	At Cycle 16, 2 cycles of study drug were dispensed. At Cycle 17, the visit was not done, and the investigator consulted the participant by phone.
12391002	1239	Italy	At Cycle 16, the following laboratory assessments were not performed: magnesium, phosphate, and GGT.
10301002	1030	Italy	At Cycle 18, the following assessments were not performed: physical examination, vital signs, ECOG-PS, laboratory evaluation (hematology, clinical chemistry, urinalysis, pregnancy test) and questionnaires. At Cycle 18, 2 cycles of study drug were dispensed.
10331002	1033	Poland	At Cycle 26, the following assessments were not performed: physical examination, vital signs, and questionnaires. The laboratory evaluation was not done. The investigator consulted the participant by phone. The study drug was dispensed to participant's relative who delivered it to the participant. The tumor assessments due at Cycle 27 was not performed.
11211001	1121	Italy	At Cycle 23, the tumor assessments and echocardiogram were not performed.
11441004	1144	Italy	At Cycle 24, the following assessments were not performed: vital signs and ECOG. The laboratory assessments were performed at an external laboratory, except for urinalysis that was not done. The investigator consulted the participant by phone. The study drug was dispensed to participant's relative who delivered it to the participant.
11441006	1144	Italy	At Cycle 15, the following assessments were not performed: tumor assessments, ECOG, vital signs, cardiac function evaluation, and questionnaires. The laboratory assessments were performed at an external laboratory, except for the following tests not done (ALT, AST, chloride, glucose, urine protein). The investigator consulted the participant by phone. The study drug was delivered via courier.
11971001	1197	Hong Kong	At Cycle 19, the cardiac evaluation was not performed. Two cycles of study drug were dispensed.
11971003	1197	Hong Kong	At Cycle 15, the cardiac evaluation was not performed. At Cycle 16, the visit was not performed at the site, and the investigator consulted the participant by phone. At Cycle 15, 2 cycles of study drug were dispensed.
12351001	1235	China	At Cycle 22, the visit was not performed at site. The following assessments were not performed: vital signs and physical exam. The questionnaires were not completed on site. The laboratory assessment was performed at another laboratory, but lipase evaluation was not done. The investigator consulted the participant by phone. The study drug was delivered via courier.
12351002	1235	China	At Cycle 21, the visit was not performed at the site. The following assessments were not performed: cardiac evaluation, vital signs, and physical exam. The laboratory assessments were performed at another facility but lipase, LDH and urine protein was not done. The questionnaires were not completed on site. Tumor assessment was delayed but completed. The study drug was delivered via courier. At Cycle 22, the visit was not performed at the site. The laboratory assessments were performed at another facility, and the following assessments were not performed: lipase, LDH, urine protein, and electrolytes.

Changes to Planned Analyses

Table 35. Important protocol deviations – Full analysis set (Protocol B7461006)

	Lorlatinib (N=149) n (%)	Crizotinib (N=147) n (%)	Total (N=296) n (%)
Patients with any important deviations	64 (43.0)	61 (41.5)	125 (42.2)
INFORMED CONSENT	29 (19.5)	22 (15.0)	51 (17.2)
ICD NOT SIGNED AT THE FIRST SUBJECT/LAR VISIT AFTER THE REVISED/APPROVED ICD WAS AVAILABLE AT SITE	15 (10.1)	12 (8.2)	27 (9.1)
ICD NOT SIGNED BY IMPARTIAL WITNESS, WHEN APPLICABLE	5 (3.4)	6 (4.1)	11 (3.7)
SUBJECT DID NOT SIGN THE OPTIONAL BIO SPECIMEN SAMPLE CONSENT	6 (4.0)	4 (2.7)	10 (3.4)
ICD SIGNED BY SUBJECT/LAR HAD NOT RECEIVED IRB/IEC APPROVAL	4 (2.7)	2 (1.4)	6 (2.0)
SUBJECT SIGNED A SUPERSEDED/OUTDATED VERSION OF THE ICD	2 (1.3)	2 (1.4)	4 (1.4)
SUBJECT DID NOT SIGN THE ICD AND DID NOT GIVE VERBAL CONSENT	2 (1.3)	0	2 (0.7)
PROCEDURES/TESTS	20 (13.4)	18 (12.2)	38 (12.8)
BASELINE TUMOR ASSESSMENT INADEQUATE/NOT PERFORMED/OUT OF PROTOCOL SPECIFIED WINDOW	16 (10.7)	13 (8.8)	29 (9.8)
ABNORMAL PROCEDURE / TEST RESULT NOT FOLLOWED UP PER PROTOCOL	3 (2.0)	5 (3.4)	8 (2.7)
PROCEDURE/TEST NOT PERFORMED PER PROTOCOL	1 (0.7)	0	1 (0.3)
INVESTIGATIONAL PRODUCT	12 (8.1)	18 (12.2)	30 (10.1)
OVERDOSING OF STUDY DRUG	6 (4.0)	2 (1.4)	8 (2.7)
DISPENSING ERROR	4 (2.7)	2 (1.4)	6 (2.0)
DOSE MODIFICATIONS (DOSE REDUCTION OR DOSE INTERRUPTION) NOT DONE IN RESPONSE TO TOXICITY AS SPECIFIED IN PROTOCOL.	1 (0.7)	5 (3.4)	6 (2.0)
DOSING/ADMINISTRATION ERROR	1 (0.7)	4 (2.7)	5 (1.7)
PATIENT NEVER STARTED TREATMENT	0	5 (3.4)	5 (1.7)
LAB	11 (7.4)	9 (6.1)	20 (6.8)
ABNORMAL LAB RESULT NOT FOLLOWED UP APPROPRIATELY	11 (7.4)	9 (6.1)	20 (6.8)
INCLUSION/EXCLUSION	7 (4.7)	7 (4.8)	14 (4.7)
SUBJECT DID NOT MEET INCLUSION CRITERIA 01 [ALK-POSITIVE NSCLC EQUAL OR UPPER ONE EXTRA CRANIAL MEASURABLE TL- ARCHIVAL TISSUE SAMPLE AVAILABLE OR COLLECTED PRIOR TO RANDOMIZATION.]	1 (0.7)	3 (2.0)	4 (1.4)
SUBJECT DID NOT MEET INCLUSION CRITERIA 10 [FEMALES OF CHILDBEARING POTENTIAL MUST HAVE A NEGATIVE SERUM PREGNANCY AT SCREENING. FEMALE OF NON-CHILDBEARING POTENTIAL MUST BE MEDICALLY CONFIRMED OR 12MO POSTMENOPAUSAL CONFIRMED WITH FSH TEST]	2 (1.3)	0	2 (0.7)
SUBJECT MET EXCLUSION CRITERIA 12 ORIGINAL PROTOCOL [CONCURRENT USE OF CYP3A SUBSTRATES WITHIN 12 DAYS PRIOR TO THE FIRST DOSE]	1 (0.7)	1 (0.7)	2 (0.7)
SUBJECT DID NOT MEET INCLUSION CRITERIA 02 [NO PRIOR SYSTEMIC NSCLC TREATMENT. ADJUVANT/NEOADJUVANT NSCLC TREATMENT MUST BE COMPLETED UPPER TO 12MO PRIOR TO RANDOMIZATION]	1 (0.7)	0	1 (0.3)
SUBJECT DID NOT MEET INCLUSION CRITERIA 05 [ADEQUATE BONE MARROW FUNCTIONS, INCLUDING A. ANC > = 1,500/MM*3 OR >= 1.5 X 109/L B. PLATELETS >= 100,000/MM*3 OR >= 100 X 109/L C. HEMOGLOBIN >= 9 G/DL]	0	1 (0.7)	1 (0.3)
SUBJECT DID NOT MEET INCLUSION CRITERIA 06 [ADEQUATE PANCREATIC FUNCTION, INCLUDING A. SERUM TOTAL AMYLASE <=1.5 X ULN (IF TOTAL AMYLASE >1.5 X ULN, BUT PANCREATIC AMYLASE IS WITHIN THE ULN, SBJ CAN BE ENROLLED) B. SERUM LIPASE <= 1.5 X ULN]	0	1 (0.7)	1 (0.3)
SUBJECT DID NOT MEET INCLUSION CRITERIA 07 [ADEQUATE RENAL FUNCTION, INCLUDING SERUM CREATININE <= 1.5 X ULN OR ESTIMATED CREATININE CLEARANCE UPPPER OR EQUAL 60 ML/MIN]	1 (0.7)	0	1 (0.3)
SUBJECT DID NOT MEET INCLUSION CRITERIA 12 [WILLING AND ABLE TO COMPLY WITH THE STUDY SCHEDULED VISITS, TREATMENT PLANS, LABORATORY TESTS AND OTHER PROCEDURES]	1 (0.7)	0	1 (0.3)
SUBJECT MET EXCLUSION CRITERIA 07[CEREBROVASCULAR ACCIDENT/STROKE, MYOCARDIAL INFARCT, UNSTABLE ANGINA, CONGESTIVE HEART FAILURE, 2-3 GRADE AV BLOCK <= 3 MONTHS. ONGOING DYSRHYTHMIAS, ATRIAL FIBRILLATION, BRADYCARDIA, QTC PROLONGED]	0	1 (0.7)	1 (0.3)
CCMEDS	4 (2.7)	6 (4.1)	10 (3.4)
TOOK PROHIBITED CONCOMITANT MEDICATION	3 (2.0)	6 (4.1)	9 (3.0)
TOOK PERMITTED CONCOMITANT MEDICATIONS/VACCINE BUT NOT AS SPECIFIED PER PROTOCOL	1 (0.7)	0	1 (0.3)
RANDOMIZATION	3 (2.0)	5 (3.4)	8 (2.7)
RANDOMIZED UNDER WRONG STRATIFICATION	3 (2.0)	5 (3.4)	8 (2.7)

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group. Decreasing order of frequency relative to Total.

Baseline data

Table 36. Demographic Characteristics - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)	Total (N=296)
Demographic			
Age (Years) [a], n (%)			
18 -< 45	26 (17.4)	35 (23.8)	61 (20.6)
45 -< 65	64 (43.0)	68 (46.3)	132 (44.6)
≥ 65	59 (39.6)	44 (29.9)	103 (34.8)
n1	149	147	296
Mean (SD)	59.1 (13.12)	55.6 (13.52)	57.4 (13.41)
Median (Q1, Q3)	61.00 (51.00, 69.00)	56.00 (45.00, 66.00)	59.00 (47.50, 68.00)
Range (Min, Max)	(30, 90)	(26, 84)	(26, 90)
Gender, n (%)			
Male	65 (43.6)	56 (38.1)	121 (40.9)
Female	84 (56.4)	91 (61.9)	175 (59.1)
Race, n (%)			
White	72 (48.3)	72 (49.0)	144 (48.6)
Black or African American	0	1 (0.7)	1 (0.3)
Asian	65 (43.6)	65 (44.2)	130 (43.9)
Other	0	0	0
Missing	12 (8.1)	9 (6.1)	21 (7.1)
Ethnicity, n (%)			
Hispanic or Latino	13 (8.7)	11 (7.5)	24 (8.1)
Not Hispanic or Latino	124 (83.2)	126 (85.7)	250 (84.5)
Unknown	0	1 (0.7)	1 (0.3)
Not reported	12 (8.1)	9 (6.1)	21 (7.1)
Racial Designation for Asian, n (%)	65	65	130
Japanese	25 (38.5)	23 (35.4)	48 (36.9)
Korean	8 (12.3)	13 (20.0)	21 (16.2)
Chinese	26 (40.0)	23 (35.4)	49 (37.7)
Other	6 (9.2)	6 (9.2)	12 (9.2)

a. Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
n1 = the number of patients with non-missing age.
The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
The denominator to calculate percentages for racial designation was based on the number of Asians within each treatment group.

Table 37. Disease Characteristics: Primary Diagnosis - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)	Total (N=296)
	n (%)	n (%)	n (%)
Primary Diagnosis			
NON-SMALL CELL LUNG CANCER	149 (100.0)	147 (100.0)	296 (100.0)
Body Side			
BILATERAL	20 (13.4)	18 (12.2)	38 (12.8)
LEFT	66 (44.3)	59 (40.1)	125 (42.2)
RIGHT	63 (42.3)	70 (47.6)	133 (44.9)
Histopathological Classification			
Adenocarcinoma	140 (94.0)	140 (95.2)	280 (94.6)
ACINAR ADENOCARCINOMA	7 (4.7)	7 (4.8)	14 (4.7)
ADENOCARCINOMA NOS	105 (70.5)	122 (83.0)	227 (76.7)
BRONCHIOLOALVEOLAR CARCINOMA	1 (0.7)	0	1 (0.3)
OTHER: SOLID ADENOCARCINOMA	1 (0.7)	0	1 (0.3)
PAPILLARY ADENOCARCINOMA	9 (6.0)	7 (4.8)	16 (5.4)
SIGNET RING ADENOCARCINOMA	4 (2.7)	1 (0.7)	5 (1.7)
SOLID ADENOCARCINOMA WITH MUCIN PRODUCTION	13 (8.7)	3 (2.0)	16 (5.4)
Non-Adenocarcinoma	9 (6.0)	7 (4.8)	16 (5.4)
ADENOSQUAMOUS CARCINOMA	6 (4.0)	5 (3.4)	11 (3.7)
LARGE CELL CARCINOMA	0	1 (0.7)	1 (0.3)
SQUAMOUS CELL CARCINOMA	3 (2.0)	1 (0.7)	4 (1.4)
TNM Stage at Initial Diagnosis			
STAGE IA	3 (2.0)	2 (1.4)	5 (1.7)
STAGE IB	2 (1.3)	0	2 (0.7)
STAGE IIA	3 (2.0)	2 (1.4)	5 (1.7)
STAGE IIB	2 (1.3)	3 (2.0)	5 (1.7)
STAGE IIIA	13 (8.7)	5 (3.4)	18 (6.1)
STAGE IIIB	12 (8.1)	6 (4.1)	18 (6.1)
STAGE IV	112 (75.2)	129 (87.8)	241 (81.4)
OTHER	1 (0.7)	0	1 (0.3)
UNKNOWN	1 (0.7)	0	1 (0.3)
TNM Current Stage			
STAGE IIIA	1 (0.7)	0	1 (0.3)
STAGE IIIB	12 (8.1)	8 (5.4)	20 (6.8)
STAGE IV	135 (90.6)	139 (94.6)	274 (92.6)
OTHER [a]	1 (0.7)	0	1 (0.3)
Extent of Disease			
LOCALLY ADVANCED	14 (9.4)	8 (5.4)	22 (7.4)
METASTATIC	135 (90.6)	139 (94.6)	274 (92.6)

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. One single patient with locally advanced disease at study entry was staged according to AJCC v8.0, instead of AJCC v7.0 as required by protocol, therefore classified under other.

Table 38. Tumour Baseline characteristics by BICR – Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149) n (%)	Crizotinib (N=147) n (%)	Total (N=296) n (%)
Measurable Disease at Baseline			
Yes	144 (96.6)	143 (97.3)	287 (97.0)
No	5 (3.4)	4 (2.7)	9 (3.0)
Adequate Baseline Assessment			
Yes	149 (100.0)	147 (100.0)	296 (100.0)
No	0	0	0
Involved Tumor Sites at Baseline[a]			
LUNG	138 (92.6)	134 (91.2)	272 (91.9)
LYMPH NODES REGIONAL and DISTANT	117 (78.5)	121 (82.3)	238 (80.4)
PLEURA	64 (43.0)	78 (53.1)	142 (48.0)
BONE	55 (36.9)	64 (43.5)	119 (40.2)
LIVER	48 (32.2)	55 (37.4)	103 (34.8)
BRAIN	42 (28.2)	43 (29.3)	85 (28.7)
ADRENAL GLAND	24 (16.1)	15 (10.2)	39 (13.2)
OTHER	20 (13.4)	32 (21.8)	52 (17.6)
MEDIASTINUM	6 (4.0)	17 (11.6)	23 (7.8)
PERITONEAL CAVITY	6 (4.0)	7 (4.8)	13 (4.4)
PERITONEUM	5 (3.4)	2 (1.4)	7 (2.4)
CHEST WALL	3 (2.0)	3 (2.0)	6 (2.0)
OMENTUM	4 (2.7)	2 (1.4)	6 (2.0)
PELVIS	1 (0.7)	4 (2.7)	5 (1.7)
ABDOMINAL WALL	1 (0.7)	2 (1.4)	3 (1.0)
KIDNEY	1 (0.7)	2 (1.4)	3 (1.0)
RETROPERITONEUM	1 (0.7)	2 (1.4)	3 (1.0)
NECK	0	2 (1.4)	2 (0.7)
COLON	0	1 (0.7)	1 (0.3)
DIAPHRAGM	1 (0.7)	0	1 (0.3)
OVARY	0	1 (0.7)	1 (0.3)
UTERUS	0	1 (0.7)	1 (0.3)
Brain Disease at Baseline[b]			
Yes	38 (25.5)	40 (27.2)	78 (26.4)
Measurable Disease	17 (11.4)	13 (8.8)	30 (10.1)
Not Measurable Disease	21 (14.1)	27 (18.4)	48 (16.2)
No	110 (73.8)	106 (72.1)	216 (73.0)
No Data	1 (0.7)	1 (0.7)	2 (0.7)

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. Per independent central radiological review.
b. Per independent central neuroradiological review.

Table 39. ECOG Performance status at baseline - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149) n (%)	Crizotinib (N=147) n (%)	Total (N=296) n (%)
ECOG Performance Status			
0	67 (45.0)	57 (38.8)	124 (41.9)
1	79 (53.0)	81 (55.1)	160 (54.1)
2	3 (2.0)	9 (6.1)	12 (4.1)

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group. Baseline was defined as the last assessment performed on or prior to date of the first dose of study treatment (on or prior to randomization for patients randomized but not dosed).

Table 40. Substance Use – Tobacco - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)	Total (N=296)
	n (%)	n (%)	n (%)
Tobacco:			
Never	81 (54.4)	94 (63.9)	175 (59.1)
Current	13 (8.7)	9 (6.1)	22 (7.4)
Former	55 (36.9)	43 (29.3)	98 (33.1)

Table 41. Prior anti-cancer therapies - Full Analysis Set (Protocol B7461006)

Anti-Cancer Therapy Status	Lorlatinib (N=149) n (%)	Crizotinib (N=147) n (%)	Total (N=296) n (%)
Patients with at least one prior anti-cancer systemic therapy			
Yes	12 (8.1)	9 (6.1)	21 (7.1)
No	137 (91.9)	138 (93.9)	275 (92.9)
Patients with at least one prior anti-cancer radiotherapy			
Yes	20 (13.4)	20 (13.6)	40 (13.5)
No	129 (86.6)	127 (86.4)	256 (86.5)
Patients with at least one prior anti-cancer surgery			
Yes	27 (18.1)	23 (15.6)	50 (16.9)
No	122 (81.9)	124 (84.4)	246 (83.1)
Patients with adjuvant anti-cancer systemic therapy	10 (6.7)	8 (5.4)	18 (6.1)
Patients with neoadjuvant anti-cancer systemic therapy	1 (0.7)	1 (0.7)	2 (0.7)

Numbers analysed

Outcomes and estimation

Primary efficacy endpoint: PFS by BIRC

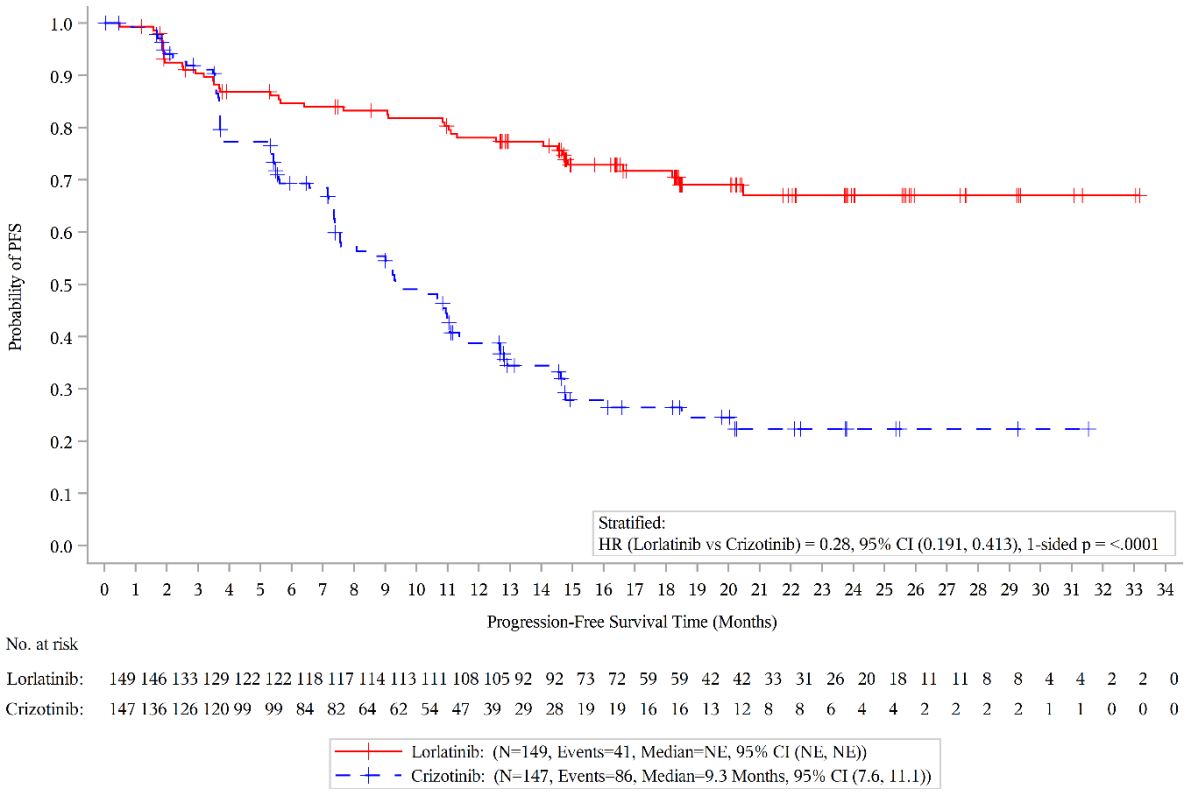
The primary efficacy endpoint of PFS by BIRC was met and statistically significantly improved at the first IA performed after 127 PFS events (72% of the 177 events planned at the final analysis of PFS) and occurred as of the data cut-off date of 20 March 2020. The median PFS follow-up duration was 18.3 months (95%CI: 16.4., 20.1) in the lorlatinib arm and 14.8 months (95%CI: 12.8, 18.4) in the crizotinib arm.

Table 42. Summary of Progression-Free Survival (Primary Analysis) Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event, n (%)	41 (27.5)	86 (58.5)
Type of event, n (%)		
Progressive disease	32 (21.5)	82 (55.8)
Death	9 (6.0)	4 (2.7)
Patients censored, n (%)	108 (72.5)	61 (41.5)
Reason for censoring, n (%)		
No adequate baseline assessment	0	0
Start of new anti-cancer therapy	10 (6.7)	24 (16.3)
Event after ≥ 2 missing or inadequate post-baseline assessments	1 (0.7)	0
Withdrawal of consent	3 (2.0)	14 (9.5)
Lost to follow-up	1 (0.7)	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	93 (62.4)	23 (15.6)
Probability of being event-free (95% CI) [a]		
at 12 months	0.781 (0.703, 0.840)	0.387 (0.298, 0.475)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	14.7 (10.8, NE)	5.4 (3.7, 7.2)
Median	NE (NE, NE)	9.3 (7.6, 11.1)
Q3	NE (NE, NE)	18.5 (14.6, NE)
Stratified analysis [c] Comparison vs Crizotinib		
Hazard Ratio [d]	0.28	
95% CI [d]	0.191, 0.413	
RCI [e]	0.175, 0.451	
1-sided p-value [f]	<.0001	
2-sided p-value [f]	<.0001	

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. CIs were derived using the log-log transformation with back transformation to original scale.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
d. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib.
e. Repeated confidence interval method used to take into account the group-sequential nature of the design as per EAST v 6.5.
f. p-value based on stratified log-rank test.

Figure 11. Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment (RECIST v1.1) - Full Analysis Set (Protocol B7461006)



Concordance rate

Table 43. Summary of PFS discordance between BICR and derived investigator assessments (RECIST v1.1) - Full Analysis Set (Protocol B7461006)

	Treatment Group		
	Lorlatinib (N=149)	Crizotinib (N=147)	Lorlatinib vs Crizotinib Difference (%)
Concordance/Discordance Type, n (%)			
a1 = Agreement by INV and BICR on timing and occurrence of event (within 7 days)	18 (12.1)	40 (27.2)	-15.1
a2 = Agreement on occurrence of event but timing of event by INV later than by BICR	8 (5.4)	31 (21.1)	-15.7
a3 = Agreement on occurrence of event but timing of event by INV earlier than by BICR	4 (2.7)	10 (6.8)	-4.1
b = Event by INV and no event by BICR	10 (6.7)	23 (15.6)	-8.9
c = No event by INV and event by BICR	11 (7.4)	5 (3.4)	4.0
d = Agreement on no event by INV and BICR	98 (65.8)	38 (25.9)	39.9
Discrepancy Rates, (%)			
Total event discrepancy rate: (b+c)/N	14.1	19.0	-4.9
Early discrepancy rate: (a3+b)/(a+b)	35.0	31.7	3.3
Late discrepancy rate: (a2+c)/(a2+a3+b+c)	57.6	52.2	5.4
Overall discrepancy rate: (a2+a3+b+c)/N	22.1	46.9	-24.8

Sensitivity analyses of PFS by BIRC

Table 44. Summary of progression-free survival based on BICR assessment (RECIST 1.1), Sensitivity analysis counting all PD and deaths as events - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event, n (%)	47 (31.5)	91 (61.9)
Type of event, n (%)		
Progressive disease	36 (24.2)	84 (57.1)
Death	11 (7.4)	7 (4.8)
Patients censored, n (%)	102 (68.5)	56 (38.1)
Reason for censoring, n (%)		
No adequate baseline assessment	0	0
Withdrawal of consent	3 (2.0)	15 (10.2)
Lost to follow-up	3 (2.0)	13 (8.8)
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	96 (64.4)	28 (19.0)
Probability of being event-free (95% CI) [a]		
at 12 months	0.775 (0.699, 0.835)	0.394 (0.309, 0.479)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	14.5 (9.1, 18.4)	5.4 (3.7, 7.2)
Median	NE (NE, NE)	9.3 (7.6, 11.1)
Q3	NE (NE, NE)	20.2 (14.6, NE)
Stratified analysis [c] Comparison vs Crizotinib		
Hazard Ratio [d]	0.30	
95% CI [d]	0.209, 0.438	
1-sided p-value [e]	<.0001	
2-sided p-value [e]	<.0001	

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
PDs and deaths were counted as events regardless of missing assessments or timing of the event (i.e. not censoring for start of new anti-cancer therapy prior to event or for missed assessments).
a. CIs were derived using the log-log transformation with back transformation to original scale.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
d. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib.
e. p-value based on stratified log-rank test.

Table 45. Summary of progression-free survival based on BICR assessment (RECIST 1.1), Sensitivity analysis stratified by brain metastases, ethnic origin and ECOG performance status - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event, n (%)	41 (27.5)	86 (58.5)
Type of event, n (%)		
Progressive disease	32 (21.5)	82 (55.8)
Death	9 (6.0)	4 (2.7)
Patients censored, n (%)	108 (72.5)	61 (41.5)
Reason for censoring, n (%)		
No adequate baseline assessment	0	0
Start of new anti-cancer therapy	10 (6.7)	24 (16.3)
Event after ≥ 2 missing or inadequate post-baseline assessments	1 (0.7)	0
Withdrawal of consent	3 (2.0)	14 (9.5)
Lost to follow-up	1 (0.7)	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	93 (62.4)	23 (15.6)
Probability of being event-free (95% CI) [a]		
at 12 months	0.781 (0.703, 0.840)	0.387 (0.298, 0.475)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	14.7 (10.8, NE)	5.4 (3.7, 7.2)
Median	NE (NE, NE)	9.3 (7.6, 11.1)
Q3	NE (NE, NE)	18.5 (14.6, NE)
Stratified analysis [c] Comparison vs Crizotinib		
Hazard Ratio [d]	0.30	
95% CI [d]	0.203, 0.444	
1-sided p-value [e]	<.0001	
2-sided p-value [e]	<.0001	

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. CIs were derived using the log-log transformation with back transformation to original scale.
b. Based on the Brookmeyer and Crowley method.
c. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values and ECOG PS (0/1 vs. 2) from CRF.
d. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib.
e. p-value based on stratified log-rank test.

Table 46. Multivariate Cox Regression analysis for progression-free survival based on BICR assessment (RECIST 1.1) - Full Analysis Set (Protocol B7461006)

Variables [a]	Levels	Parameter Estimate	Standard Error	Wald Chi-Square Statistic	p-value	Hazard Ratio	95% CI
Treatment Group	1: Lorlatinib	-1.307	0.2008	42.35	<.0001	0.27	0.183, 0.401
	2: Crizotinib						
Presence of Brain Metastases	1: Yes	0.475	0.1974	5.79	0.0161	1.61	1.092, 2.367
	2: No						
Ethnic Origin	1: Asian	0.035	0.1830	0.04	0.8470	1.04	0.724, 1.483
	2: Non-Asian						
ECOG Performance Status	1: 0/1	-1.566	0.3448	20.64	<.0001	0.21	0.106, 0.410
	2: 2						
Histology	1: Adenocarcinoma	-1.149	0.3396	11.46	0.0007	0.32	0.163, 0.616
	2: Non-Adenocarcinoma						

Secondary endpoints

OS – overall survival

Figure 12. Kaplan-Meier plot of overall survival – Full analysis set (Protocol B7461006)

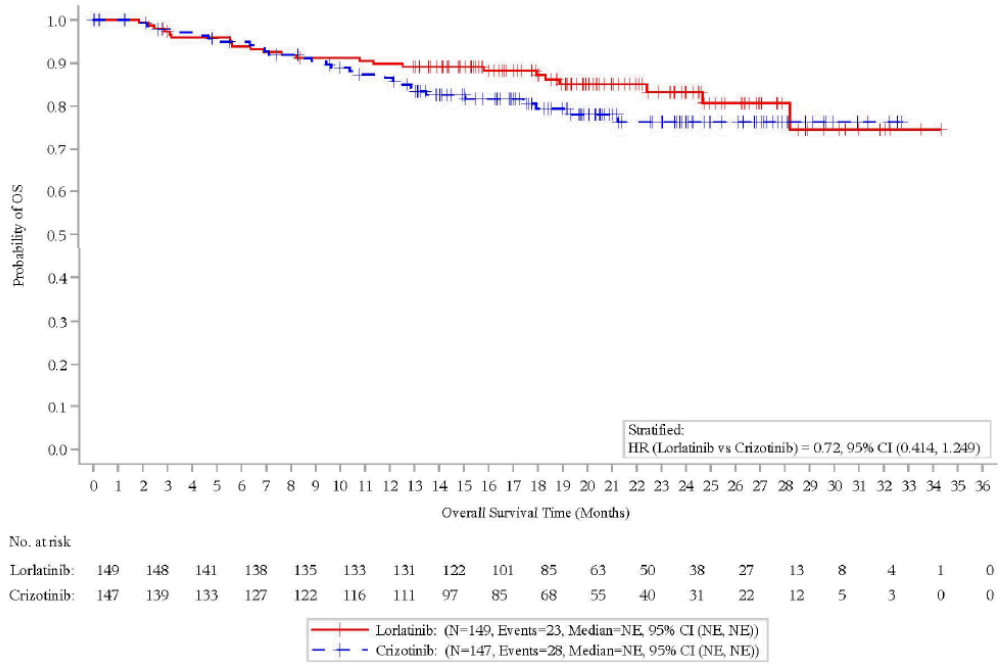


Table 47. Summary of overall survival - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Patients with event, n (%)	23 (15.4)	28 (19.0)
Patients censored, n (%)	126 (84.6)	119 (81.0)
Reason for censoring, n (%)		
Withdrawal of consent	4 (2.7)	18 (12.2)
Lost to follow-up [a]	0	2 (1.4)
Alive	122 (81.9)	99 (67.3)
Probability of being event-free (95% CI) [b]		
at 12 months	0.898 (0.837, 0.937)	0.866 (0.795, 0.913)
at 24 months	0.833 (0.748, 0.891)	0.763 (0.670, 0.833)
at 36 months	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [c]		
Q1	28.2 (24.7, NE)	NE (17.4, NE)
Median	NE (NE, NE)	NE (NE, NE)
Q3	NE (NE, NE)	NE (NE, NE)
Stratified analysis [d] Comparison vs Crizotinib		
Hazard Ratio [e]	0.72	
95% CI [e]	0.414, 1.249	

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. Included patients deemed to be lost to follow-up by the investigator and patients with last follow-up > 365 days prior to data cutoff (20MAR2020).
b. CIs were derived using the log-log transformation with back transformation to original scale.
c. Based on the Brookmeyer and Crowley method.
d. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
e. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib.

PFS by INV

Table 48. Key Efficacy Results per Investigator - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Endpoint		
Progression-Free Survival		
Patients with event, n (%)	40 (26.8)	104 (70.7)
Kaplan-Meier Estimates of Median Time to Event (months) (95% CI) [a]	NE (NE, NE)	9.1 (7.4, 10.9)
Probability of Being Event-Free at 12 Months (95% CI) [b]	0.802 (0.727, 0.859)	0.351 (0.269, 0.434)
Stratified Analysis [c] Lorlatinib vs Crizotinib		
Hazard Ratio [d]	0.21	
95% CI [d]	0.144, 0.307	
1-sided p-value [e]	<.0001	
Objective Response (CR+PR), n (%)	120 (80.5)	91 (61.9)
95% CI [f]	73.3, 86.6	53.5, 69.8
Stratified Analysis [c] Lorlatinib vs Crizotinib		
Odds Ratio	2.499	
95% CI [g]	1.484, 4.594	
1-sided p-value [h]	0.0002	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
Abbreviations: CI=confidence interval; CR=complete response; NE=not evaluable; N/n=number of patients; PR=partial response;
a. CIs were calculated using Brookmeyer and Crowley method;
b. CIs were derived using the log-log transformation with back transformation to original scale;
c. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization, derived from IRT stratification data;
d. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib;
e. P-value based on the stratified log-rank test;
f. Clopper-Pearson method used;
g. Odds ratio was estimated using Mantel-Haenszel method. Odds Ratio >1 indicates better outcome for Lorlatinib compared to Crizotinib; exact CI was calculated;
h. P-value based on Cochran-Mantel-Haenszel test.

ORR and DOR

Table 49. Summary of best overall response and objective response (confirmed) based on BICR assessment (RECIST 1.1) - Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=149)	Crizotinib (N=147)
Confirmed Best Overall Response, n (%)		
Complete response (CR)	4 (2.7)	0
Partial response (PR)	109 (73.2)	85 (57.8)
Stable disease (SD)	19 (12.8)	41 (27.9)
Non-CR/Non-PD	3 (2.0)	3 (2.0)
Progressive disease (PD)	10 (6.7)	7 (4.8)
Not evaluable (NE)	4 (2.7)	11 (7.5)
Objective Response (CR+PR), n (%)	113 (75.8)	85 (57.8)
95% CI [a]	68.2, 82.5	49.4, 65.9
Stratified analysis of Objective Response Rate [b] Comparison vs Crizotinib		
Odds Ratio	2.254	
95% CI [c]	1.353, 3.891	
1-sided p-value [d]	0.0005	
2-sided p-value [d]	0.0010	

The denominator to calculate percentages was N, the number of patients in the full analysis set within each treatment group.
a. Clopper-Pearson method used.
b. Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
c. Odds ratio was estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for Lorlatinib relative to Crizotinib; Exact CI was calculated.
d. p-value based on Cochran-Mantel-Haenszel test.

The investigator-assessed ORR was numerically higher in the lorlatinib arm (80.5% [95%CI: 73.3, 86.6] versus 61.9% [95%CI: 53.5, 69.8], p=0.0002) (Table not shown).

Table 50. Summary of duration of response based on BICR assessment (RECIST 1.1) – Patients with confirmed CR or PR in the Full Analysis Set (Protocol B7461006)

	Lorlatinib (N=113)	Crizotinib (N=85)
Patients with event, n (%)	18 (15.9)	45 (52.9)
Type of event, n (%)		
Progressive disease	14 (12.4)	45 (52.9)
Death	4 (3.5)	0
Patients censored, n (%)	95 (84.1)	40 (47.1)
Reason for censoring, n (%)		
No adequate baseline assessment	0	0
Start of new anti-cancer therapy	6 (5.3)	16 (18.8)
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0
Withdrawal of consent	3 (2.7)	5 (5.9)
Lost to follow-up	1 (0.9)	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	85 (75.2)	19 (22.4)
Probability of being event-free (95% CI) [a]		
at 12 months	0.875 (0.794, 0.926)	0.475 (0.352, 0.589)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	NE (16.5, NE)	5.7 (5.6, 8.5)
Median	NE (NE, NE)	11.0 (9.0, 12.9)
Q3	NE (NE, NE)	NE (12.9, NE)
Duration of response		
Range (Min, Max)	0.9, 31.3	1.1, 27.5
Response duration, n (%)		
≥ 6 months	101 (89.4)	53 (62.4)
≥ 12 months	79 (69.9)	23 (27.1)
≥ 18 months	34 (30.1)	9 (10.6)

The denominator to calculate percentages was N, the number of patients with confirmed complete response or partial response in the full analysis set within each treatment group.
a. CIs were derived using the log-log transformation with back transformation to original scale.
b. Based on the Brookmeyer and Crowley method.

Time to Tumour Response by BICR

In participants with a confirmed overall response by BICR assessment, the median (Q1, Q3) TTR was the same in both treatment arms (1.8 months [1.7, 1.9]), and occurred at the approximate time of the first scan taken on treatment.

Intracranial efficacy

Table 51. Intracranial Efficacy Results per BICR (Intracranial Time to Progression) - Full Analysis Set (Protocol B7461006)

	Patients without Brain Metastases at Baseline		Patients with Brain Metastases at Baseline		Overall	
Endpoint	**Lorlatinib (N=111)**	**Crizotinib (N=107)**	**Lorlatinib (N=38)**	**Crizotinib (N=40)**	**Lorlatinib (N=149)**	**Crizotinib (N=147)**
Patients with event, n (%)	1 (0.9)	19 (17.8)	4 (10.5)	26 (65.0)	5 (3.4)	45 (30.6)
Kaplan-Meier Estimates of Median Time to Event (months) (95% CI)	NE (NE, NE)	NE (16.6, NE)	NE (NE, NE)	7.3 (3.7, 9.3)	NE (NE, NE)	16.6 (11.1, NE)
Probability of Being Event-Free at 12 Months (95% CI) [a]	0.990 (0.934, 0.999)	0.753 (0.623, 0.843)	0.883 (0.718, 0.955)	0.217 (0.081, 0.395)	0.962 (0.911, 0.984)	0.597 (0.487, 0.690)
Stratified Analysis [b] - Comparison vs Crizotinib						
Hazard Ratio [c]	0.03		0.08		0.07	
95% CI [c]	0.004, 0.230		0.026, 0.227		0.026, 0.170	
1-sided p-value [d]	<.0001		<.0001		<.0001	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
Abbreviations: CI=confidence interval; NE=not evaluable; N/n=number of patients;
a. CIs were derived using the log-log transformation with back transformation to original scale;
b. Stratified by ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values;
c. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of Lorlatinib compared to Crizotinib;
d. P-value based on the stratified log-rank test.

Figure 13. Kaplan-Meier Plot of intra-cranial time to progression based on BICR Assessment (RECIST v1.1) - Full Analysis Set (Protocol B7461006)

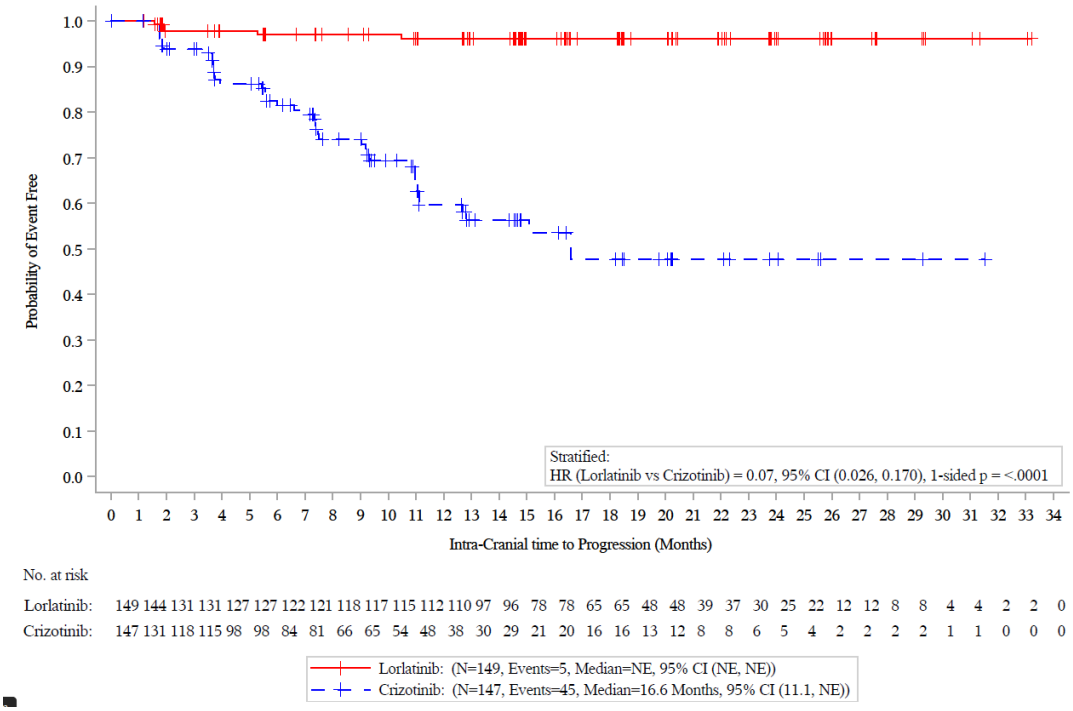


Table 52. Summary of best intra-cranial overall response and objective response (confirmed) based on BICR Assessment (modified RECIST v1.1) – Patients with brain metastases at baseline in the full analysis set (Protocol B7461006)

	Lorlatinib (N=38)	Crizotinib (N=40)
Confirmed Best Overall Response, n (%)		
Complete response (CR)	23 (60.5)	6 (15.0)
Partial response (PR)	2 (5.3)	2 (5.0)
Stable disease (SD)	1 (2.6)	5 (12.5)
Non-CR/Non-PD	10 (26.3)	17 (42.5)
Progressive disease (PD)	2 (5.3)	7 (17.5)
Not evaluable (NE)	0	3 (7.5)
Objective Response (CR+PR), n (%)	25 (65.8)	8 (20.0)
95% CI [a]	48.6, 80.4	9.1, 35.6
Stratified analysis of Objective Response Rate [b] Comparison vs Crizotinib		
Odds Ratio	8.407	
95% CI [c]	2.586, 27.233	
1-sided p-value [d]	<.0001	
2-sided p-value [d]	<.0001	

The denominator to calculate percentages was N, the number of patients with brain metastases at baseline in the full analysis set within each treatment group.
a. Clopper-Pearson method used.
b. Stratified by ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
c. Odds ratio was estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for Lorlatinib relative to Crizotinib; Exact CI was calculated.
d. p-value based on Cochran-Mantel-Haenszel test.

Table 53. Summary of intra-cranial duration of response based on BICR Assessment (modified RECIST v1.1) – Patients with brain metastases at baseline and confirmed CR or PR in the full analysis set (Protocol B7461006)

	Lorlatinib (N=25)	Crizotinib (N=8)
Patients with event, n (%)	3 (12.0)	4 (50.0)
Type of event, n (%)		
Progressive disease	1 (4.0)	2 (25.0)
Death without progression	2 (8.0)	2 (25.0)
Patients censored, n (%)	22 (88.0)	4 (50.0)
Reason for censoring, n (%)		
No baseline assessment	0	0
Start of new anti-cancer therapy	3 (12.0)	3 (37.5)
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0
Withdrawal of consent	0	1 (12.5)
Lost to follow-up	0	0
Ongoing without an event	19 (76.0)	0
Probability of being event-free (95% CI) [a]		
at 12 months	0.868 (0.644, 0.956)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [b]		
Q1	NE (10.8, NE)	7.5 (6.0, 9.4)
Median	NE (NE, NE)	9.4 (6.0, 11.1)
Q3	NE (NE, NE)	11.1 (7.5, 11.1)
Duration of response		
Range (Min, Max)	1.9, 31.4	3.5, 11.1
Response duration, n (%)		
≥ 12 months	18 (72.0)	0

The denominator to calculate percentages was N, the number of patients with brain metastases at baseline and confirmed complete response or partial response in the full analysis set within each treatment group.
a. CIs were derived using the log-log transformation with back transformation to original scale.
b. Based on the Brookmeyer and Crowley method.

In participants with any baseline brain metastases who had confirmed CR or PR, the median IC-TTRs (Q1, Q3) were similar between treatment arms, with 1.9 months (1.8, 3.7) in the lorlatinib arm and 1.8 months (1.7, 2.7) in the crizotinib arm, which was about the time of the first tumor assessment scan.

PRO – Patient-reported outcomes

The PRO results are presented in detail for the first 18 cycles. Later cycles had a smaller (approximately ≤20%) number of participants in each arm, which limited the interpretation of the data. At baseline, all participants who were eligible to complete the questionnaires (EORTC QLQ-C30 and QLQ-LC13) answered at least 1 question. The percentage of participants who completed at least one question was ≥96% through Cycle 18 in both treatment arms. The completion rate for the EQ-5D-5L questionnaire was similar to the completion rates of the EORTC QLQ-C30 and QLQ-LC13 questionnaires.

EORTC QLQ-C30 Functional and Symptoms Scales

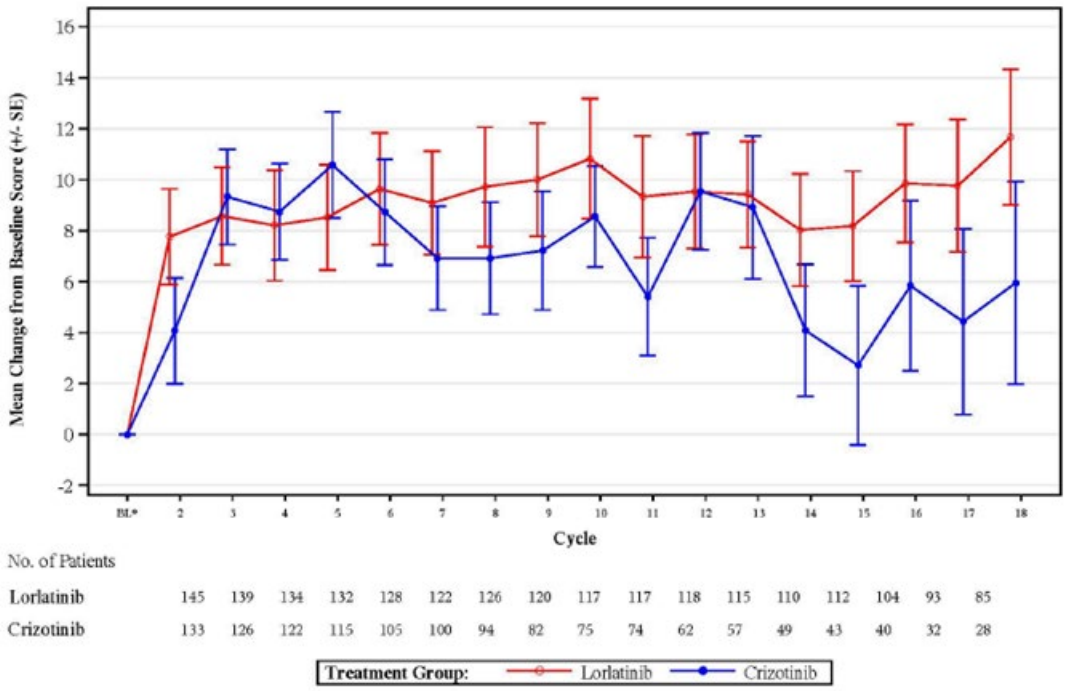
Mean baseline scores in global QoL were 64.6 (SE ±1.82) in the lorlatinib arm and 59.8 (SE ±1.90) in the crizotinib arm.

- There was a numerical improvement from baseline in the EORTC QLQ-C30 global QoL in the lorlatinib arm compared with the crizotinib arm (estimated mean difference of 4.65 [95%CI: 1.14, 8.16].
- Global QoL improvements in mean change from baseline were seen as early as Cycle 2 and maintained over time in the lorlatinib arm (Figure 14).

- There were no clinically meaningful (≥10 points difference) or notable numerical differences between treatment arms in any EORTC QLQ-C30 functioning domain.

The proportion of participants with improvement (≥10-point change from baseline) or stable in EORTC QLQ-C30 global QoL was similar between the lorlatinib arm (41.8% and 39.7%, respectively) and crizotinib arm (42.6% and 38.2%, respectively).

Figure 14. Plot of mean change from baseline (±) SE over time for EORTC QLQ-C30 (Global QOL) by visit – PRO analysis set (Protocol B7461006)



BL*: Baseline was defined as the last assessment performed on or prior to date of the first dose of study treatment.
Based on EORTC QLQ-C30 PRO analysis set within each treatment group.
Mean change from baseline were shown through cycle 18 to correspond with the median follow-up time.

Biomarker analysis

ALK status was determined by the Ventana ALK (D5F3) CDx IHC test performed on the Ventana ULTRA or XT platforms. Participants were enrolled based on the presence of an ALK gene rearrangement as determined by local or central Ventana ALK (D5F3) CDx IHC testing of their archived tumour tissue. Screening plasma CNA samples were retrospectively analysed at a central laboratory (Guardant Health) utilizing the G360 IUO assay on samples from enrolled participants and therefore known to be ALK positive based on IHC result.

Table 54. Summary of patients with none vs. ≥ 1 ALK mutation at screening – Tumour tissue analysis set (Protocol B7461006)

		Lorlatinib (N=118)	Crizotinib (N=104)
No ALK Mutation Detected	n (%)	107 (90.7)	92 (88.5)
	Responders, n (%)	82 (76.6)	56 (60.9)
	Confirmed Best Overall Response (%)		
	Complete response (CR)	4 (3.7)	0
	Partial response (PR)	78 (72.9)	56 (60.9)
	Stable disease (SD)	14 (13.1)	23 (25.0)
	Non-CR/Non-PD	2 (1.9)	3 (3.3)
	Progressive disease (PD)	7 (6.5)	5 (5.4)
	Not evaluable (NE)	2 (1.9)	5 (5.4)
	Median DOR (months), (95% CI)	NE (NE, NE)	11.0 (7.8, 16.6)
	Median PFS (months), (95% CI)	NE (NE, NE)	10.7 (7.6, 12.8)
≥ 1 ALK Mutation	n (%)	0	1 (1.0)
	Responders, n (%)		0
	Confirmed Best Overall Response (%)		
	Complete response (CR)		0
	Partial response (PR)		0
	Stable disease (SD)		0
	Non-CR/Non-PD		0
	Progressive disease (PD)		0
	Not evaluable (NE)		1 (100.0)
	Median DOR (months), (95% CI)		NE (NE, NE)
	Median PFS (months), (95% CI)		NE (NE, NE)
Other*	n (%)	11 (9.3)	11 (10.6)
	Responders, n (%)	7 (63.6)	8 (72.7)
	Confirmed Best Overall Response (%)		
	Complete response (CR)	0	0
	Partial response (PR)	7 (63.6)	8 (72.7)
	Stable disease (SD)	2 (18.2)	2 (18.2)
	Non-CR/Non-PD	1 (9.1)	0
	Progressive disease (PD)	0	1 (9.1)
	Not evaluable (NE)	1 (9.1)	0
	Median DOR (months), (95% CI)	NE (NE, NE)	7.4 (5.3, NE)
	Median PFS (months), (95% CI)	NE (16.6, NE)	9.0 (5.4, NE)

Based on Blinded Independent Central Review by Kaplan Meier estimates, based on Brookmeyer and Crowley method.
Other*: Sample failed analysis, uninformative, or not analyzed.

A total of 122 and 123 participants in the Lorlatinib and Crizotinib Arms, respectively, had valid results for assessment of plasma genotyping (i.e., included participants' ALK gene rearrangement status by blood-based Guardant Health G360 IUO test) (Table 55).

ALK gene rearrangement were detected:

- In the Lorlatinib Arm, 59 (48.4%; 95% CI: 39.2, 57.6).

- In the Crizotinib Arm, 62 (50.4%; 95% CI: 41.2, 59.5).

ALK gene arrangement were not detected:

- In the Lorlatinib Arm, 63 (51.6%).

- In the Crizotinib Arm, 61 (49.6%).

The concordance assessment of plasma genotyping for ALK fusion versus tumour IHC for ALK fusion expression at screening is presented in the following table.

Table 55. Concordance assessment of plasma genotyping for ALK gene rearrangement vs tumour IHC at screening – cfDNA diagnostic analysis set (Protocol B7461006)

	Lorlatinib (N=122)		Crizotinib (N=123)		Total (N=245)	
	n (%)	95% CI[b]	n (%)	95% CI[b]	n (%)	95% CI[b]
Patients with valid results[a]	122 (100.0)		123 (100.0)		245 (100.0)	
ALK gene rearrangement detected	59 (48.4)	(39.2, 57.6)	62 (50.4)	(41.2, 59.5)	121 (49.4)	(43.0, 55.8)
ALK gene rearrangement not detected	63 (51.6)		61 (49.6)		124 (50.6)	

Table 56. Summary of plasma CNA EML4-ALK fusion variant and ALK mutation analysis – CNA peripheral blood analysis set (Protocol B7461006)

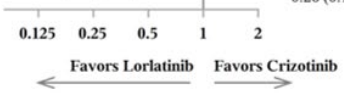
		Lorlatinib						Crizotinib					
		SCREENING (N=130)	C2D1 (N=125)	C7D1 (N=103)	ORR (95% CI)	Median PFS (95% CI)	Median DOR (95% CI)	SCREENING (N=125)	C2D1 (N=118)	C7D1 (N=84)	ORR (95% CI)	Median PFS (95% CI)	Median DOR (95% CI)
EML4-ALK Variant 1	**n**	19 (14.6)	1 (0.8)	0	78.9 (54.4, 93.9)	NE (NE, NE)	NE (NE, NE)	25 (20.0)	7 (5.9)	5 (6.0)	52.0 (31.3, 72.2)	7.4 (5.5, 9.3)	5.7 (5.6, NE)
	No ALK mutation	18 (13.8)	1 (0.8)	0	77.8 (52.4, 93.6)	NE (NE, NE)	NE (NE, NE)	23 (18.4)	6 (5.1)	4 (4.8)	52.2 (30.6, 73.2)	7.4 (5.5, 11.1)	5.7 (5.6, NE)
	≥ 1 ALK mutation	1 (0.8)	0	0	100.0 (2.5, 100.0)	NE (NE, NE)	NE (NE, NE)	2 (1.6)	1 (0.8)	1 (1.2)	50.0 (1.3, 98.7)	6.6 (3.8, 9.3)	7.4 (NE, NE)
EML4-ALK Variant 2	**n**	7 (5.4)	2 (1.6)	0	85.7 (42.1, 99.6)	NE (NE, NE)	NE (NE, NE)	2 (1.6)	0	1 (1.2)	50.0 (1.3, 98.7)	NE (3.7, NE)	NE (NE, NE)
	No ALK mutation	7 (5.4)	2 (1.6)	0	85.7 (42.1, 99.6)	NE (NE, NE)	NE (NE, NE)	2 (1.6)	0	0	50.0 (1.3, 98.7)	NE (3.7, NE)	NE (NE, NE)
	≥ 1 ALK mutation	0	0	0				0	0	1 (1.2)			
EML4-ALK Variant 3	**n**	18 (13.8)	2 (1.6)	0	72.2 (46.5, 90.3)	NE (14.7, NE)	NE (12.8, NE)	21 (16.8)	2 (1.7)	4 (4.8)	76.2 (52.8, 91.8)	7.6 (5.4, 9.2)	6.5 (3.7, 9.2)
	No ALK mutation	17 (13.1)	2 (1.6)	0	70.6 (44.0, 89.7)	NE (14.7, NE)	NE (12.8, NE)	21 (16.8)	2 (1.7)	3 (3.6)	76.2 (52.8, 91.8)	7.6 (5.4, 9.2)	6.5 (3.7, 9.2)
	≥ 1 ALK mutation	1 (0.8)	0	0	100.0 (2.5, 100.0)	NE (NE, NE)	NE (NE, NE)	0	0	1 (1.2)			
EML4-ALK Other	**n**	15 (11.5)	2 (1.6)	0	86.7 (59.5, 98.3)	NE (12.6, NE)	NE (16.5, NE)	9 (7.2)	1 (0.8)	1 (1.2)	66.7 (29.9, 92.5)	11.0 (7.2, 16.0)	9.3 (5.6, 14.6)
	No ALK mutation	15 (11.5)	2 (1.6)	0	86.7 (59.5, 98.3)	NE (12.6, NE)	NE (16.5, NE)	7 (5.6)	0	0	71.4 (29.0, 96.3)	11.0 (7.2, 16.0)	11.9 (5.6, 14.6)
	≥ 1 ALK mutation	0	0	0				2 (1.6)	1 (0.8)	1 (1.2)	50.0 (1.3, 98.7)	9.0 (NE, NE)	5.3 (NE, NE)
ALK Rearrangement Other	**n**	2 (1.5)	0	0	100.0 (15.8, 100.0)	14.3 (14.1, 14.5)	12.9 (NE, NE)	4 (3.2)	0	2 (2.4)	25.0 (0.6, 80.6)	10.8 (3.5, NE)	NE (NE, NE)
	No ALK mutation	2 (1.5)	0	0	100.0 (15.8, 100.0)	14.3 (14.1, 14.5)	12.9 (NE, NE)	4 (3.2)	0	2 (2.4)	25.0 (0.6, 80.6)	10.8 (3.5, NE)	NE (NE, NE)
	≥ 1 ALK mutation	0	0	0				0	0	0			
ALK Rearrangement Not Detected	**n**	32 (24.6)	61 (48.8)	48 (46.6)	62.5 (43.7, 78.9)	NE (NE, NE)	NE (NE, NE)	36 (28.8)	48 (40.7)	34 (40.5)	55.6 (38.1, 72.1)	11.4 (7.6, NE)	12.9 (9.5, NE)
	No ALK mutation	29 (22.3)	59 (47.2)	45 (43.7)	58.6 (38.9, 76.5)	NE (11.3, NE)	NE (NE, NE)	34 (27.2)	47 (39.8)	33 (39.3)	55.9 (37.9, 72.8)	11.4 (7.6, NE)	12.9 (9.5, NE)
	≥ 1 ALK mutation	3 (2.3)	2 (1.6)	3 (2.9)	100.0 (29.2, 100.0)	NE (NE, NE)	NE (NE, NE)	2 (1.6)	1 (0.8)	1 (1.2)	50.0 (1.3, 98.7)	6.4 (3.5, 9.3)	7.8 (NE, NE)
No cfDNA Detected	**n**	32 (24.6)	53 (42.4)	52 (50.5)	81.3 (63.6, 92.8)	NE (NE, NE)	NE (NE, NE)	25 (20.0)	58 (49.2)	35 (41.7)	76.0 (54.9, 90.6)	20.2 (14.8, NE)	18.4 (12.9, NE)
Other*	**n**	5 (3.8)	4 (3.2)	3 (2.9)	60.0 (14.7, 94.7)	14.9 (1.9, NE)	NE (12.9, NE)	3 (2.4)	2 (1.7)	2 (2.4)	33.3 (0.8, 90.6)	7.4 (5.4, 9.5)	3.8 (NE, NE)

Based on Blinded Independent Central Review by Kaplan Meier estimates, based on Brookmeyer and Crowley method, at Screening.
N = the number of patients in the CNA peripheral blood analysis set within each treatment group at the specified visit.
Other*: Sample failed analysis, uninformative, or not analyzed.

Ancillary analyses

Figure 15. Forest plot of progression free survival based on BICR assessment (RECIST v1.1) by subgroups – Full analysis set (Protocol B7461006)

Subgroup	Number of Patients, n (%) Lorlatinib	Number of Patients, n (%) Crizotinib	Number of Events/ Number of Patients (N) Lorlatinib	Number of Events/ Number of Patients (N) Crizotinib	Hazard Ratio (95% CI)	1-sided p-value	2-sided p-value
All patients (stratified)	149 (100.0)	147 (100.0)	41/149	86/147	0.28 (0.191, 0.413)	<.0001	<.0001
All patients (unstratified)	149 (100.0)	147 (100.0)	41/149	86/147	0.28 (0.194, 0.414)	<.0001	<.0001
Presence of Brain Metastases							
Yes	38 (25.5)	40 (27.2)	11/38	27/40	0.20 (0.097, 0.431)	<.0001	<.0001
No	111 (74.5)	107 (72.8)	30/111	59/107	0.32 (0.202, 0.492)	<.0001	<.0001
Ethnic Origin							
Asian	66 (44.3)	65 (44.2)	23/66	31/65	0.47 (0.271, 0.815)	0.0030	0.0060
Non-Asian	83 (55.7)	82 (55.8)	18/83	55/82	0.19 (0.108, 0.321)	<.0001	<.0001
ECOG Performance Status							
0/1	146 (98.0)	138 (93.9)	39/146	78/138	0.28 (0.193, 0.422)	<.0001	<.0001
Gender							
Male	65 (43.6)	56 (38.1)	20/65	35/56	0.31 (0.176, 0.537)	<.0001	<.0001
Female	84 (56.4)	91 (61.9)	21/84	51/91	0.26 (0.157, 0.444)	<.0001	<.0001
Age							
< 65 Years	90 (60.4)	103 (70.1)	20/90	60/103	0.22 (0.132, 0.370)	<.0001	<.0001
≥ 65 Years	59 (39.6)	44 (29.9)	21/59	26/44	0.35 (0.195, 0.641)	0.0002	0.0004
Smoking Status							
Never	81 (54.4)	94 (63.9)	20/81	56/94	0.24 (0.140, 0.396)	<.0001	<.0001
Current/Former	68 (45.6)	52 (35.4)	21/68	29/52	0.36 (0.200, 0.632)	0.0001	0.0002
Extent of Disease							
Metastatic	135 (90.6)	139 (94.6)	36/135	83/139	0.26 (0.177, 0.394)	<.0001	<.0001
Histology							
Adenocarcinoma	140 (94.0)	140 (95.2)	36/140	81/140	0.26 (0.176, 0.392)	<.0001	<.0001



Presence of Brain Metastases subgroup was based on mRECIST BICR baseline data.
Hazard ratios were not calculated due to insufficient numbers of events (<10 events on either treatment arm within the defined subset), as dictated by the Statistical Analysis Plan, for patients who had ECOG performance status of 2 (2 vs. 8), Extent of disease of Locally Advanced (5 vs. 3) or Histology of Non-Adenocarcinoma (5 vs. 5).
Stratified by presence of brain metastases (Yes/No) and ethnic origin (Asian/Non-Asian) at randomization from IRT stratification values.
Percentages were calculated based on the number of patients in the full analysis set in each treatment group. Plot presented on log scale (base=2).

Table 57. Summary of progression free survival based on BICR assessment (RECIST v1.1) by ECOG PS (0 vs 1) – Full analysis set (Protocol B7461006)

	Lorlatinib (N=146)			Crizotinib (N=138)			Lorlatinib vs Crizotinib			
Subgroup	n (%) [a]	# Events (%) [b]	Median PFS (95% CI) (Months) [c]	n (%) [a]	# Events (%) [b]	Median PFS (95% CI) (Months) [c]	HR [d]	95% CI [d]	1-sided p-value [e]	2-sided p-value [e]
ECOG Performance Status										
0	67 (45.9)	15 (22.4)	NE (NE, NE)	57 (41.3)	31 (54.4)	10.7 (7.6, 12.9)	0.21	0.112, 0.401	<.0001	<.0001
1	79 (54.1)	24 (30.4)	NE (NE, NE)	81 (58.7)	47 (58.0)	10.9 (7.4, 14.6)	0.35	0.211, 0.576	<.0001	<.0001

Subsequent therapies

Table 58. Subsequent anti-cancer systemic therapies - Full analysis set (Protocol B7461006)

	Lorlatinib (N=149) n (%)	Crizotinib (N=147) n (%)
Study treatment ongoing	103 (69.1)	31 (21.1)
Death/withdrawal informed consent	10 (6.7)	19 (12.9)
No subsequent therapy reported	10 (6.7)	11 (7.5)
At least one subsequent therapy	26 (17.4)	86 (58.5)
1st subsequent therapy (N1)	26	86
ALK TKI (N2)	17 (65.4)	79 (91.9)
ALECTINIB	9 (52.9)	53 (67.1)
CRIZOTINIB	4 (23.5)	4 (5.1)
CERITINIB	2 (11.8)	2 (2.5)
BRIGATINIB	1 (5.9)	17 (21.5)
LORLATINIB	1 (5.9)	3 (3.8)
CHEMO +/- ANTI-ANGIOGENIC	8 (30.8)	3 (3.5)
IMMUNO	1 (3.8)	0
OTHER	0	4 (4.7)
2nd subsequent therapy (N1)	11	26
ALK TKI (N2)	7 (63.6)	15 (57.7)
ALECTINIB	3 (42.9)	5 (33.3)
CRIZOTINIB	3 (42.9)	0
BRIGATINIB	1 (14.3)	2 (13.3)
CERITINIB	0	2 (13.3)
LORLATINIB	0	6 (40.0)
CHEMO +/- ANTI-ANGIOGENIC	3 (27.3)	9 (34.6)
IMMUNO	1 (9.1)	0
OTHER	0	2 (7.7)
3rd subsequent therapy (N1)	6	10
ALK TKI (N2)	3 (50.0)	7 (70.0)
LORLATINIB	2 (66.7)	4 (57.1)
ALECTINIB	1 (33.3)	2 (28.6)
CERITINIB	0	1 (14.3)
CHEMO +/- ANTI-ANGIOGENIC	3 (50.0)	2 (20.0)
IMMUNO	0	1 (10.0)
4th subsequent therapy	3	3
5th subsequent therapy	1	2
6th subsequent therapy	1	2
7th subsequent therapy	0	1

Patients were counted only once within each category and PT.
N = number of patients in the full analysis set within each treatment group.
N1 = number of patients in the full analysis set within each treatment group and subsequent therapy category, denominator for percentage of the category.
N2 = number of patients in the full analysis set within each treatment group and subsequent therapy sub-category (ALK TKI), denominator for percentage of the sub-category.
Decreasing order of frequency relative to Lorlatinib.
WHO DDE v201903 coding dictionary applied.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 59. Summary of Efficacy for Study B7461006

Study identifier	Study B7461006		
Design	Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in previously untreated advanced ALK-positive NSCLC patients.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		11 May 2017 to 28 February 2019 Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Lorlatinib arm		Lorlatinib monotherapy 100 mg QD orally in 28-day cycles, n=149.
	Crizotinib arm		Crizotinib monotherapy 250 mg BID orally in 28-day cycles, n=147.
Endpoints and definitions	Primary endpoint	PFS by BIRC	PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by blinded independent review with use of RECIST v1.1, or death from any cause, whichever occurs first
	Secondary endpoint	OS	Overall Survival defined as the time from randomization to death from any cause
	Other secondary endpoints:	ORR and DOR by BIRC	Overall response rate and duration of response by blinded independent review
Database lock	20 Mar 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, first IA		
Descriptive statistics and estimate variability	Treatment group	Lorlatinib	Crizotinib
	Number of subjects	149	147
	PFS by BIRC (Months)	NE	9.3
	95%CI	NE; NE	7.6; 11.1
	OS (Months)	NE	NE
	95%CI	NE; NE	NE; NE
	ORR by BIRC (%) 95%CI	75.8 68.2; 82.5	57.8 49.4; 65.9
	DOR (Months) 95%CI	NE NE; NE	11.0 9.0, 12.9

Effect estimate per comparison	Primary endpoint PFS by BIRC	Comparison groups	Lorlatinib vs crizotinib
		HR	0.28
		95%CI	0.191, 0.413
		P-value (1-sided)	<0.0001
	Secondary endpoint OS*	Comparison groups	Lorlatinib vs crizotinib
		HR	0.72
		95%CI	0.41, 1.25
		P-value	Not applicable

	Secondary endpoint ORR by BIRC	Comparison groups	Lorlatinib vs crizotinib
		Odds ratio	2.254; 1-sided p-value
		95%CI	1.353, 3.891
		P-value (1-sided)	<0.0005
Notes	*OS data immature, final OS data will be provided as an Annex II condition.		

Analysis performed across trials (pooled analyses and meta-analysis)

Follow-up efficacy from the EXP-1 cohort of the Phase 1/2 Study 1001 are included for completeness. However, the development phase and study designs were different between Study 1001 and Study 1006. Study 1001 was a Phase 1/2 uncontrolled trial for estimating antitumor activity in participants with several disease characteristics. The EXP-1 cohort focused on patients with previously untreated advanced NSCLC and was limited to 30 participants. Phase 3 Study 1006 is a randomized study of 296 participants with an active control arm.

Given the limited sample size and the uncontrolled design of the EXP-1 cohort in Phase 1/2 Study 1001, comparative statements to the Phase 3 Study 1006 were not deemed appropriate and pooled analyses were not prepared.

Clinical studies in special populations

Elderly (≥ 65 years): Due to the limited data on this population, no dose recommendation can be made for patients aged 65 years and older.

Renal impairment: No dose adjustment is needed for patients with normal renal function and mild or moderate (CL_{cr}: ≥ 30mL/min) renal impairment based on a population pharmacokinetic analysis. Information for lorlatinib use in patients with severe (CL_{cr}: < 30 mL/min) renal impairment is very limited. Therefore, lorlatinib is not recommended in patients with severe renal impairment.

Hepatic impairment: No dose adjustments are recommended for patients with mild hepatic impairment. No information is available for lorlatinib in patients with moderate or severe hepatic impairment. Therefore, lorlatinib is not recommended in patients with moderate to severe hepatic impairment (see section 5.2).

Table 60. Summary of progression free survival based on BICR assessment (RECIST v1.1) by Age (<65, 65-74, ≥75) – Full analysis set (Protocol B7461006)

	Lorlatinib (N=149)			Crizotinib (N=147)			Lorlatinib vs Crizotinib			
Subgroup	n (%) [a]	# Events (%) [b]	Median PFS (95% CI) (Months) [c]	n (%) [a]	# Events (%) [b]	Median PFS (95% CI) (Months) [c]	HR [d]	95% CI [d]	1-sided p-value [e]	2-sided p-value [e]
Age										
< 65 Years	90 (60.4)	20 (22.2)	NE (NE, NE)	103 (70.1)	60 (58.3)	10.8 (9.0, 14.6)	0.22	0.132, 0.370	<.0001	<.0001
65 - 74 Years	47 (31.5)	18 (38.3)	NE (14.1, NE)	34 (23.1)	19 (55.9)	7.6 (5.6, 11.4)	0.41	0.210, 0.795	0.0033	0.0067
≥ 75 Years	12 (8.1)	3 (25.0)	NE (14.7, NE)	10 (6.8)	7 (70.0)	5.3 (3.6, 10.9)	0.23	0.055, 0.919	0.0125	0.0251

Supportive study

The results from Study 1001 were previously provided to health authorities as part of the initial MAA lorlatinib submissions. The study has been fully enrolled, and participants continue to be followed for efficacy and safety. In this procedure, only efficacy results per BICR assessment for the EXP-1 cohort

are provided. The EXP-1 cohort included previously untreated participants with advanced ALK-positive NSCLC with or without CNS metastases (N=30). Participants with baseline CNS metastases had to be clinically asymptomatic. All participants received 100 mg QD lorlatinib as the starting dose.

Table 61. Patient disposition – Long-term follow-up phase- EXP-1, Safety analysis set (Protocol B7461001)

	EXP-1 (N=30)
Disposition Status	**n (%)**
Disposition Phase: Long-Term Follow-Up	
Discontinued	7 (23.3)
Death	6 (20.0)
Lost to follow-up	1 (3.3)
Completed	0
Study terminated by sponsor	0
Withdrawal by subject	0
Other	0
Ongoing	23 (76.7)

Table 62. Demographic characteristics - EXP-1, Safety analysis set (Protocol B7461001)

	EXP-1 (N=30)
Demographic	**n (%)**
Age (Years) [a], n (%)	
18 -< 45	4 (13.3%)
45 -< 65	18 (60.0%)
≥ 65	8 (26.7%)
n1	30
Mean (SD)	57.4 (12.07)
Median (Q1, Q3)	59.00 (48.00, 68.00)
Range (Min, Max)	(27, 75)
Gender, n (%)	
Male	17 (56.7%)
Female	13 (43.3%)
Race, n (%)	
White	10 (33.3%)
Black or African American	1 (3.3%)
Asian	17 (56.7%)
Other	1 (3.3%)
Missing	1 (3.3%)

N=the number of patients in the safety analysis set within each treatment group and used as the denominator to calculate percentages.
a. Age at Screening (years)=(date of collection-date of birth + 1)/365.25.
n1=the number of patients with non-missing age.

Table 63. Lorlatinib Key Efficacy Results per ICR - EXP-1 Full Analysis Set (Protocol B7461001)

Endpoint	EXP-1 (N=30)
Median PFS (95% CI)[a], months	16.6 (11.8, 28.3)
ORR[b] % (95% CI)	90.0 (73.5, 97.9)
Median DoR (95% CI)[a], months	17.2 (12.5, 35.1)
IC-ORR[b] % (95% CI)	75.0 (34.9, 96.8)
Median IC-DoR (95% CI)[a], months	NE (8.3, NE)

a. Based on the Brookmeyer and Crowley method.
b. Clopper-Pearson method used.
N is the number of subjects in the full analysis set.

Real-world data - Post-second generation ALK TKI setting

As part the current application, the MAH proposed to downgrade the specific obligation to conduct a single arm study in patients who progressed after alectinib or ceritinib to a recommendation and convert the conditional MA to a full MA based on efficacy, safety and mutational analysis data from Phase 3 Study B7461006 in patients with previously untreated, advanced ALK-positive advanced NSCLC.

To support this claim, real world efficacy data were also submitted from new additional 32 patients progressing on or after one second-generation ALK TKI with or without prior chemotherapy from three recent publications of real-world datasets:

Two real-world data sets were derived from the Early Access Program (EAP) for lorlatinib in Austria (Hochmair et al.) and Russia (Orlov et al.). To participate in the EAP, patients had to have progressed on at least one other systemic treatment for metastatic NSCLC (including chemotherapy and a prior ALK-TKI) or resistance mutations not covered by approved ALK TKIs, or leptomeningeal disease.

- Hochmair et al. performed a retrospective real-world data analysis in 51 patients registered in an early access program in Austria, who received second- or later-line lorlatinib between January 2016 and May 2020. The ALK-positive cohort consisted of 37 patients with a mean age at metastatic diagnosis of 53.0 years (range, 29–77), including 19 patients (51.4%) presenting with brain metastasis at diagnosis. Patients received multiple lines of therapy before switching to lorlatinib (median number of prior treatments was 4; range, 2–9). The ORR in patients who received only one prior second generation ALK-TKI before lorlatinib treatment (N=10) was 40% (95%CI 12, 74). The median duration of treatment (DoT) was 4.4 months (95%CI: 0.5; 8.2).
- Orlov et al. reported a single-center experience (I.P. Pavlov Medical University, St.- Petersburg, Russia) of the use of lorlatinib within the compassionate use program that was accessible in Russia within 2017–2019. The study included 35 subjects with ALK-rearranged NSCLC. The mean age was 46.7 years (range: 24–80 years). The median follow-up time was 17.5 months. The ORR observed in 14 patients treated with prior ceritinib only was 29% (95%CI: 8, 58) and the median PFS was 15 months (95%CI: 6.2; 21.8).

Moreover, an international real-world analysis published by Zhu et al. included 76 patients with ALK positive NSCLC enrolled in the compassionate use program in Hong Kong, Singapore, South Korea, Taiwan, Thailand, and in the US Expanded Access Program (NCT03178071). The median age was 53 years (13-73). In 84% of the patients, brain metastases were present at the start of lorlatinib therapy and 14% had leptomeningeal carcinomatosis. Of these 76 patients, 9 had received a second-generation

ALK TKI as the only ALK-TKI received which included ceritinib (n=8) and brigatinib (n=1). The ORR for the 8 evaluable patients was 13% (95%CI: 0, 53).

In summary, the lorlatinib early access program made available to patients with advanced ALK positive NSCLC after failure of at least one ALK-TKI has resulted in 3 publications of 10 + 14 + 8 (n=32) patients, respectively, who were treated in the second-line post a second-generation TKI and the ORRs were 40%, 29%, and 13%, respectively.

2.4.2. Discussion on clinical efficacy

Several ALK-targeted TKIs are approved for the treatment of advanced ALK+ NSCLC in patients, who are either treatment-naïve or have received one or two prior ALK-TKIs. Lorlatinib is already approved for the treatment in the second and third-line setting for advanced NSCLC.

This application has been submitted to extend the lorlatinib indication to the treatment of ALK-positive advanced NSCLC in patients who are not previously treated with an ALK-TKI, i.e. prior chemotherapy is allowed.

Design and conduct of clinical studies

To support this application, the MAH submitted the results from a phase III, randomized, open-label study (Study 1006), comparing lorlatinib to a standard-of care TKI, crizotinib. Crizotinib was still the standard of care for the first-line treatment of ALK+ NSCLC at the time of study initiation so the control arm is considered adequate. However, alectinib monotherapy is now the preferred first-line treatment option.

Lorlatinib and crizotinib are both oral treatments given continuously in 28-days cycles and no crossover was allowed from the control arm.

The **primary endpoint** was progression free survival (PFS) by blinded independent review (BIRC) and **secondary endpoints** were OS, PFS by investigator (INV), objective response rate (ORR), duration of response (DOR), intracranial ORR plus DOR and patient-reported outcomes (PRO). The objectives and endpoints for the pivotal study are endorsed. PFS by BIRC as primary endpoint is especially supported since the pivotal study was unblinded.

Overall, **eligibility criteria** clearly define the target population.

The **sample size** calculations and stratification factors for **randomization** (brain metastases and ethnic origin) are considered appropriate.

The study was **open-label** and measurements were in place to minimize the impact of knowing the assigned treatment on the main outcomes. Patients were allowed to continue with the randomized treatment despite radiological disease progression, if they experienced clinical benefit. This is not optimal since the investigators were not blinded to treatment and may have called PD late and continued treatment with lorlatinib in absence of clinical progression. Reversely, the investigators might have called PD early in the crizotinib-treated patients, as this was expected to have inferior efficacy, especially in the brain. However, since cross-over was not allowed and the primary endpoint was assessed by the BICR, which was blinded to the assigned treatment, this is acceptable. Nonetheless, lorlatinib is not recommended to be used beyond radiological PD and it is reflected in the SmPC that treatment duration should be until disease progression or unacceptable toxicity.

Overall, the **statistical methods** implemented to calculate PFS and OS are endorsed. Several sensitivity analyses were planned to assess the robustness of the model. It was noted that censoring

patients who discontinue treatment after 126 days or start a new anti-cancer therapy corresponds to a HR where treatment discontinuation and treatment switch do not occur, which is not considered plausible in clinical practice. A supplementary analysis was performed to test the effect of the censoring rules on the results. For this analysis, all PDs and deaths were considered events regardless of missing assessments or timing of the event. OS was calculated in a similar manner to PFS. Patients, who did not die during follow-up, were censored. Sensitivity analyses were also presented to assess the effect of the covariates on the results. In addition, the statistical methods used to calculate and compare ORR are endorsed.

The approach implemented by the MAH to control the type I error due to multiple IA is acceptable. It is noted that the 1st IA for PFS was performed with 127 events. The MAH updated the efficacy boundaries according to the observed numbers of events. This is acceptable.

OS and PFS were controlled for multiplicity using a hierarchical approach, which is agreed. The other secondary endpoints are considered exploratory.

The changes to the PFS analyses were planned and implemented in the protocol before the MAH had access to the PFS results. Therefore, the changes made in the SAP are not expected to compromise the interpretation of the results of the study.

Efficacy data and additional analyses

The **study population** comprised a total of 296 randomized patients (149 in the lorlatinib arm vs 147 in the crizotinib arm). The primary efficacy analyses were based on this population.

Patient recruitment seems overall unbiased. It is noted that the vast majority of patients, who discontinued lorlatinib did so due to PD, or adverse events and only 4 patients withdrew from the study. In the crizotinib arm, 5 patients withdrew even before treatment start. Moreover, after treatment start a further 8 patients withdrew from the study, while 3 patients discontinued due to 'global deterioration' called by the investigator. This may have caused bias and led to an under-performance of the control arm.

The **COVID-19-related changes** to study conduct described are to be expected, acceptable and are not expected to have had any major impact on the study results.

The **important protocol deviations** in the pivotal study were equally distributed between the treatment arms (~42%).

The treatment arms were generally well balanced with regards to the **baseline characteristics** of age, race, ethnicity and smoking status. There were slightly more males and less females in the lorlatinib arm, which may have favoured the control arm, but this is acceptable as gender was not a stratification factor.

Disease baseline characteristics indicated a similar number of patients with brain involvement at baseline (28.2% vs 29.3%) per independent central radiological review. Fewer patients with pleural metastases (43.0% vs 53.1%) were allocated to lorlatinib, which may have favoured this arm due to the clinical impact and the potential complications from the drainage of pleural fluids. However, this small imbalance is unlikely to have affected study results and is acceptable.

It is noted that significantly more patients with ECOG performance status (PS) 2 were included in the crizotinib arm, while slightly less patients with PS 0 were included in the crizotinib arm, both factors which may favour outcome of the active arm with lorlatinib. However, the performance of the control arm regarding the primary endpoint PFS by BIRC (9.3 months (95%CI: 7.6, 11.1) is in line with other

studies with crizotinib in a similar first-line setting, which is reassuring. The use of prior local or systemic anti-cancer therapies was comparable between groups.

The primary efficacy endpoint of **PFS by BIRC** was met and statistically significantly improved at the first IA performed after 72% events as of the data cut-off date of 20 March 2020. The median PFS follow-up duration was 18.3 months (95%CI: 16.4., 20.1) in the lorlatinib arm and 14.8 months (95%CI: 12.8, 18.4) in the crizotinib arm. The HR was 0.28 (95%CI: 0.191, 0.413) in favour of lorlatinib because the median PFS by BIRC was not estimable (95%CI: NE, NE) with lorlatinib versus 9.3 months (95%CI: 7.6, 11.1) in the crizotinib arm. The KM curves clearly separate after 4 months of therapy corresponding to the markedly fewer PFS events with lorlatinib (27.5% vs 58.5% events). There was a high number of censoring and it is noted that 16.3% in the crizotinib arm vs 6.7% in the lorlatinib were censored due to start of new anti-cancer therapy.

The sensitivity analyses of PFS by BIRC counting all PD and deaths as events shows a HR of 0.30, which is consistent with the primary analyses (HR 0.28). The sensitivity analyses stratified by brain metastases, ethnic origin, and ECOG performance status were also consistent (HR 0.30) with the primary analysis. The multivariate cox regression analysis showed that treatment group and ECOG PS status significantly affected the outcome, which is consistent with the statistically and clinically significantly better PFS in the lorlatinib arm and with previous findings showing that ECOG PS status is a strong prognostic factor in most clinical trials in oncology.

PFS by INV is overall in line with the PFS by BIRC results regarding PFS by INV events in the lorlatinib arm (26.8% vs 27.5% events). However, markedly more patients had a PFS by INV event in the crizotinib arm (70.7% vs 58.5%), which is probably due to the open-label trial design. The control arm with crizotinib fairs quite similarly regarding both PFS by BIRC versus by INV (9.3 months vs 9.1 months). Based on Investigator assessment, both an earlier timing and more frequent number of events were reported, while the BICR assessment offers a more conservative analysis of data. However, lack of concordance in event registration questions the quality and strength of evidence and can be expected to have an impact on the initiation of subsequent lines of therapy.

OS data is immature with only 17% events and a similar number of patients are censored in both treatment arms. Considering the prognosis of the treated disease (median OS with crizotinib is ~57 months) and the first-line setting, this is acceptable for now. Acknowledging the limitations of an immature analysis (<20% of total events), no gain in OS was demonstrated for lorlatinib relative to crizotinib. Similar findings were observed in previously performed trials comparing next-generation ALK-Is against crizotinib. It is likely that subsequent therapies might have had an impact on this clinical outcome, particularly in view of the demonstrated benefit deriving from the sequential use of different ALK-Is upon disease progression. The MAH will provide updated OS data as part of the final clinical study report for the pivotal Study B7461006 (CROWN) by 30 June 2025. These mature OS results are requested as an Annex II condition in order to rule out any detrimental effect on OS.

As mentioned, **post-study treatments** are likely to have impacted on the overall survival. More than half of the population of patients initially assigned to crizotinib (58.5%) were initiated to a 1st post-study treatment, generally with a next-generation ALK-TKIs and alectinib and brigatinib were the most widely used. Lorlatinib was prescribed as 2nd post-study treatment in the control group (6 out of 26 patients undergoing a 2nd sequential ALK-TKI-based treatment). This reflects current clinical practice. Within the lorlatinib group, only 17.4% of patients underwent a 1st subsequent therapy, generally with a second-generation ALK-TKI and it would be of interest to assess **PFS2** under these alternative options, in order to ascertain response to therapy following lorlatinib as 1st TKI and the potential influence of development of resistance mutations. In the absence of a mature OS analysis, PFS2 data are desirable to assess the clinical relevance of treatment in the intended front-line indication and within the current therapy landscape characterised by the availability of different ALK-Is that are generally used subsequently.

Section 5.1 of the SmPC therefore reports the absence of PFS2 at the present data cut-off, and the MAH has agreed to provide PFS2 data in the context of the next annual renewal (Recommendation).

ORR by BIRC was clinically significantly improved with lorlatinib to 75.8% (95%CI: 68.2, 82.5) versus 57.8% (95%CI: 49.4, 65.9) with crizotinib. It is noted that complete responses (CR) was only observed with lorlatinib (2.7%) and the improved ORR was mainly driven by the larger rate of partial responses (PR) in the lorlatinib arm (73.2% vs 57.8%). **Duration of response by BIRC** also clinically significantly prolonged with lorlatinib vs crizotinib (NE versus 11.0 months (95%CI: 9.0; 12.9) and it is noted that 30% of the patients in the lorlatinib arm had a duration response of ≥18 months. Time to tumour response was less than 2 months and in line with TTR results from other available ALK TKIs.

Efficacy in the brain was clearly improved with lorlatinib, which is best demonstrated by the time to intracranial progression by BIRC in the ITT population (HR 0.07 (95%CI: 0.026; 0.170). The intracranial ORR in patients with brain metastases at baseline is also improved with lorlatinib, and although the numbers here are limited (N=78), there is a clear IC-ORR difference between the treatment arms i.e. 65.8% (95%CI: 48.6; 80.4) vs 20.0 % with crizotinib. The intracranial DOR was also improved significantly with lorlatinib (NE vs 9.4 months, n=33). The number of patients with brain metastases at baseline were similar in both treatment arms and the median timing from prior radiotherapy to study entry were comparable between groups, thus providing a controlled analysis of lorlatinib effect on CNS disease. Overall, it can be concluded that lorlatinib prevents intracranial progression of disease and produced more and longer clinically relevant intracranial responses in patients with brain metastases at baseline compared to crizotinib.

Overall, no clinically relevant differences are considered observed between the treatment arms regarding **patient-reported outcomes**. Since the study was open label, the PRO results should be interpreted with caution and are not displayed in the SmPC.

ALK status was determined by the Ventana ALK (D5F3) CDx IHC test performed on the Ventana ULTRA or XT platforms. The low level of detection of ALK mutations within tumour samples in the study population (around 10% of total participants) is expected given the lack of exposure of patients to prior ALK targeted therapies. Considering that only 1 patient in the crizotinib group was found positive to ≥ 1 ALK mutation, any data analysis and result interpretation by ALK mutation status is hampered.

The CAN peripheral blood analysis showed very poor concordance with tumour sample analysis for ALK gene arrangement detection (around 50% regardless of treatment arm). Based on the available information, it remains unclear the diagnostic value of the CAN blood peripheral analysis. The test was carried out using an assay set up for tumour mutation profiling; moreover, the correspondence between solid tissue and peripheral blood cells in the expression of ALK gene mutations is dubious. Given the limited applicability of the CAN blood peripheral analysis in clinical practice, these uncertainties are considered of limited impact on patient management and the issue is not further pursued.

In any case, the low accuracy of the test makes the biomarker study, which relies entirely upon the plasma based ALK mutation detection, of limited interpretability and clinical utility. Hence the MAH's conclusions on higher efficacy for lorlatinib than crizotinib regardless of ALK mutation status and variants can only be given a speculative sense. Information about the importance of detection of ALK positive NSCLC for selection of patients for treatment with lorlatinib was included in section 4.2 of the SmPC.

The treatment effect of lorlatinib according to PFS by BIRC is consistent across **important subgroups** regardless of presence of brain metastases at baseline, gender, age and smoking status. The vast majority of the patients included had ECOG PS 0 (n=124) or 1 (n=160), in total ~96%, while only 12 patients had ECOG PS 2. Even though the pivotal study was not stratified for ECOG PS status, it was considered clinically relevant to confirm efficacy in both groups, so the MAH was asked to provide an

analysis of PFS by BIRC regarding ECOG PS 0 vs 1, which confirmed clinically relevant PFS by BIRC results for patients with ECOG PS 0 (HR 0.21) and PS 1 (HR 0.35), respectively.

Efficacy data was also provided according to **specific age categories** (i.e. <65; 65-74, ≥75 years), which overall confirm clinically relevant HRs for PFS in patients of more than 65 years of age (n= 47, HR 0.41) and in the small subgroup of patients of 65-74 years of age (n=12, HR 0.23). This is acceptable. No further data was provided renal/hepatic impairment.

The results from the **supportive study cohort (n=30)** showed a PFS of 16.6 months, an ORR of 90%, a median DOR of 17.2 months and an IC-ORR of 75%. These results are from a small cohort of patients with metastatic ALK+ NSCLC in the first-line setting and they are not directly comparable to the pivotal randomized phase 3 Study 1006. However, the efficacy of lorlatinib in the first-line setting is considered to be supported by these results.

As part the current application, the MAH proposed to downgrade the second specific obligation (SOB) to a recommendation and convert the conditional MA to a full MA. A prospective single arm study (B7461027) to test lorlatinib in this clinical setting was agreed as a SOB at the time of the initial conditional MA of lorlatinib, as a result of a relatively limited sample size of patients in the pivotal Study B7461001 who previously underwent second-generation ALK TKI treatment as 1st targeted therapy (alectinib, ceritinib, brigatinib). The MAH claims that the new efficacy and safety data derived from Study 1006 together with the biomarker study conducted as part of study 1006 provides further evidence of efficacy of lorlatinib in the presence of ALK mutation variants, which can develop subsequently to TKI therapy. However, the newly submitted data only refer to untreated individuals who harbour ALK-positive NSCLC, thus providing an efficacy analysis of lorlatinib against crizotinib in a preceding line of therapy. Moreover, the biomarker study carries concerns on methodological aspects other than being limited in terms of number and variants of ALK mutations detected, given the untreated nature of subjects. These limitations hamper the clinical interpretability of results and any translatability of efficacy data to the 2nd or subsequent lines of treatment, where prior exposure to a specific ALK-I is known to give rise to specific resistance mutations that can compromise the subsequent response to therapy. Real-world evidence from the LORLATU (an expanded access program) with 197 ALK-positive patients treated with lorlatinib in 2L+ (median follow-up of 17 months) is considered supportive of efficacy of lorlatinib in this setting, as the ORR was 50.6%, the median PFS was 9.7 months (95%CI: 5.6-12), and median OS was 32.9 months (95%CI: 18.7- not reached), but only 8 patients had been pre-exposed to second-generation ALK TKIs, and thus of limited value.

During the current procedure, real world efficacy data from new additional 32 patients progressing on or after one second-generation ALK-TKI with or without prior chemotherapy were submitted. The lorlatinib early access program made available to patients with advanced ALK positive NSCLC after failure of at least one ALK-TKI has resulted in 3 publications of 10 + 14 + 8 (n=32) patients, who were treated in the second-line post a second-generation ALK-TKI and the ORRs were 40%, 29%, and 13%, respectively. Taking into account that clinical trial data from the same setting in the Exp-3B cohort of the pivotal study for the CMA (n=28) showed an ORR of 42.9%, these RWE results somewhat deviate. Hence, it is not agreed that RWE from 32 patients with an ORR ranging from 13-40% is consistent with already assessed clinical trial data.

Therefore, the conduct of the planned study B7461027 is still merited and should be conducted as planned with recruitment of approximately 70 patients in the second-line setting post a second-generation ALK-TKI (SOB). The MAH has clarified that this study is being conducted in 6 countries with a total of 25 investigational sites which are all active. The first patient was enrolled in September 2020. As of 11 June 2021, 18 patients have been enrolled in the study, reaching 25% of the total sample size. Enrolment is anticipated to complete in October 2022 with a readout (clinical study report) by June 2024, which is considered acceptable.

2.4.3. Conclusions on the clinical efficacy

Treatment with lorlatinib has shown a statistically and clinically meaningful improvement of efficacy compared to crizotinib in the treatment of adult patients with ALK-positive advanced NSCLC not previously treated with an ALK inhibitor. Although OS data are immature, the primary efficacy endpoint is supported by an improvement in overall response and duration of response both systemically and intracranially.

Therefore, submission of the results of Study 1006 fulfilled the respective specific obligation. Since OS data are immature, the MAH will submit final OS data of the Phase III CROWN study (B7461006) as an Annex II condition (PAES).

The clinical efficacy in patients previously treated with ALK inhibitors still requires confirmation and the clinical study report of study B7461027 will be submitted by 30 June 2024 (SOB).

The following measures are considered necessary to address issues related to efficacy:

- Annex II condition

Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of lorlatinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor, the MAH will submit the results including overall survival (OS) data of the Phase III CROWN study (B7461006) comparing lorlatinib versus crizotinib in that same setting. The clinical study report will be submitted by 30 June 2025.

- Recommendation

In the absence of a mature OS analysis, and with the aim to clarify the benefit deriving from treatment of patients with ALK positive advanced NSCLC previously not treated with an ALK inhibitor, the MAH has agreed to provide PFS2 data for the CROWN (B7461006) study in the context of the next annual renewal.

- Specific obligation (from initial MAA)

In order to confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK TKI therapy, the MAH should conduct a single-arm study investigating patients in that same setting (B7461027) and submit the clinical study report by 30 June 2024.

2.5. Clinical safety

Introduction

The safety data to support the use of lorlatinib for the treatment of adult patients with previously untreated and previously treated ALK-positive advanced NSCLC are from pivotal Study B7461006 and the supporting Study B7461001 (hereafter referred to as Studies 1006 and 1001, respectively).

Study 1006 (n=291): Safety data from this study, at the time of interim analysis, are provided from the Safety Analysis Set of 149 participants treated with lorlatinib 100 mg QD and 142 participants treated with crizotinib 250 mg BID. The data cut-off date was 20 March 2020.

Study 1001 (n=295): Study 1001 is an ongoing Phase 1/2 study in participants with ALK-positive or ROS1-positive advanced NSCLC and including participants who were either treatment-naïve or previously treated with one or more ALK TKIs or ROS1 TKIs with or without chemotherapy. Initial results from Study 1001 were previously reported in the initial MAA submission that led to the approval of lorlatinib. Multiple doses of lorlatinib were evaluated in Study 1001; summaries of deaths, SAEs, and Grade 5 AEs were updated only for the 295 participants from Study 1001 treated with lorlatinib 100 mg QD. There were 20 additional months of follow-up compared to the data originally presented with cut-off date 15 September 2017. The new data cut-off date was 14 May 2019.

Patient exposure

Table 64. Exposure to study treatment – Duration of treatment – Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	Lorlatinib 100-mg QD Pooled (N=476)
Treatment Duration (Months) [a]					
n	149	142	295	32	476
Mean (SD)	16.6 (8.32)	10.4 (6.90)	19.6 (15.38)	11.4 (8.79)	18.1 (13.34)
Median (Q1, Q3)	16.7 (12.9, 22.4)	9.6 (4.7, 14.5)	16.3 (4.8, 34.9)	9.1 (4.0, 22.0)	16.3 (6.0, 29.7)
Range (Min, Max)	(0.13, 34.30)	(0.23, 32.56)	(0.03, 55.03)	(0.89, 27.33)	(0.03, 55.03)

a. Duration of treatment was defined as Duration (Months)=(last dose date - cycle 1 day 1 date + 1)/30.4375.
One Patient from the Phase 1/2 portion of Study B7461001 only received the lead-in dose; for this patient the treatment duration was defined as 1 day. For other patients, the calculations are carried out considering the treatment period in the study except lead-in cycle.
BID=twice daily; QD=once daily

For Study 1006, the proportion of participants who remained on study treatment for ≥12 months duration was 75.8% (113 of 149) in the lorlatinib arm, and 34.5% (49 of 142) in the crizotinib arm, with 69.1% and 21.8% of participants, respectively, still on treatment at the time of data cut-off (data not shown).

Adverse events

Table 65. Treatment-emergent adverse events (all causalities, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

Adverse Event Disposition	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD n (%)	Crizotinib 250-mg BID n (%)	Lorlatinib Phase 1/2 100-mg QD n (%)	Lorlatinib DDI 100-mg QD n (%)	Lorlatinib 100-mg QD Pooled n (%)
Patients evaluable for adverse events	149	142	295	32	476
Number of adverse events	2023	1729	4652	470	7145
Patients with adverse events	149 (100.0)	140 (98.6)	294 (99.7)	32 (100.0)	475 (99.8)
Patients with serious adverse events	51 (34.2)	39 (27.5)	125 (42.4)	12 (37.5)	188 (39.5)
Patients with Maximum Grade 3 or 4 adverse events	108 (72.5)	79 (55.6)	181 (61.4)	18 (56.3)	307 (64.5)
Patients with Maximum Grade 5 adverse events	7 (4.7)	7 (4.9)	36 (12.2)	5 (15.6)	48 (10.1)
Patients discontinued from study due to adverse events[a]	7 (4.7)	8 (5.6)	24 (8.1)	2 (6.3)	33 (6.9)
Patients discontinued study treatment due to adverse events[b]	10 (6.7)	13 (9.2)	27 (9.2)	4 (12.5)	41 (8.6)
Patients with dose reduced or temporary discontinuation due to adverse events	79 (53.0)	71 (50.0)	140 (47.5)	13 (40.6)	232 (48.7)

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
BID=twice daily; QD=once daily
Except for the Number of adverse events patients were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
a. Patients who had an AE record that caused study discontinuation.
b. Patients who had an AE record that caused treatment discontinuation.
MedDRA v23.0 coding dictionary applied.

Table 66. Treatment-emergent adverse events (treatment related, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

Adverse Event Disposition	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD n (%)	Crizotinib 250-mg BID n (%)	Lorlatinib Phase 1/2 100-mg QD n (%)	Lorlatinib DDI 100-mg QD n (%)	Lorlatinib 100-mg QD Pooled n (%)
Patients evaluable for adverse events	149	142	295	32	476
Number of adverse events	1029	923	2207	187	3423
Patients with adverse events	144 (96.6)	133 (93.7)	281 (95.3)	31 (96.9)	456 (95.8)
Patients with serious adverse events	12 (8.1)	7 (4.9)	25 (8.5)	1 (3.1)	38 (8.0)
Patients with Maximum Grade 3 or 4 adverse events	83 (55.7)	52 (36.6)	140 (47.5)	16 (50.0)	239 (50.2)
Patients with Maximum Grade 5 adverse events	2 (1.3)	0	0	0	2 (0.4)
Patients discontinued from study due to adverse events[a]	2 (1.3)	0	7 (2.4)	1 (3.1)	10 (2.1)
Patients discontinued study treatment due to adverse events[b]	7 (4.7)	7 (4.9)	8 (2.7)	3 (9.4)	18 (3.8)
Patients with dose reduced or temporary discontinuation due to adverse events	60 (40.3)	54 (38.0)	89 (30.2)	9 (28.1)	158 (33.2)

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
BID=twice daily; QD=once daily
Except for the Number of adverse events patients were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
a. Patients who had an AE record that caused study discontinuation.
b. Patients who had an AE record that caused treatment discontinuation.
MedDRA v23.0 coding dictionary applied.

Table 67. Summary of TEAEs by MedDRA PT or cluster term and max CTCAE grade (any grade, grade 3 and 4) of ≥10% in decreasing freq. (all cause, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006						B7461001						Overall		
	Lorlatinib 100-mg QD (N=149)			Crizotinib 250-mg BID (N=142)			Lorlatinib Phase 1/2 100-mg QD (N=295)			Lorlatinib DDI 100-mg QD (N=32)			Lorlatinib 100-mg QD Pooled (N=476)		
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with Any Adverse Event	149 (100.0)	87 (58.4)	21 (14.1)	140 (98.6)	67 (47.2)	12 (8.5)	294 (99.7)	143 (48.5)	38 (12.9)	32 (100.0)	18 (56.3)	0	475 (99.8)	248 (52.1)	59 (12.4)
HYPERCHOLESTEROLEMIA	105 (70.5)	23 (15.4)	1 (0.7)	5 (3.5)	0	0	251 (85.1)	47 (15.9)	6 (2.0)	30 (93.8)	10 (31.3)	0	386 (81.1)	80 (16.8)	7 (1.5)
HYPERTRIGLYCERIDEMIA	95 (63.8)	19 (12.8)	11 (7.4)	8 (5.6)	0	0	199 (67.5)	46 (15.6)	9 (3.1)	26 (81.3)	7 (21.9)	0	320 (67.2)	72 (15.1)	20 (4.2)
EDEMA	82 (55.0)	6 (4.0)	0	56 (39.4)	2 (1.4)	0	165 (55.9)	7 (2.4)	0	18 (56.3)	0	0	265 (55.7)	13 (2.7)	0
PERIPHERAL NEUROPATHY	50 (33.6)	3 (2.0)	0	21 (14.8)	1 (0.7)	0	144 (48.8)	9 (3.1)	0	14 (43.8)	1 (3.1)	0	208 (43.7)	13 (2.7)	0
Weight increased	57 (38.3)	25 (16.8)	0	18 (12.7)	3 (2.1)	0	81 (27.5)	21 (7.1)	0	9 (28.1)	2 (6.3)	0	147 (30.9)	48 (10.1)	0
COGNITIVE EFFECTS	32 (21.5)	3 (2.0)	0	8 (5.6)	0	0	91 (30.8)	9 (3.1)	0	9 (28.1)	2 (6.3)	0	132 (27.7)	14 (2.9)	0
FATIGUE	29 (19.5)	2 (1.3)	0	46 (32.4)	4 (2.8)	0	89 (30.2)	4 (1.4)	0	12 (37.5)	0	0	130 (27.3)	6 (1.3)	0
Dyspnoea	30 (20.1)	4 (2.7)	0	23 (16.2)	3 (2.1)	0	88 (29.8)	16 (5.4)	4 (1.4)	10 (31.3)	2 (6.3)	0	128 (26.9)	22 (4.6)	4 (0.8)
Arthralgia	28 (18.8)	1 (0.7)	0	16 (11.3)	0	0	78 (26.4)	3 (1.0)	0	6 (18.8)	0	0	112 (23.5)	4 (0.8)	0
Diarrhoea	32 (21.5)	2 (1.3)	0	74 (52.1)	1 (0.7)	0	72 (24.4)	5 (1.7)	0	5 (15.6)	0	0	109 (22.9)	7 (1.5)	0
MOOD EFFECTS	24 (16.1)	2 (1.3)	0	7 (4.9)	0	0	69 (23.4)	5 (1.7)	0	7 (21.9)	0	0	100 (21.0)	7 (1.5)	0
Cough	24 (16.1)	0	0	26 (18.3)	0	0	67 (22.7)	0	0	7 (21.9)	0	0	98 (20.6)	0	0
Anaemia	29 (19.5)	4 (2.7)	0	11 (7.7)	4 (2.8)	0	52 (17.6)	15 (5.1)	0	7 (21.9)	1 (3.1)	0	88 (18.5)	20 (4.2)	0
Headache	25 (16.8)	0	0	25 (17.6)	1 (0.7)	0	56 (19.0)	3 (1.0)	0	4 (12.5)	0	0	85 (17.9)	3 (0.6)	0
Nausea	22 (14.8)	1 (0.7)	0	74 (52.1)	3 (2.1)	0	59 (20.0)	1 (0.3)	1 (0.3)	3 (9.4)	0	0	84 (17.6)	2 (0.4)	1 (0.2)
Constipation	26 (17.4)	0	0	42 (29.6)	1 (0.7)	0	49 (16.6)	0	0	8 (25.0)	1 (3.1)	0	83 (17.4)	1 (0.2)	0
VISION DISORDER	27 (18.1)	0	0	56 (39.4)	1 (0.7)	0	52 (17.6)	1 (0.3)	0	3 (9.4)	0	0	82 (17.2)	1 (0.2)	0
Pain in extremity	26 (17.4)	0	0	12 (8.5)	0	0	49 (16.6)	1 (0.3)	0	5 (15.6)	0	0	80 (16.8)	1 (0.2)	0
Back pain	22 (14.8)	1 (0.7)	0	16 (11.3)	0	0	49 (16.6)	2 (0.7)	0	6 (18.8)	0	0	77 (16.2)	3 (0.6)	0
Pyrexia	25 (16.8)	1 (0.7)	1 (0.7)	18 (12.7)	2 (1.4)	0	47 (15.9)	3 (1.0)	1 (0.3)	3 (9.4)	0	0	75 (15.8)	4 (0.8)	2 (0.4)
Dizziness	16 (10.7)	0	0	20 (14.1)	0	0	51 (17.3)	3 (1.0)	0	6 (18.8)	0	0	73 (15.3)	3 (0.6)	0
Alanine aminotransferase increased	26 (17.4)	4 (2.7)	0	48 (33.8)	5 (3.5)	1 (0.7)	41 (13.9)	3 (1.0)	2 (0.7)	1 (3.1)	0	0	68 (14.3)	7 (1.5)	2 (0.4)
Aspartate aminotransferase increased	21 (14.1)	3 (2.0)	0	39 (27.5)	5 (3.5)	0	44 (14.9)	2 (0.7)	2 (0.7)	2 (6.3)	0	0	67 (14.1)	5 (1.1)	2 (0.4)
Vomiting	19 (12.8)	1 (0.7)	0	55 (38.7)	2 (1.4)	0	43 (14.6)	3 (1.0)	0	2 (6.3)	0	0	64 (13.4)	4 (0.8)	0
Hypertension	27 (18.1)	15 (10.1)	0	3 (2.1)	0	0	33 (11.2)	13 (4.4)	0	2 (6.3)	1 (3.1)	0	62 (13.0)	29 (6.1)	0
Upper respiratory tract infection	17 (11.4)	1 (0.7)	0	11 (7.7)	2 (1.4)	0	41 (13.9)	1 (0.3)	0	3 (9.4)	1 (3.1)	0	61 (12.8)	3 (0.6)	0
Lipase increased	14 (9.4)	3 (2.0)	2 (1.3)	17 (12.0)	5 (3.5)	1 (0.7)	44 (14.9)	22 (7.5)	6 (2.0)	1 (3.1)	0	0	59 (12.4)	25 (5.3)	8 (1.7)
Myalgia	16 (10.7)	0	0	5 (3.5)	0	0	38 (12.9)	0	0	4 (12.5)	0	0	58 (12.2)	0	0
SLEEP EFFECTS	17 (11.4)	1 (0.7)	1 (0.7)	14 (9.9)	0	0	35 (11.9)	0	0	3 (9.4)	0	0	55 (11.6)	1 (0.2)	1 (0.2)
Amylase increased	13 (8.7)	0	0	16 (11.3)	1 (0.7)	0	38 (12.9)	11 (3.7)	1 (0.3)	3 (9.4)	1 (3.1)	0	54 (11.3)	12 (2.5)	1 (0.2)
Chest pain	16 (10.7)	2 (1.3)	0	20 (14.1)	1 (0.7)	0	32 (10.8)	3 (1.0)	0	2 (6.3)	0	0	50 (10.5)	5 (1.1)	0
Pneumonia	11 (7.4)	2 (1.3)	1 (0.7)	12 (8.5)	4 (2.8)	1 (0.7)	35 (11.9)	15 (5.1)	0	4 (12.5)	2 (6.3)	0	50 (10.5)	19 (4.0)	1 (0.2)
Rash	15 (10.1)	0	0	11 (7.7)	0	0	31 (10.5)	1 (0.3)	0	3 (9.4)	0	0	49 (10.3)	1 (0.2)	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to any grade of Overall Lorlatinib 100-mg QD Pooled group.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily
With any adverse events row included all patients without cutoff.

Grade 3-4 AEs

Table 68. Summary of TEAEs by MedDRA PT or cluster term and max CTCAE grade (any grade, grade 3 and 4) of ≥10% in decreasing freq. (treatment related, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006						B7461001						Overall		
	Lorlatinib 100-mg QD (N=149)			Crizotinib 250-mg BID (N=142)			Lorlatinib Phase 1/2 100-mg QD (N=295)			Lorlatinib DDI 100-mg QD (N=32)			Lorlatinib 100-mg QD Pooled (N=476)		
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with Any Adverse Event	144 (96.6)	70 (47.0)	13 (8.7)	133 (93.7)	45 (31.7)	7 (4.9)	281 (95.3)	117 (39.7)	23 (7.8)	31 (96.9)	16 (50.0)	0	456 (95.8)	203 (42.6)	36 (7.6)
HYPERCHOLESTEROLEMIA	103 (69.1)	22 (14.8)	1 (0.7)	3 (2.1)	0	0	249 (84.4)	47 (15.9)	5 (1.7)	30 (93.8)	10 (31.3)	0	382 (80.3)	79 (16.6)	6 (1.3)
HYPERTRIGLYCERIDEMIA	93 (62.4)	19 (12.8)	10 (6.7)	6 (4.2)	0	0	198 (67.1)	46 (15.6)	9 (3.1)	26 (81.3)	7 (21.9)	0	317 (66.6)	72 (15.1)	19 (4.0)
EDEMA	67 (45.0)	5 (3.4)	0	41 (28.9)	1 (0.7)	0	135 (45.8)	6 (2.0)	0	11 (34.4)	0	0	213 (44.7)	11 (2.3)	0
PERIPHERAL NEUROPATHY	33 (22.1)	3 (2.0)	0	12 (8.5)	0	0	101 (34.2)	6 (2.0)	0	10 (31.3)	0	0	144 (30.3)	9 (1.9)	0
Weight increased	39 (26.2)	16 (10.7)	0	9 (6.3)	1 (0.7)	0	70 (23.7)	15 (5.1)	0	8 (25.0)	2 (6.3)	0	117 (24.6)	33 (6.9)	0
COGNITIVE EFFECTS	25 (16.8)	2 (1.3)	0	2 (1.4)	0	0	70 (23.7)	5 (1.7)	0	6 (18.8)	0	0	101 (21.2)	7 (1.5)	0
FATIGUE	17 (11.4)	1 (0.7)	0	31 (21.8)	1 (0.7)	0	49 (16.6)	1 (0.3)	0	3 (9.4)	0	0	69 (14.5)	2 (0.4)	0
MOOD EFFECTS	13 (8.7)	2 (1.3)	0	1 (0.7)	0	0	46 (15.6)	3 (1.0)	0	4 (12.5)	0	0	63 (13.2)	5 (1.1)	0
Diarrhoea	23 (15.4)	1 (0.7)	0	65 (45.8)	1 (0.7)	0	37 (12.5)	1 (0.3)	0	1 (3.1)	0	0	61 (12.8)	2 (0.4)	0
Alanine aminotransferase increased	24 (16.1)	2 (1.3)	0	45 (31.7)	5 (3.5)	1 (0.7)	33 (11.2)	2 (0.7)	0	1 (3.1)	0	0	58 (12.2)	4 (0.8)	0
Aspartate aminotransferase increased	19 (12.8)	3 (2.0)	0	38 (26.8)	4 (2.8)	0	37 (12.5)	1 (0.3)	0	2 (6.3)	0	0	58 (12.2)	4 (0.8)	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to any grade of Overall Lorlatinib 100-mg QD Pooled group.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily

Table 69. Adverse Drug Reactions in Patients Treated with Lorlatinib - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

System organ class and adverse reaction	Frequency category	All Grades %	Grades 3-4 %
Blood and lymphatic system disorders			
Anaemia	Very common	18.5	4.2
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	81.1	18.3
Hypertriglyceridaemia[b]	Very common	67.2	19.3
Hyperglycaemia	Common	9.2	3.2
Psychiatric disorders			
Mood effects[c]	Very common	21.0	1.5
Psychotic effects[d]	Common	6.5	0.4
Mental status changes	Common	2.0	1.7
Nervous system disorders			
Cognitive effects[e]	Very common	27.7	2.9
Peripheral neuropathy[f]	Very common	43.7	2.7
Headache	Very common	17.9	0.6
Speech effects[g]	Common	8.2	0.6
Eye disorders			
Vision disorder[h]	Very common	17.2	0.2
Vascular disorders			
Hypertension	Very common	13.0	6.1

Respiratory, thoracic and mediastinal disorders			
Pneumonitis[i]	Common	1.9	0.6
Gastrointestinal disorders			
Diarrhoea	Very common	22.9	1.5
Nausea	Very common	17.6	0.6
Constipation	Very common	17.4	0.2
Skin and subcutaneous tissue disorders			
Rash[j]	Very common	13.7	0.2
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	23.5	0.8
Myalgia[k]	Very common	19.3	0.2
General disorders and administration site conditions			
Oedema[l]	Very common	55.7	2.7
Fatigue[m]	Very common	27.3	1.3
Investigations			
Weight increased	Very common	30.9	10.1
Lipase increased	Very common	12.4	6.9
Amylase increased	Very common	11.3	2.7
Electrocardiogram PR prolongation	Uncommon	0.8	0

Adverse reactions that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.

[a] Hypercholesterolaemia (including blood cholesterol increased, hypercholesterolaemia).

[b] Hypertriglyceridaemia (including blood triglycerides increased, hypertriglyceridaemia).

[c] Mood effects (including affective disorder, affect lability, aggression, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, irritability, mania, mood altered, mood swings, panic attack, personality change, stress).

[d] Psychotic effects (including auditory hallucination, hallucination, visual hallucination).

[e] Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder). Within these effects, terms from SOC Nervous system disorders were more frequently reported than terms from SOC Psychiatric disorder.

[f] Peripheral neuropathy (including burning sensation, dysaesthesia, formication, gait disturbance, hypoaesthesia, motor dysfunction, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, sensory disturbance).

[g] Speech effects (dysarthria, slow speech, speech disorder).

[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

[i] Pneumonitis (including interstitial lung disease, lung opacity, pneumonitis).

[j] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).

[k] Myalgia (including musculoskeletal pain, myalgia).

[l] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).

[m] Fatigue (including asthenia, fatigue).

Serious adverse event/deaths/other significant events

SAEs

Table 70. Summary of serious TEAEs by MedDRA PT or cluster term and max CTCAE grade (any grade, grade 3 and 4) of ≥1% in decreasing freq. (all cause, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006						B7461001						Overall		
	Lorlatinib 100-mg QD (N=149)			Crizotinib 250-mg BID (N=142)			Lorlatinib Phase 1/2 100-mg QD (N=295)			Lorlatinib DDI 100-mg QD (N=32)			Lorlatinib 100-mg QD Pooled (N=476)		
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with Any Adverse Event	51 (34.2)	28 (18.8)	6 (4.0)	39 (27.5)	19 (13.4)	6 (4.2)	125 (42.4)	55 (18.6)	13 (4.4)	12 (37.5)	6 (18.8)	0	188 (39.5)	89 (18.7)	19 (4.0)
Disease progression	1 (0.7)	0	0	1 (0.7)	0	0	24 (8.1)	0	0	5 (15.6)	0	0	30 (6.3)	0	0
Pneumonia	7 (4.7)	2 (1.3)	1 (0.7)	5 (3.5)	3 (2.1)	1 (0.7)	13 (4.4)	10 (3.4)	0	1 (3.1)	1 (3.1)	0	21 (4.4)	13 (2.7)	1 (0.2)
Dyspnoea	4 (2.7)	4 (2.7)	0	0	0	0	9 (3.1)	7 (2.4)	2 (0.7)	1 (3.1)	1 (3.1)	0	14 (2.9)	12 (2.5)	2 (0.4)
Pyrexia	3 (2.0)	0	1 (0.7)	3 (2.1)	2 (1.4)	0	9 (3.1)	3 (1.0)	1 (0.3)	0	0	0	12 (2.5)	3 (0.6)	2 (0.4)
COGNITIVE EFFECTS	3 (2.0)	1 (0.7)	0	0	0	0	6 (2.0)	5 (1.7)	0	2 (6.3)	2 (6.3)	0	11 (2.3)	8 (1.7)	0
Fall	0	0	0	0	0	0	6 (2.0)	6 (2.0)	0	1 (3.1)	0	0	7 (1.5)	6 (1.3)	0
PNEUMONITIS	2 (1.3)	0	0	2 (1.4)	1 (0.7)	0	3 (1.0)	2 (0.7)	1 (0.3)	1 (3.1)	0	0	6 (1.3)	2 (0.4)	1 (0.2)
Respiratory failure	4 (2.7)	3 (2.0)	0	0	0	0	2 (0.7)	2 (0.7)	0	0	0	0	6 (1.3)	5 (1.1)	0
Embolism	0	0	0	0	0	0	5 (1.7)	3 (1.0)	0	0	0	0	5 (1.1)	3 (0.6)	0
Mental status changes	0	0	0	0	0	0	5 (1.7)	4 (1.4)	0	0	0	0	5 (1.1)	4 (0.8)	0
Pericardial effusion	2 (1.3)	1 (0.7)	0	1 (0.7)	0	0	3 (1.0)	2 (0.7)	0	0	0	0	5 (1.1)	3 (0.6)	0
Pleural effusion	2 (1.3)	1 (0.7)	0	2 (1.4)	1 (0.7)	1 (0.7)	3 (1.0)	3 (1.0)	0	0	0	0	5 (1.1)	4 (0.8)	0
Pulmonary embolism	1 (0.7)	0	0	2 (1.4)	1 (0.7)	0	3 (1.0)	3 (1.0)	0	1 (3.1)	0	1 (3.1)	5 (1.1)	3 (0.6)	1 (0.2)
Urinary tract infection	1 (0.7)	1 (0.7)	0	0	0	0	4 (1.4)	3 (1.0)	0	0	0	0	5 (1.1)	4 (0.8)	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to any grade of Overall Lorlatinib 100-mg QD Pooled group.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily
With any adverse events row included all patients without cutoff.

Table 71. Serious Adverse Drug Reactions in Patients Treated with lorviqua in Study B7461001 and B7461006

		Lorlatinib 100-mg QD Pooled (N=476)	
		All Grades	Grade 3 or 4
System Organ Class	Adverse Drug Reaction	n (%)	n (%)
	Patients with Any Adverse Event	35 (7.4)	25 (5.3)
Metabolism and nutrition disorders	Hypertriglyceridemia [b]	3 (0.6)	3 (0.6)
	Hypercholesterolemia [a]	2 (0.4)	2 (0.4)
Psychiatric disorders	Mental status changes	5 (1.1)	4 (0.8)
	Psychotic effects [d]	1 (0.2)	1 (0.2)
Nervous system disorders	Cognitive effects [f]	11 (2.3)	8 (1.7)
	Peripheral neuropathy [e]	3 (0.6)	0
	Speech effects [g]	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	Pneumonitis [i]	6 (1.3)	3 (0.6)
Gastrointestinal disorders	Diarrhoea	2 (0.4)	2 (0.4)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.2)	1 (0.2)
General disorders and administration site conditions	Edema [j]	3 (0.6)	3 (0.6)

Preferred terms (PTs) are listed according to MedDRA version 23.0.
Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in the table above. Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse reaction are indicated in parentheses, as listed below.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n/N=number of patients; SOC=system organ class.
a. Hypercholesterolemia (including blood cholesterol increased, Hypercholesterolemia).
b. Hypertriglyceridemia (including blood triglycerides increased, Hypertriglyceridemia).
c. Mood effects (including affective disorder, affect lability, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, irritability, mood altered, mood swings, stress).
d. Psychotic effects (including delusion, hallucination, hallucination auditory, hallucination visual).
e. Peripheral neuropathy (including, dysaesthesia, gait disturbance, hyposesthesia, muscular weakness, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, motor dysfunction).
f. Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: confusional state, delirium, disorientation). Within these effects, terms from SOC Nervous system disorders were more frequently reported than terms from SOC Psychiatric disorders.
g. Speech effects (including dysarthri, slow speech, speech disorder).
h. Vision disorder (including diplopia, photopsia, photophobia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).
i. Pneumonitis (including, pneumonitis, interstitial lung disease, lung infiltration).
j. Edema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
k. Fatigue (including asthenia, fatigue).

Deaths

Table 72. Lorlatinib summary of deaths - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149) n (%)	Crizotinib 250-mg BID (N=142) n (%)	Lorlatinib Phase 1/2 100-mg QD (N=295) n (%)	Lorlatinib DDI 100-mg QD (N=32) n (%)	100-mg QD Pooled (N=476) n (%)
Death	23 (15.4)	28 (19.7)	128 (43.4)	14 (43.8)	165 (34.7)
Cause of Death					
AE not related to study treatment	2 (1.3)	2 (1.4)	0	0	2 (0.4)
Disease progression	17 (11.4)	23 (16.2)	112 (38.0)	14 (43.8)	143 (30.0)
Other	1 (0.7)	1 (0.7)	8 (2.7)	0	9 (1.9)
Study treatment toxicity	2 (1.3)	0	0	0	2 (0.4)
Unknown	1 (0.7)	2 (1.4)	8 (2.7)	0	9 (1.9)
Deaths within 28 days after last dose of study treatment	6 (4.0)	8 (5.6)	40 (13.6)	5 (15.6)	51 (10.7)
Cause of Death					
AE not related to study treatment	2 (1.3)	2 (1.4)	0	0	2 (0.4)
Disease progression	2 (1.3)	5 (3.5)	34 (11.5)	5 (15.6)	41 (8.6)
Other	0	0	6 (2.0)	0	6 (1.3)
Study treatment toxicity	1 (0.7)	0	0	0	1 (0.2)
Unknown	1 (0.7)	1 (0.7)	0	0	1 (0.2)
Deaths within 30 days after first dose of study treatment	0	0	5 (1.7)	0	5 (1.1)
Cause of Death					
Disease progression	0	0	5 (1.7)	0	5 (1.1)

N=the number of patients in the safety analysis set within each treatment group and used as the denominator to calculate percentages.
BID=twice daily; QD=once daily

Table 73. Summary of TEAEs by MedDRA PT or Cluster Term and Max CTCAE Grade (Grade 5) in Decreasing Freq. (All Cause, Trt Rel, All Cycles) - Safety Analysis Set (Protocol B7461006)

	All Causalities		Treatment Related	
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)
Preferred AE Term/CLUSTER Term	Grade 5 n (%)	Grade 5 n (%)	Grade 5 n (%)	Grade 5 n (%)
Patients with Any Adverse Event	7 (4.7)	7 (4.9)	2 (1.3)	0
Cardiac failure acute	1 (0.7)	0	1 (0.7)	0
Death	1 (0.7)	1 (0.7)	0	0
Disease progression	1 (0.7)	1 (0.7)	0	0
Lung neoplasm malignant	1 (0.7)	0	0	0
Pneumonia	1 (0.7)	0	0	0
Pulmonary embolism	1 (0.7)	0	0	0
Respiratory failure	1 (0.7)	0	1 (0.7)	0
Clostridium difficile colitis	0	1 (0.7)	0	0

	All Causalities		Treatment Related	
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)
Preferred AE Term/CLUSTER Term	Grade 5 n (%)	Grade 5 n (%)	Grade 5 n (%)	Grade 5 n (%)
Malignant neoplasm progression	0	2 (1.4)	0	0
Neoplasm progression	0	1 (0.7)	0	0
Pericardial effusion	0	1 (0.7)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of Lorlatinib 100-mg QD group.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily
PFIZER CONFIDENTIAL Source Data: adae Output File: ./B746e_1L/B746_pool/adae_s063_16_imm Date of Generation: 27AUG2020 (01:25)
Included data of B7461006 (Cutoff Date: 20MAR2020 Snapshot Date: 26JUN2020).
Table 14.3.1.2.14.sub is for Pfizer internal use.

Other significant adverse events – Study 1006

Hypertension

Hypertension is a new safety finding for lorlatinib and considered an ADR. Hypertension was *more* frequent in the lorlatinib arm compared to the crizotinib arm:

- Lorlatinib arm: 18.1% (2.0% treatment-related)
- Crizotinib arm: 2.1% (0.7% treatment-related)

Grade 3 AEs only occurred in the lorlatinib arm (15 [10.1%]); one of the grade 3 events was treatment-related. There were no Grade 4 AEs.

Hypertension was manageable and there were no events of hypertension leading to permanent treatment discontinuation or dose reduction in the lorlatinib arm. Temporary treatment discontinuation occurred in 4 (2.7%) participants in the lorlatinib arm (all Grade 3) and in 1 (0.7%) participant in the crizotinib arm. Overall, 23/27 (85.2%) of participants were administered at least one concomitant anti-hypertensive medication, 19 participants without other intervention and 4 in combination with temporary treatment discontinuation. The median time to onset of anti-hypertensive medication was 62 days (range: 0-722). Of the participants with hypertension, 20/27 (74%) had an outcome of resolved; in 13/23 (56.5%) participants who were treated with anti-hypertensive medication, the event resolved with medication alone.

Hyperglycaemia

Hyperglycaemia is a new safety finding for lorlatinib, and considered an ADR. Hyperglycaemia was *more* frequent in the lorlatinib arm compared to the crizotinib arm:

- Lorlatinib arm: 10.1% all-causality and 5.4% treatment-related
- Crizotinib arm: 3.5 % all-causality and 1.4% treatment-related

Grade 3 AEs of hyperglycaemia occurred in the lorlatinib arm only (5 [3.4%]); 1 event was treatment-related. There were no Grade 4 AEs and no events of hyperglycaemia led to permanent treatment discontinuation or dose modifications.

Adverse events of Special interest (AESI) - Study 1006

Table 74. Summary of AESIs and OAEIs - Study 1006

	Any Grade, %	
Adverse Event of Special Interest	**Lorlatinib**	**Crizotinib**
AESIs Most Relevant to Lorlatinib		
HYPERCHOLESTEROLEMIA	70.5	3.5
HYPERTRIGLYCERIDEMIA	63.8	5.6
EDEMA	55.0	39.4
Weight gain	38.3	12.7
CNS-related effects		
COGNITIVE EFFECTS	21.5	5.6
MOOD EFFECTS	16.1	4.9
SPEECH EFFECTS	4.7	0
PSYCHOTIC EFFECTS	3.4	0
AV blockPPP[a]	2.7	0
AESIs Not Specific to Lorlatinib		
PERIPHERAL NEUROPATHY	33.6	14.8
Liver function tests increasedPPP[a]	20.8	37.3
VISION DISORDER	18.1	39.4
PancreatitisPPP[a]	15.4	18.3
QTc interval prolongationPPP[a]	3.4	5.6
PNEUMONITIS	1.3	2.8
OAEIs (CNS-related)		
SLEEP EFFECTS	11.4	9.9
Seizures	0	0
Mental status change	0	0

AESI - CNS-related effects

Table 75. Summary of cognitive effects AEs by MedDRA PT and Max CTCAE grade in decreasing freq. (all cause, trt rel, all cycles) – Overall pooled lorlatinib 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)					
	All-causality			Treatment-related		
Parameter/PT	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	132 (27.7)	14 (2.9)	0	101 (21.2)	7 (1.5)	0
Memory impairment	54 (11.3)	0	0	41 (8.6)	0	0
Amnesia	31 (6.5)	0	0	26 (5.5)	0	0
Cognitive disorder	27 (5.7)	4 (0.8)	0	24 (5.0)	3 (0.6)	0
Confusional state	26 (5.5)	8 (1.7)	0	13 (2.7)	3 (0.6)	0
Disturbance in attention	21 (4.4)	0	0	21 (4.4)	0	0
Delirium	6 (1.3)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Mental impairment	6 (1.3)	0	0	5 (1.1)	0	0
Attention deficit hyperactivity disorder	2 (0.4)	0	0	2 (0.4)	0	0
Disorientation	2 (0.4)	1 (0.2)	0	1 (0.2)	0	0
Dementia	1 (0.2)	0	0	0	0	0
Reading disorder	1 (0.2)	0	0	0	0	0
Any SAE	11 (2.3)	8 (1.7)	0	5 (1.1)	4 (0.8)	0
Confusional state	6 (1.3)	5 (1.1)	0	2 (0.4)	2 (0.4)	0
Cognitive disorder	3 (0.6)	2 (0.4)	0	2 (0.4)	1 (0.2)	0
Delirium	2 (0.4)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Any AE Leading to Permanent Treatment Discontinuation	4 (0.8)	3 (0.6)	0	4 (0.8)	3 (0.6)	0
Confusional state	3 (0.6)	2 (0.4)	0	3 (0.6)	2 (0.4)	0
Cognitive disorder	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Any AE Leading to Temporary Treatment Discontinuation	25 (5.3)	4 (0.8)	0	21 (4.4)	1 (0.2)	0
Cognitive disorder	7 (1.5)	0	0	7 (1.5)	0	0
Confusional state	6 (1.3)	3 (0.6)	0	4 (0.8)	1 (0.2)	0
Amnesia	5 (1.1)	0	0	5 (1.1)	0	0
Memory impairment	5 (1.1)	0	0	5 (1.1)	0	0
Disturbance in attention	4 (0.8)	0	0	4 (0.8)	0	0
Delirium	2 (0.4)	0	0	0	0	0
Disorientation	2 (0.4)	1 (0.2)	0	1 (0.2)	0	0
Any AE Leading to Dose Reduction	19 (4.0)	3 (0.6)	0	16 (3.4)	1 (0.2)	0
Cognitive disorder	8 (1.7)	1 (0.2)	0	8 (1.7)	1 (0.2)	0
Amnesia	3 (0.6)	0	0	3 (0.6)	0	0
Memory impairment	3 (0.6)	0	0	3 (0.6)	0	0
Confusional state	2 (0.4)	1 (0.2)	0	0	0	0
Disorientation	2 (0.4)	1 (0.2)	0	1 (0.2)	0	0
Mental impairment	1 (0.2)	0	0	1 (0.2)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of any grade.
MedDRA v23.0 coding dictionary applied.
AE=adverse event; QD=once daily; PT=preferred term; SAE=Serious adverse event;
COGNITIVE EFFECTS was any event having a HLGT that equalled to Cognitive and attention disorders and disturbances or Deliria (incl confusion) or Mental impairment disorders.

Table 76. Summary of mood effects AEs by MedDRA PT and Max CTCAE grade in decreasing freq. (all cause, trt rel, all cycles) – Overall pooled lorlatinib 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)					
	All-causality			Treatment-related		
Parameter/PT	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	100 (21.0)	7 (1.5)	0	63 (13.2)	5 (1.1)	0
Anxiety	31 (6.5)	1 (0.2)	0	10 (2.1)	0	0
Depression	24 (5.0)	2 (0.4)	0	15 (3.2)	2 (0.4)	0
Irritability	21 (4.4)	4 (0.8)	0	20 (4.2)	3 (0.6)	0
Affect lability	11 (2.3)	0	0	8 (1.7)	0	0
Affective disorder	8 (1.7)	0	0	8 (1.7)	0	0
Agitation	8 (1.7)	1 (0.2)	0	4 (0.8)	1 (0.2)	0
Mood altered	6 (1.3)	0	0	4 (0.8)	0	0
Personality change	5 (1.1)	0	0	4 (0.8)	0	0
Depressed mood	4 (0.8)	0	0	2 (0.4)	0	0
Mood swings	4 (0.8)	0	0	3 (0.6)	0	0
Euphoric mood	3 (0.6)	0	0	3 (0.6)	0	0
Mania	3 (0.6)	0	0	2 (0.4)	0	0
Aggression	2 (0.4)	0	0	2 (0.4)	0	0
Anger	2 (0.4)	0	0	2 (0.4)	0	0
Stress	2 (0.4)	0	0	0	0	0
Bipolar I disorder	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Depressive symptom	1 (0.2)	0	0	1 (0.2)	0	0
Panic attack	1 (0.2)	0	0	1 (0.2)	0	0
Any SAE	0	0	0	0	0	0
Any AE Leading to Permanent Treatment Discontinuation	2 (0.4)	1 (0.2)	0	1 (0.2)	0	0
Affect lability	1 (0.2)	0	0	1 (0.2)	0	0
Anxiety	1 (0.2)	1 (0.2)	0	0	0	0
Any AE Leading to Temporary Treatment Discontinuation	15 (3.2)	4 (0.8)	0	14 (2.9)	3 (0.6)	0
Depression	4 (0.8)	1 (0.2)	0	4 (0.8)	1 (0.2)	0
Anxiety	3 (0.6)	0	0	3 (0.6)	0	0
Affect lability	2 (0.4)	0	0	2 (0.4)	0	0
Irritability	2 (0.4)	2 (0.4)	0	1 (0.2)	1 (0.2)	0
Affective disorder	1 (0.2)	0	0	1 (0.2)	0	0
Agitation	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Anger	1 (0.2)	0	0	1 (0.2)	0	0
Bipolar I disorder	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Mania	1 (0.2)	0	0	1 (0.2)	0	0
Personality change	1 (0.2)	0	0	1 (0.2)	0	0
Any AE Leading to Dose Reduction	14 (2.9)	3 (0.6)	0	14 (2.9)	3 (0.6)	0
Affect lability	3 (0.6)	0	0	3 (0.6)	0	0
Depression	3 (0.6)	2 (0.4)	0	3 (0.6)	2 (0.4)	0
Irritability	2 (0.4)	2 (0.4)	0	2 (0.4)	2 (0.4)	0
Agitation	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Anger	1 (0.2)	0	0	1 (0.2)	0	0
Anxiety	1 (0.2)	0	0	1 (0.2)	0	0
Bipolar I disorder	1 (0.2)	0	0	1 (0.2)	0	0
Depressive symptom	1 (0.2)	0	0	1 (0.2)	0	0
Mania	1 (0.2)	0	0	1 (0.2)	0	0
Mood swings	1 (0.2)	0	0	1 (0.2)	0	0
Personality change	1 (0.2)	0	0	1 (0.2)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of any grade.
MedDRA v23.0 coding dictionary applied.
AE=adverse event; QD=once daily; PT=preferred term; SAE=Serious adverse event;
MOOD EFFECTS was any event having a HLGT that equalled to Anxiety disorders and symptoms or Depressed mood disorders and disturbances or Manic and bipolar mood disorders and disturbances or Mood disorders and disturbances NEC or Personality disorders and disturbances in behaviour.

Table 77. Summary of speech effects AEs by MedDRA PT and Max CTCAE grade in decreasing freq. (all cause, trt rel, all cycles) – Overall pooled lorlatinib 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)					
	All-causality			Treatment-related		
Parameter/PT	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	39 (8.2)	3 (0.6)	0	31 (6.5)	2 (0.4)	0
Dysarthria	19 (4.0)	1 (0.2)	0	13 (2.7)	0	0
Slow speech	11 (2.3)	1 (0.2)	0	11 (2.3)	1 (0.2)	0
Speech disorder	9 (1.9)	1 (0.2)	0	7 (1.5)	1 (0.2)	0
Any SAE	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Speech disorder	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Any AE Leading to Permanent Treatment Discontinuation	0	0	0	0	0	0
Any AE Leading to Temporary Treatment Discontinuation	4 (0.8)	1 (0.2)	0	3 (0.6)	1 (0.2)	0
Dysarthria	2 (0.4)	0	0	2 (0.4)	0	0
Speech disorder	2 (0.4)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Any AE Leading to Dose Reduction	3 (0.6)	0	0	3 (0.6)	0	0
Dysarthria	3 (0.6)	0	0	3 (0.6)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of any grade.
MedDRA v23.0 coding dictionary applied.
AE=adverse event; QD=once daily; PT=preferred term; SAE=Serious adverse event;
SPEECH EFFECTS was any event having a HLT that equalled to Speech and language abnormalities.

Table 78. Summary of psychotic effects AEs by MedDRA PT and Max CTCAE grade in decreasing freq. (all cause, trt rel, all cycles) – Overall pooled lorlatinib 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)					
	All-causality			Treatment-related		
Parameter/PT	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	33 (6.9)	2 (0.4)	1 (0.2)	27 (5.7)	1 (0.2)	1 (0.2)
Hallucination	14 (2.9)	0	0	12 (2.5)	0	0
Hallucination, auditory	10 (2.1)	1 (0.2)	0	8 (1.7)	1 (0.2)	0
Hallucination, visual	10 (2.1)	1 (0.2)	0	7 (1.5)	0	0
Delusion	2 (0.4)	0	0	2 (0.4)	0	0
Schizophreniform disorder	1 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Any SAE	1 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Schizophreniform disorder	1 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Any AE Leading to Permanent Treatment Discontinuation	2 (0.4)	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Hallucination, auditory	1 (0.2)	0	0	1 (0.2)	0	0
Hallucination, visual	1 (0.2)	0	0	1 (0.2)	0	0
Schizophreniform disorder	1 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.2)
Any AE Leading to Temporary Treatment Discontinuation	8 (1.7)	2 (0.4)	0	6 (1.3)	1 (0.2)	0
Hallucination	3 (0.6)	0	0	3 (0.6)	0	0
Hallucination, auditory	2 (0.4)	1 (0.2)	0	2 (0.4)	1 (0.2)	0
Hallucination, visual	2 (0.4)	1 (0.2)	0	0	0	0
Delusion	1 (0.2)	0	0	1 (0.2)	0	0
Any AE Leading to Dose Reduction	6 (1.3)	1 (0.2)	0	5 (1.1)	1 (0.2)	0
Hallucination	3 (0.6)	0	0	3 (0.6)	0	0
Hallucination, auditory	2 (0.4)	1 (0.2)	0	2 (0.4)	1 (0.2)	0
Hallucination, visual	2 (0.4)	0	0	1 (0.2)	0	0
Delusion	1 (0.2)	0	0	1 (0.2)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of any grade.
MedDRA v23.0 coding dictionary applied.
AE=adverse event; QD=once daily; PT=preferred term; SAE=Serious adverse event;
PSYCHOTIC EFFECTS was any event having a PT that belonged to SMQ narrow Psychosis and psychotic disorders or equalled to Psychotic symptom.

AESI- Peripheral neuropathy

Table 79. Summary of peripheral neuropathy AEs by MedDRA PT and Max CTCAE grade in decreasing freq. (all cause, trt rel, all cycles) – Overall pooled lorlatinib 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)					
	All-causality			Treatment-related		
Parameter/PT	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	208 (43.7)	13 (2.7)	0	144 (30.3)	9 (1.9)	0
Paraesthesia	71 (14.9)	3 (0.6)	0	47 (9.9)	1 (0.2)	0
Neuropathy peripheral	57 (12.0)	6 (1.3)	0	47 (9.9)	6 (1.3)	0
Peripheral sensory neuropathy	39 (8.2)	1 (0.2)	0	35 (7.4)	1 (0.2)	0
Muscular weakness	24 (5.0)	1 (0.2)	0	3 (0.6)	0	0
Gait disturbance	19 (4.0)	1 (0.2)	0	4 (0.8)	0	0
Hypoaesthesia	19 (4.0)	0	0	12 (2.5)	0	0
Dysaesthesia	12 (2.5)	0	0	7 (1.5)	0	0
Neuralgia	8 (1.7)	1 (0.2)	0	4 (0.8)	1 (0.2)	0
Neurotoxicity	3 (0.6)	0	0	3 (0.6)	0	0
Motor dysfunction	2 (0.4)	0	0	1 (0.2)	0	0
Peripheral motor neuropathy	2 (0.4)	0	0	2 (0.4)	0	0
Peroneal nerve palsy	2 (0.4)	0	0	0	0	0
Burning sensation	1 (0.2)	0	0	1 (0.2)	0	0
Formication	1 (0.2)	0	0	1 (0.2)	0	0
Sensory disturbance	1 (0.2)	0	0	0	0	0
Any SAE	3 (0.6)	0	0	1 (0.2)	0	0
Gait disturbance	1 (0.2)	0	0	0	0	0
Muscular weakness	1 (0.2)	0	0	0	0	0
Peripheral sensory neuropathy	1 (0.2)	0	0	1 (0.2)	0	0
Any AE Leading to Permanent Treatment Discontinuation	3 (0.6)	2 (0.4)	0	2 (0.4)	1 (0.2)	0
Hypoaesthesia	1 (0.2)	0	0	1 (0.2)	0	0
Neuropathy peripheral	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Paraesthesia	1 (0.2)	1 (0.2)	0	0	0	0
Any AE Leading to Temporary Treatment Discontinuation	19 (4.0)	5 (1.1)	0	15 (3.2)	4 (0.8)	0
Paraesthesia	6 (1.3)	2 (0.4)	0	5 (1.1)	1 (0.2)	0
Peripheral sensory neuropathy	4 (0.8)	0	0	4 (0.8)	0	0
Neuropathy peripheral	3 (0.6)	2 (0.4)	0	2 (0.4)	2 (0.4)	0
Gait disturbance	2 (0.4)	0	0	0	0	0
Dysaesthesia	1 (0.2)	0	0	1 (0.2)	0	0
Hypoaesthesia	1 (0.2)	0	0	1 (0.2)	0	0
Neuralgia	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Neurotoxicity	1 (0.2)	0	0	1 (0.2)	0	0
Peripheral motor neuropathy	1 (0.2)	0	0	1 (0.2)	0	0
Any AE Leading to Dose Reduction	22 (4.6)	8 (1.7)	0	20 (4.2)	7 (1.5)	0
Neuropathy peripheral	9 (1.9)	4 (0.8)	0	9 (1.9)	4 (0.8)	0
Paraesthesia	6 (1.3)	2 (0.4)	0	4 (0.8)	1 (0.2)	0
Peripheral sensory neuropathy	3 (0.6)	1 (0.2)	0	3 (0.6)	1 (0.2)	0
Hypoaesthesia	2 (0.4)	0	0	2 (0.4)	0	0
Gait disturbance	1 (0.2)	0	0	1 (0.2)	0	0
Neuralgia	1 (0.2)	1 (0.2)	0	1 (0.2)	1 (0.2)	0
Neurotoxicity	1 (0.2)	0	0	1 (0.2)	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of any grade.
MedDRA v23.0 coding dictionary applied.
AE=adverse event; QD=once daily; PT=preferred term; SAE=Serious adverse event;
PERIPHERAL NEUROPATHY was any event having a PT that belonged to SMQ Peripheral neuropathy.

Laboratory findings

Table 80. Lorlatinib shift summary results of labs from baseline maximum NCI-CTCAE Grade ≤2 to Grade 3 or 4 (Haematology, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006						B7461001						Overall		
	Lorlatinib 100-mg QD			Crizotinib 250-mg BID			Lorlatinib Phase 1/2 100-mg QD			Lorlatinib DDI 100-mg QD			Lorlatinib 100-mg QD Pooled		
Parameter	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)
ANEMIA	149	3 (2.0)	NA	141	4 (2.8)	NA	292	16 (5.5)	NA	32	1 (3.1)	NA	473	20 (4.2)	NA
HEMOGLOBIN INCREASED	149	0	NA	141	0	NA	292	0	NA	32	0	NA	473	0	NA
LYMPHOCYTE COUNT DECREASED	149	2 (1.3)	2 (1.3)	141	7 (5.0)	1 (0.7)	291	10 (3.4)	1 (0.3)	32	1 (3.1)	0	472	13 (2.8)	3 (0.6)
LYMPHOCYTE COUNT INCREASED	149	0	NA	141	0	NA	291	0	NA	32	0	NA	472	0	NA
NEUTROPHIL COUNT DECREASED	149	1 (0.7)	1 (0.7)	141	19 (13.5)	4 (2.8)	291	1 (0.3)	3 (1.0)	32	0	0	472	2 (0.4)	4 (0.8)
PLATELET COUNT DECREASED	149	0	0	141	1 (0.7)	0	292	0	2 (0.7)	32	0	0	473	0	2 (0.4)
WHITE BLOOD CELL DECREASED	149	0	0	141	5 (3.5)	0	292	2 (0.7)	1 (0.3)	32	0	0	473	2 (0.4)	1 (0.2)

Baseline was defined as the last evaluation prior to the first dose of study treatment.
N=the number of patients who had at least one on-study assessment for the parameter of interest.
n=the number of patients whose lab results met the CTCAE Grade criteria.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
BID=twice daily; QD=once daily.
CTCAE v4.03 applied.
NA: CTCAE grade not defined.

Table 81. Lorlatinib shift summary results of labs from baseline maximum NCI-CTCAE Grade ≤2 to Grade 3 or 4 (chemistries, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	B7461006						B7461001						Overall		
	Lorlatinib 100-mg QD			Crizotinib 250-mg BID			Lorlatinib Phase 1/2 100-mg QD			Lorlatinib DDI 100-mg QD			Lorlatinib 100-mg QD Pooled		
Parameter	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)
ALANINE AMINOTRANSFERASE INCREASED	149	4 (2.7)	0	141	5 (3.5)	1 (0.7)	292	3 (1.0)	2 (0.7)	32	0	0	473	7 (1.5)	2 (0.4)
ALKALINE PHOSPHATASE INCREASED	149	0	0	141	1 (0.7)	0	292	5 (1.7)	0	32	1 (3.1)	0	473	6 (1.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	149	3 (2.0)	0	141	4 (2.8)	1 (0.7)	292	4 (1.4)	2 (0.7)	32	1 (3.1)	0	473	8 (1.7)	2 (0.4)
BLOOD BILIRUBIN INCREASED	149	0	0	141	0	0	292	1 (0.3)	1 (0.3)	32	1 (3.1)	0	473	2 (0.4)	1 (0.2)
CPK INCREASED	149	3 (2.0)	0	141	5 (3.5)	2 (1.4)	23	2 (8.7)	1 (4.3)	2	0	0	174	5 (2.9)	1 (0.6)
CREATININE INCREASED	149	1 (0.7)	0	141	3 (2.1)	0	292	1 (0.3)	0	32	0	0	473	2 (0.4)	0
GGT INCREASED	149	9 (6.0)	0	141	8 (5.7)	1 (0.7)	18	3 (16.7)	0	1	0	0	168	12 (7.1)	0
HYPERCALCEMIA	149	0	0	141	0	0	291	1 (0.3)	0	32	0	0	472	1 (0.2)	0
HYPERGLYCEMIA	149	9 (6.0)	1 (0.7)	141	3 (2.1)	0	292	14 (4.8)	1 (0.3)	32	2 (6.3)	0	473	25 (5.3)	2 (0.4)
HYPERKALEMIA	149	2 (1.3)	0	141	3 (2.1)	0	292	3 (1.0)	1 (0.3)	32	0	0	473	5 (1.1)	1 (0.2)
HYPERMAGNESEMIA	149	2 (1.3)	0	141	1 (0.7)	0	291	1 (0.3)	0	32	0	0	472	3 (0.6)	0
HYPERNATREMIA	149	0	0	141	0	0	292	0	0	32	0	0	473	0	0
HYPOALBUMINEMIA	149	1 (0.7)	NA	141	9 (6.4)	NA	291	4 (1.4)	NA	32	0	NA	472	5 (1.1)	NA
HYPOCALCEMIA	149	1 (0.7)	0	141	0	0	291	1 (0.3)	0	32	0	0	472	2 (0.4)	0
HYPOGLYCEMIA	149	0	0	141	0	1 (0.7)	292	0	0	32	0	0	473	0	0
HYPOKALEMIA	149	0	0	141	3 (2.1)	0	292	5 (1.7)	1 (0.3)	32	0	0	473	5 (1.1)	1 (0.2)
HYPOMAGNESEMIA	149	0	0	141	0	0	291	0	0	32	0	0	472	0	0
HYPONATREMIA	149	5 (3.4)	0	141	10 (7.1)	1 (0.7)	292	8 (2.7)	0	32	3 (9.4)	0	473	16 (3.4)	0
HYPOPHOSPHATEMIA	149	3 (2.0)	0	141	4 (2.8)	0	291	10 (3.4)	0	32	0	0	472	13 (2.8)	0
LIPASE INCREASED	149	8 (5.4)	3 (2.0)	141	6 (4.3)	1 (0.7)	290	27 (9.3)	7 (2.4)	32	0	0	471	35 (7.4)	10 (2.1)
SERUM AMYLASE INCREASED	148	1 (0.7)	0	141	2 (1.4)	0	284	13 (4.6)	1 (0.4)	32	1 (3.1)	0	464	15 (3.2)	1 (0.2)

Baseline was defined as the last evaluation prior to the first dose of study treatment.
N=the number of patients who had at least one on-study assessment for the parameter of interest.
n=the number of patients whose lab results met the CTCAE Grade criteria.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
BID=twice daily; QD=once daily.
CTCAE v4.03 applied.
NA: CTCAE grade not defined.

Safety in special populations

Intrinsic factors

Table 82. Summary of AEs by Age Subgroup

	Lorlatinib Arm		Crizotinib Arm	
	<65 years n=90	≥65 years n=59	<65 years n=100	≥65 years n=42
Any Grade	100.0%	100.0%	99.0%	97.6%
Grade 3	57.8%	59.3%	39.0%	66.7%
Grade 4	14.4%	13.6%	9.0%	7.1%

Source: 1006 Table 14.3.1.2.2.7

Table 83. Summary of AEs by Gender Subgroup

	Lorlatinib Arm		Crizotinib Arm	
	Female n=84	Male n=65	Female n=87	Male n=55
Any Grade	100%	100%	100%	96.4%
Grade 3	61.9%	53.8%	49.4%	43.6%
Grade 4	10.7%	18.5%	6.9%	10.9%

Source: 1006 Table 14.3.1.2.2.8

Table 84. Summary of AEs by Race Subgroup

	Lorlatinib Arm		Crizotinib Arm	
	Asian n=66	Non-Asian n=83	Asian n=64	Non-Asian n=78
Any Grade	100%	100%	100%	97.4%
Grade 3	56.1%	60.2%	45.3%	48.7%
Grade 4	19.7%	9.6%	12.5%	5.1%

Source: 1006 Table 14.3.1.2.2.9

Extrinsic Factors

There is no new information regarding extrinsic factors based on biopharmaceutical studies compared to the initial MAA submission.

Safety related to drug-drug interactions and other interactions

Please refer to the clinical pharmacology section.

Discontinuation due to adverse events

Table 85. TEAEs leading to permanent discontinuation by MedDRA PT or cluster term and Max CTCAE grade (any grade) of ≥ 1% in decreasing frequency (all cause, trt rel, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	All Causalities				
	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	Lorlatinib 100-mg QD Pooled (N=476)
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)
Patients with Any Adverse Event	10 (6.7)	13 (9.2)	30 (10.2)	4 (12.5)	44 (9.2)

	Treatment Related				
	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	Lorlatinib 100-mg QD Pooled (N=476)
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)
Patients with Any Adverse Event	7 (4.7)	7 (4.9)	10 (3.4)	3 (9.4)	20 (4.2)

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of Overall Lorlatinib 100-mg QD Pooled group.
With any adverse events row included all patients without cutoff.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily

Table 86. TEAEs leading to permanent discontinuation by MedDRA PT or cluster (PTs) and Max CTCAE grade in decreasing frequency (all cause) - Overall pooled 100 mg QD group, safety analysis set (Protocols B7461001, B7461006)

	Overall Lorlatinib 100-mg QD Pooled (N=476)						
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing or Unknown	Total
Preferred AE Term/CLUSTER Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with Any Adverse Event	1 (0.2)	8 (1.7)	20 (4.2)	9 (1.9)	6 (1.3)	0	44 (9.2)
COGNITIVE EFFECTS [e]	0	1 (0.2)	3 (0.6)	0	0	0	4 (0.8)
Confusional state	0	1 (0.2)	2 (0.4)	0	0	0	3 (0.6)
Cognitive disorder	0	0	1 (0.2)	0	0	0	1 (0.2)
PERIPHERAL NEUROPATHY [d]	0	1 (0.2)	2 (0.4)	0	0	0	3 (0.6)
Hypoaesthesia	0	1 (0.2)	0	0	0	0	1 (0.2)
Neuropathy peripheral	0	0	1 (0.2)	0	0	0	1 (0.2)
Paraesthesia	0	0	1 (0.2)	0	0	0	1 (0.2)
PNEUMONITIS [l]	0	2 (0.4)	0	1 (0.2)	0	0	3 (0.6)
Pneumonitis	0	2 (0.4)	0	1 (0.2)	0	0	3 (0.6)
Acute respiratory failure	0	0	1 (0.2)	1 (0.2)	0	0	2 (0.4)
Dyspnoea	0	0	1 (0.2)	1 (0.2)	0	0	2 (0.4)
MOOD EFFECTS [f]	0	1 (0.2)	1 (0.2)	0	0	0	2 (0.4)
Affect lability	0	1 (0.2)	0	0	0	0	1 (0.2)
Anxiety	0	0	1 (0.2)	0	0	0	1 (0.2)
PSYCHOTIC EFFECTS [h]	0	1 (0.2)	0	1 (0.2)	0	0	2 (0.4)
Hallucination, auditory	0	1 (0.2)	0	0	0	0	1 (0.2)
Hallucination, visual	0	1 (0.2)	0	0	0	0	1 (0.2)
Schizophreniform disorder	0	0	0	1 (0.2)	0	0	1 (0.2)
Respiratory failure	0	0	0	2 (0.4)	0	0	2 (0.4)
Acute leukaemia	0	1 (0.2)	0	0	0	0	1 (0.2)
Acute myeloid leukaemia	0	0	1 (0.2)	0	0	0	1 (0.2)
Acute myocardial infarction	0	0	0	0	1 (0.2)	0	1 (0.2)
Asphyxia	0	0	0	0	1 (0.2)	0	1 (0.2)
Brain compression	0	0	0	1 (0.2)	0	0	1 (0.2)
Cardiac failure	0	0	1 (0.2)	0	0	0	1 (0.2)
Chronic obstructive pulmonary disease	0	0	1 (0.2)	0	0	0	1 (0.2)
Disease progression	0	0	0	0	1 (0.2)	0	1 (0.2)
Dizziness	1 (0.2)	0	0	0	0	0	1 (0.2)
EDEMA [c]	0	0	1 (0.2)	0	0	0	1 (0.2)
Peripheral swelling	0	0	1 (0.2)	0	0	0	1 (0.2)
Embolism	0	0	0	0	1 (0.2)	0	1 (0.2)
Follicle centre lymphoma, follicular grade I, II, III	0	0	1 (0.2)	0	0	0	1 (0.2)
Headache	0	1 (0.2)	0	0	0	0	1 (0.2)
Hydrocephalus	0	0	1 (0.2)	0	0	0	1 (0.2)
Hyperlipidaemia	0	0	1 (0.2)	0	0	0	1 (0.2)
Hypoxia	0	0	0	1 (0.2)	0	0	1 (0.2)
Left ventricular dysfunction	0	0	1 (0.2)	0	0	0	1 (0.2)
Leukocytosis	0	0	1 (0.2)	0	0	0	1 (0.2)
Loss of consciousness	0	0	0	1 (0.2)	0	0	1 (0.2)
Mental status changes	0	0	1 (0.2)	0	0	0	1 (0.2)
Myalgia	0	1 (0.2)	0	0	0	0	1 (0.2)
Myocardial infarction	0	0	0	0	1 (0.2)	0	1 (0.2)
Parkinsonian gait	0	1 (0.2)	0	0	0	0	1 (0.2)
Pneumonia	0	0	0	0	1 (0.2)	0	1 (0.2)
Proteinuria	0	0	1 (0.2)	0	0	0	1 (0.2)
Renal cyst haemorrhage	0	0	1 (0.2)	0	0	0	1 (0.2)
SLEEP EFFECTS [j]	0	0	0	1 (0.2)	0	0	1 (0.2)
Nightmare	0	0	0	1 (0.2)	0	0	1 (0.2)
Seizure	0	0	1 (0.2)	0	0	0	1 (0.2)
Thalamus haemorrhage	0	0	0	1 (0.2)	0	0	1 (0.2)
Thoracic vertebral fracture	0	0	1 (0.2)	0	0	0	1 (0.2)
Thrombocytopenia	0	0	1 (0.2)	0	0	0	1 (0.2)
Tinnitus	0	1 (0.2)	0	0	0	0	1 (0.2)
Vomiting	0	0	1 (0.2)	0	0	0	1 (0.2)

a. HYPERCHOLESTEROLEMIA was any event having a PT that equalled to Blood cholesterol increased or Hypercholesterolaemia.
b. HYPERTRIGLYCERIDEMIA was any event having a PT that equalled to Blood triglycerides increased or Hypertriglyceridaemia.
c. EDEMA was any event having a PT that equalled to Generalised oedema or Oedema or Oedema peripheral or Peripheral swelling or Swelling.
d. PERIPHERAL NEUROPATHY was any event having a PT that belonged to SMQ Peripheral neuropathy.
e. COGNITIVE EFFECTS was any event having a HLGT that equalled to Cognitive and attention disorders and disturbances or Deliria (incl confusion) or Mental impairment disorders.
f. MOOD EFFECTS was any event having a HLGT that equalled to Anxiety disorders and symptoms or Depressed mood disorders and disturbances or Manic and bipolar mood disorders and disturbances or Mood disorders and disturbances NEC or Personality disorders and disturbances in behaviour.
g. SPEECH EFFECTS was any event having a HLT that equalled to Speech and language abnormalities.
h. PSYCHOTIC EFFECTS was any event having a PT that belonged to SMQ narrow Psychosis and psychotic disorders or equalled to Psychotic symptom.
i. VISION DISORDER was any event having a PT that equalled to Chromatopsia or Diplopia or Halo vision or Photophobia or Photopsia or Vision blurred or Visual acuity reduced or Visual brightness or Visual impairment or Visual perseveration or Vitreous floaters.
j. SLEEP EFFECTS was any event having a PT that equalled to Abnormal dreams or Insomnia or Nightmare or Sleep disorder or Sleep talking or Somnambulism.
k. FATIGUE was any event having a PT that equalled to Asthenia or Fatigue.
l. PNEUMONITIS was any event having a PT that belonged to SMQ Interstitial lung disease.

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to Total.
MedDRA v23.0 coding dictionary applied.
QD=once daily

Dose-reductions or interruptions due to AEs

Table 87. Summary of TEAEs leading to dose interruptions by MedDRA PT or cluster term and Max CTCAE grade (any grade) of ≥ 2% in decreasing frequency (all cause, trt rel, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	All Causalities					Treatment Related				
	B7461006		B7461001		Overall	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	Lorlatinib 100-mg QD Pooled (N=476)	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	Lorlatinib 100-mg QD Pooled (N=476)
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)
Patients with Any Adverse Event	73 (49.0)	67 (47.2)	158 (53.6)	14 (43.8)	245 (51.5)	51 (34.2)	47 (33.1)	104 (35.3)	10 (31.3)	165 (34.7)
HYPERTRIGLYCERIDEMIA	11 (7.4)	0	19 (6.4)	3 (9.4)	33 (6.9)	11 (7.4)	0	19 (6.4)	3 (9.4)	33 (6.9)
EDEMA	8 (5.4)	2 (1.4)	18 (6.1)	1 (3.1)	27 (5.7)	8 (5.4)	1 (0.7)	17 (5.8)	1 (3.1)	26 (5.5)
COGNITIVE EFFECTS	6 (4.0)	0	16 (5.4)	3 (9.4)	25 (5.3)	5 (3.4)	0	15 (5.1)	1 (3.1)	21 (4.4)
Pneumonia	7 (4.7)	5 (3.5)	13 (4.4)	1 (3.1)	21 (4.4)	0	0	1 (0.3)	0	1 (0.2)
PERIPHERAL NEUROPATHY	3 (2.0)	1 (0.7)	14 (4.7)	2 (6.3)	19 (4.0)	2 (1.3)	0	12 (4.1)	1 (3.1)	15 (3.2)
HYPERCHOLESTEROLEMIA	5 (3.4)	0	11 (3.7)	2 (6.3)	18 (3.8)	5 (3.4)	0	11 (3.7)	2 (6.3)	18 (3.8)
Lipase increased	3 (2.0)	2 (1.4)	13 (4.4)	0	16 (3.4)	3 (2.0)	2 (1.4)	10 (3.4)	0	13 (2.7)
MOOD EFFECTS	5 (3.4)	0	9 (3.1)	1 (3.1)	15 (3.2)	5 (3.4)	0	8 (2.7)	1 (3.1)	14 (2.9)
Diarrhoea	3 (2.0)	2 (1.4)	8 (2.7)	1 (3.1)	12 (2.5)	1 (0.7)	2 (1.4)	5 (1.7)	0	6 (1.3)
Amylase increased	1 (0.7)	1 (0.7)	8 (2.7)	1 (3.1)	10 (2.1)	1 (0.7)	1 (0.7)	4 (1.4)	0	5 (1.1)
Hypertension	4 (2.7)	1 (0.7)	6 (2.0)	0	10 (2.1)	0	0	3 (1.0)	0	3 (0.6)
Pyrexia	4 (2.7)	2 (1.4)	5 (1.7)	1 (3.1)	10 (2.1)	0	0	0	0	0

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of Overall Lorlatinib 100-mg QD Pooled group.
With any adverse events row included all patients without cutoff.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily

Table 88. Summary of TEAEs leading to dose reductions by MedDRA PT or cluster term and Max CTCAE grade (any grade) of ≥ 2% in decreasing frequency (all cause, trt rel, all cycles) - Overall pooled, safety analysis set (Protocols B7461001, B7461006)

	All Causalities					Treatment Related				
	B7461006		B7461001		Overall	B7461006		B7461001		Overall
	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Phase 1/2 100-mg QD (N=295)	DDI 100-mg QD (N=32)	100-mg QD Pooled (N=476)	Lorlatinib 100-mg QD (N=149)	Crizotinib 250-mg BID (N=142)	Lorlatinib Phase 1/2 100-mg QD (N=295)	Lorlatinib DDI 100-mg QD (N=32)	100-mg QD Pooled (N=476)
Preferred AE Term/CLUSTER Term	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)	Any Grade n (%)
Patients with Any Adverse Event	31 (20.8)	22 (15.5)	75 (25.4)	11 (34.4)	117 (24.6)	29 (19.5)	20 (14.1)	70 (23.7)	7 (21.9)	106 (22.3)
EDEMA	8 (5.4)	5 (3.5)	18 (6.1)	0	26 (5.5)	8 (5.4)	5 (3.5)	18 (6.1)	0	26 (5.5)
PERIPHERAL NEUROPATHY	5 (3.4)	0	14 (4.7)	3 (9.4)	22 (4.6)	5 (3.4)	0	13 (4.4)	2 (6.3)	20 (4.2)
COGNITIVE EFFECTS	3 (2.0)	0	13 (4.4)	3 (9.4)	19 (4.0)	3 (2.0)	0	12 (4.1)	1 (3.1)	16 (3.4)
MOOD EFFECTS	3 (2.0)	0	10 (3.4)	1 (3.1)	14 (2.9)	3 (2.0)	0	10 (3.4)	1 (3.1)	14 (2.9)
HYPERTRIGLYCERIDEMIA	6 (4.0)	0	6 (2.0)	1 (3.1)	13 (2.7)	6 (4.0)	0	6 (2.0)	1 (3.1)	13 (2.7)

Patients were only counted once per treatment group per event.
Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
Decreasing order of frequency relative to all causalities of Overall Lorlatinib 100-mg QD Pooled group.
With any adverse events row included all patients without cutoff.
MedDRA v23.0 coding dictionary applied.
BID=twice daily; QD=once daily

Post marketing experience

Post-marketing surveillance has been conducted since lorlatinib' s initial approval in 2018. The cumulative exposure to lorlatinib from marketing experience since product approval is estimated to be 1070 patient-years. The overall safety data originating from post-marketing sources have been consistent with the known lorlatinib safety profile. No new safety findings have been identified from post-marketing sources.

2.5.1. Discussion on clinical safety

The **safety database** to characterise the safety of lorlatinib comes from both the currently assessed Phase 3 1006 study and updated safety data from the phase 1/2 Study 1001. Hence, a review of pooled safety data from all patients, who had received the recommended dose of 100 mg QD was performed (n=476).

In the pivotal study supporting the applied indication, the median **exposure** of lorlatinib was 16.7 months versus 10.4 months with crizotinib. Moreover, 75.8% of the patients in the lorlatinib arm were exposed for ≥12 months duration and 69.1% of the patients were still on treatment at the time of data cut-off. The median relative dose intensity of lorlatinib was similar in both the 1006 and 1001 studies i.e. 100%, which is considered reassuring, as the longer exposure in the 1001 study did not seem to have had a significant impact on this. For the pooled population, the median exposure is 16.3 months, which allows an assessment of longer-term safety with lorlatinib.

In the pivotal study 1006, all patients had **adverse events** (AEs) with lorlatinib and ~97% of the AEs were treatment related. Grade 3-4 AEs were observed more frequently in the lorlatinib arm (72.5% vs 55.6%); as well as treatment-related grade 3-4 events (55.7% vs 36.6%). For the pooled population, the overall frequencies of AEs, grade 3 (52.1%) and grade 4 AEs (12.4%) is in line with the pivotal 1006 study. The most common AEs of any grade in the pooled population were also overall consistent to the frequencies observed in the pivotal study and the adverse events were mostly manageable and an acceptable guidance for handling is provided in the SmPC.

In the pivotal 1006 study, the TEAEs more commonly observed with lorlatinib compared to crizotinib are (≥10% absolute difference): hypercholesterolemia 70.5% vs 3.5%; hypertriglyceridemia 63.8% vs 5.6%; oedema 55.0% vs 39.4%; weight increased 38.3% vs 12.7%; peripheral neuropathy 33.6% vs 14.8%; cognitive effects 21.5% vs 5.6%; anaemia 19.5% vs 7.7%; hypertension 18.1% vs 2.1%; mood effects 16.1% vs 4.9% and hyperlipidaemia 10.7% vs 0. Notably, more grade 3 AEs (≥5% absolute difference) were also observed with lorlatinib: hypercholesterolemia 15.4% vs 0; hypertriglyceridemia 12.8% vs 0; weight increased 16.8% vs 2.1% and hypertension 10.1% vs 0; while more grade 4 hypertriglyceridemia events were observed with lorlatinib vs crizotinib (7.4% vs 0).

AEs that occurred more frequently in the crizotinib arm were: (≥10% absolute difference): Diarrhoea, fatigue, vision disorder, ALT increased, nausea, vomiting, constipation; AST increased, decreased appetite, dysgeusia, and bradycardia. Hence, some of the GI toxicity observed with many ALK-targeted TKIs including crizotinib were less frequent with lorlatinib, while it is noted that clinically significantly more dyslipidaemia, oedema, neuropathy, cognitive effects, and hypertension were observed with lorlatinib, also regarding high-grade events. Grade 3/4 events were rare except for hypercholesterolemia (16.8%/1.5%) and hypertriglyceridemia (15.1%/4.2%) and these events were mostly handled medically (see table 1 in section 4.2 of the SmPC).

Adverse drug reactions (ADR) frequencies were updated in section 4.8 of the SmPC as part of the current procedure using data from the pooled population (n=476). The most frequently reported **adverse reactions** were hypercholesterolaemia (81.1%), hypertriglyceridaemia (67.2%), oedema

(55.7%), peripheral neuropathy (43.7%), weight increased (30.9%), cognitive effects (27.7%), fatigue (27.3%), arthralgia (23.5%), diarrhoea (22.9%) and mood effects (21.0%). **Serious adverse reactions** were reported in 7.4% of patients receiving lorlatinib. The most frequent serious adverse drug reactions were cognitive effects and pneumonitis.

There were two **new safety findings** with lorlatinib: **Hypertension** was one and it is noted that treatment-related cases were rare (2%). This is a known class effect of other ALK-inhibitors. **Hyperglycemia** was also a new safety finding and although this was also observed in the crizotinib arm, the event is more frequent overall (10.1%) and as a treatment-related event (5.4%) with lorlatinib. Five patients experienced a grade 3 event. However, the ADRs of hyperglycaemia and hypertension were assessed in the context of another procedure (II/13).

Adverse events of special interest with lorlatinib consists of hypercholesterolemia, hypertriglyceridemia, oedema, weight gain and CNS-related effects. The main focus for this assessment was the CNS-related effects and peripheral neuropathy, while the remaining AESIs are well known with lorlatinib and the incidences are considered acceptable. **CNS-related effects** are common with lorlatinib and was the main dose-limiting toxicity in the phase 1 study. The CNS-related toxicity has been difficult to distinguish from effects of the underlying disease, especially from brain metastases in the second- and third-line setting (~60% of the patients present with brain metastases at start of second-line treatment). However, in the pivotal 1006 study conducted in the first-line setting where brain metastases are less frequent (~20-40%), the CNS-related toxicity is still often observed with lorlatinib treatment. Cognitive effects occurred more frequently in the lorlatinib arm than in the crizotinib arm (21.5% vs 5.6%) and grade 3 AEs occurred in the lorlatinib arm only (2.9%); there were no Grade 4 AEs. The most frequent cognitive effect of any grade in the overall pooled lorlatinib 100 mg QD safety analysis set was memory impairment (11.3%), and the most frequent Grade 3 or 4 reactions were confusional state and cognitive disorder (1.7% and 0.8%, respectively). Mood effects were also *more* frequent in the lorlatinib arm than in the crizotinib arm (16.1% vs 4.9%) and there were 2 Grade 3 AEs, both in the lorlatinib arm. The most frequent mood effect of any grade in the overall pooled lorlatinib 100 mg QD safety analysis set was anxiety (6.5%), and the most frequent Grade 3 and 4 reactions were irritability and depression (0.8% and 0.4%, respectively). Speech effects AEs occurred only with lorlatinib (4.7%), but only one grade 3 event and no discontinuations. The most frequent speech effect of any grade in the overall pooled lorlatinib 100 mg QD safety analysis set was dysarthria (4.0%), and the Grade 3 or 4 reactions were dysarthria, slow speech and speech disorder (0.2% each). AEs of psychotic effects also occurred in the lorlatinib arm only (3.4%), but no grade 3 or 4 events were observed. Overall, the CNS-related effects from lorlatinib are correctly mentioned in section 4.4 (warnings) and 4.8 (dose-modifications and incidences) of the SmPC, and since most events are of low grade, this is considered adequate information for the prescriber. **Peripheral neuropathy** was frequent in any grade (43.7%) and considered treatment-related in 30.3% of the patients of the pooled population. However, grade 3 AEs occurred at a low frequency (2.7%, all causality) and only 1 treatment-related event led to permanent treatment discontinuation. Hence, peripheral neuropathy is frequent with lorlatinib, but since grade 3 events were rare, this is considered manageable.

Serious adverse events (SAEs) were observed in a similar number of patients in both arms of the pivotal 1006 study (34.2% vs 27.5%); however, only 8.1% vs 4.9% of the SAEs were assessed to be treatment-related. SAEs in the pooled population is consistent i.e. 39.5% SAEs, of which 8.0% were treatment-related. The most common SAEs observed in the pooled population was disease progression (6.3%), pneumonia (4.4%) and dyspnea (2.9%), which is acceptable and reflects the profile of the targeted disease.

Deaths due to treatment toxicity were rare in the pivotal study 1006 (1.3%, 2 patients) and patients most frequently died due to disease progression, both in the pivotal 1006 study (11.4%) and in the

pooled population (30%). The two treatment-related deaths from lorlatinib were cardiac failure and respiratory failure and from the narratives provided, it is agreed that it cannot be ruled out that the two deaths were treatment-related, although the underlying disease also contributed to death in both cases. Considering the targeted disease and the non-curative setting, this is acceptable.

Haematological toxicity with lorlatinib was less frequent and could also be due to the underlying treated disease. Grade 3-4 events were rare and manageable. **Laboratory shifts** are summarized in Table 81 and since high-grade events were rare, this is considered overall acceptable and manageable. There were no Hy's law cases.

Regarding the safety performance of lorlatinib in **special populations**, AEs according to age group does not seem affected in the lorlatinib-treated patients, while more grade AEs were observed in the high age-group treated with crizotinib. No clinically meaningful differences are observed regarding AEs by gender subgroup in either treatment arm. More grade 4 AEs were observed in the Asian subgroup compared to non-Asians receiving lorlatinib (19.7% vs 9.6%) and crizotinib (12.5% vs 5.1%). The MAH has clarified that of the increased grade 4 AEs reported in Asian patients who received lorlatinib, hypertriglyceridaemia was the most frequently reported. The remaining AEs reported did not exhibit a discernible pattern either based on the mechanism of action of lorlatinib or a specific system organ class. Although there are some reports suggesting that Asians may have higher incidence of hypertriglyceridemia compared to non-Hispanic Whites (Ariel et al, 2014), the relative higher frequency of hypertriglyceridemia in Asian patients in Study B7461006 was not observed in Study B7461001 (hypertriglyceridaemia reported in 3 (2.8%) of Asian patients and 3 (1.9%) of non-Asian patients). Moreover, a review of the data from both the lorlatinib and crizotinib programs did not provide causal evidence for a higher risk of Grade 4 AEs in Asian patients compared to non-Asian patients. It is a possibility that the differential findings from Study B7461006 may have been due to factors unrelated to race; however, the MAH will continue to monitor the reports of Grade 4 AEs among Asians and non-Asians as part of regular safety surveillance. This is acceptable.

Discontinuations due to AEs in the pooled population were 9.2%, of which 4.2% of the events were considered treatment-related. It is noted that grade 3 events of cognitive effects and peripheral neuropathy were the most frequent events to led to discontinuation, although rare with 3 and 2 patients in each group. The rate of discontinuations is acceptable considered the non-curative setting. **Dose-interruptions** due to AEs were frequent in both treatment arms in the pivotal 1006 study (49% vs 47.2%) in the lorlatinib arm vs the crizotinib arm. This is in line with the frequency observed for the pooled population (34.7%), where the most common AE leading to dose-interruptions were hypertriglyceridemia, oedema and cognitive effects. **Dose-reductions** were slightly less common and occurred in 22.3% of the pooled population, most often due to oedema, peripheral neuropathy, and cognitive effects. Of note, the SmPC describes dose reductions due to adverse reactions, which occurred in 20.0% of patients receiving lorlatinib, and permanent treatment discontinuation associated with adverse reactions, which occurred in 3.2% of patients receiving lorlatinib (data not shown in this report).

Furthermore, sections 4.4 and 4.8 of the SmPC have been updated to reflect the safety data from the overall pooled, safety analysis set (protocols B7461001, B7461006) for hypercholesterolaemia, hypertriglyceridaemia, central nervous system effects and lipase and amylase increase (data not shown in this report). The median time to onset for both hypercholesterolaemia and hypertriglyceridaemia was 15 days (hypercholesterolaemia range: 1 to 784 days; hypertriglyceridaemia range: 1 to 796 days). The median duration of hypercholesterolaemia and hypertriglyceridaemia was 451 and 427 days, respectively. Median time of occurrence of severe increase in serum cholesterol and triglycerides is 104 days (range: 29 to 518 days) and 120 days (range: 15 to 780 days), respectively. Median time of occurrence of increase in serum lipase and amylase is 141 days (range: 1 to 1091 days) and 138 days (range: 1 to 1112 days), respectively. Median time to onset for cognitive, mood, speech and psychotic

effects was 109, 43, 49 and 23 days, respectively. Median duration of cognitive, mood, speech and psychotic effects was 223, 143, 147 and 74 days, respectively.

2.5.2. Conclusions on clinical safety

The safety profile of lorlatinib compared to crizotinib is well-described and the size of the safety database (n=476) and median exposure of lorlatinib is sufficient to assess longer-term safety. The two new safety findings of hyperglycaemia and hypertension identified in the study 1006 have been included in the SmPC as part of a separate variation (EMEA/H/C/004646/II/0013). The rate of discontinuation is considered acceptable (9.2%). Overall, the adverse events of lorlatinib are considered overall manageable and acceptable considering the non-curative setting and the underlying disease.

Hence, the safety data provided from both the pivotal Study 1006 and Study 1001 have addressed the outstanding uncertainties on safety as identified in the context of the conditional marketing authorisation of lorlatinib for patients with ALK-positive advanced NSCLC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

-to update Annex 5 of the RMP (to align with SmPC Annex II condition and to reflect RMP version number and date of final sign off).

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 90. Summary of Safety Concerns

Important Identified Risks	CNS Effects
	ILD/pneumonitis
Important Potential Risks	AV block
	Pancreatitis
	Embryo-foetal toxicity
Missing Information	Patients with moderate or severe hepatic impairment

No changes to the list of safety concerns were made as a result of the new indication.

Pharmacovigilance plan

Table 91. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Lorlatinib Hepatic Impairment Trial (B7461009)	To minimize toxicity in patients with hepatic impairment.	Missing information on patients with moderate or severe hepatic impairment	Final Protocol Submission: Study/Trial Completion: Final Report Submission:	09/07/2018 31/03/2023 28/02/2024

No changes to the pharmacovigilance plan were made as a result of the new indication.

Risk minimisation measures

Table 92. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
CNS effects	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.7, and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow up questionnaire Additional pharmacovigilance activities: None
ILD/pneumonitis	Routine risk minimisation measures: SmPC section 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks		
AV block	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities:

Table 92. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		None
Pancreatitis	Routine risk minimisation measures: SmPC section 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC sections 4.4, 4.6, 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Missing Information		
Patients with moderate or severe hepatic impairment	Routine risk minimisation measures: SmPC sections 4.2, 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Lorlatinib Hepatic Impairment Trial (B7461009)

No changes were made to the risk minimisation measures as a result of the new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to include minor editorial changes in the PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

With the current application the overall content of the PL is not changed significantly compared to information already included.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking an extension of indication to include treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK-inhibitor. The proposed revised wording of indication is the following:

Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.

Lorlatinib is conditionally approved as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or crizotinib and at least one other ALK TKI.

The aim of therapy is to prolong progression-free survival (PFS) in the palliative setting.

3.1.2. Available therapies and unmet medical need

Alectinib, ceritinib, and brigatinib are second-generation ALK-TKIs that prolong PFS and have CNS anti-tumor effects. These therapies are recommended for treating patients with previously untreated advanced ALK-positive NSCLC, with alectinib being the preferred treatment option in the first-line setting.

Most patients with ALK-positive NSCLC derive clinical benefit from first-line treatment with second-generation ALK TKIs. However, emergence of resistance mechanisms, including ALK mutations continues to be a treatment challenge. Therefore, there is an unmet medical need for additional ALK TKIs with broader mutational coverage and CNS penetration.

Lorlatinib is a third-generation, selective, ATP-competitive, brain-penetrant, small molecule inhibitor of the ALK tyrosine kinase that was designed to overcome or prevent major mechanisms of resistance that develop following previous ALK-inhibitor treatment. It was also designed to penetrate the blood-brain-barrier. These features indicate that lorlatinib has potential as therapy for previously untreated ALK-positive NSCLC.

3.1.3. Main clinical studies

The pivotal study for this application is the multicentre, randomised phase 3 CROWN trial, comparing lorlatinib with crizotinib in the TKI-naïve setting. 296 patients were randomised 1:1 in 104 sites in 23 countries during less than 2 years and efficacy data presented are with less than 18 months of follow-up for PFS in the lorlatinib arm and from data cut-off 20 March 2020.

The primary endpoint is PFS by BIRC and the key secondary endpoints are OS, PFS by investigator (INV), objective response rate (ORR), duration of response (DOR), and intracranial ORR plus DOR.

Crizotinib was still the standard of care for the first-line treatment of ALK+ NSCLC at the time of study initiation so the control arm is considered adequate. However, alectinib monotherapy is now the preferred first-line treatment option.

Lorlatinib and crizotinib are both oral treatments given continuously in 28-days cycles and no crossover was allowed from the control arm.

3.2. Favourable effects

The primary efficacy endpoint of **PFS by BIRC** was met and statistically significantly improved at the first IA performed after 72% events as of the data cut-off date of 20 March 2020. The median PFS follow-up duration was 18.3 months (95%CI: 16.4., 20.1) in the lorlatinib arm and 14.8 months (95%CI: 12.8, 18.4) in the crizotinib arm. The HR was 0.28 (95%CI: 0.191, 0.413) in favour of lorlatinib because the median PFS by BIRC was not estimable (95%CI: NE, NE) with lorlatinib versus 9.3 months (95%CI: 7.6, 11.1) in the crizotinib arm. The KM curves clearly separate after 4 months of therapy.

PFS by INV is overall in line with the PFS by BIRC results regarding PFS by INV events in the lorlatinib arm (26.8% vs 27.5% events).

OS data is immature with only 17% events and a similar number of patients are censored in both treatment arms.

ORR by BIRC was improved with lorlatinib to 75.8% (95%CI: 68.2, 82.5) versus 57.8% (95%CI: 49.4, 65.9) with crizotinib. Complete responses (CR) were only observed with lorlatinib (2.7%) and the improved ORR was mainly driven by the larger rate of partial responses (PR) in the lorlatinib arm (73.2% vs 57.8%).

Duration of response by BIRC was prolonged with lorlatinib vs crizotinib (NE (95%CI: NE, NE) versus 11.0 months (95%CI: 9.0; 12.9)) and 30% of the patients in the lorlatinib arm had a duration response of ≥18 months. Time to tumour response was less than 2 months and in line with TTR results from other available ALK TKIs.

Efficacy in the brain was improved with lorlatinib regarding time to intracranial progression by BIRC in the ITT population (HR 0.07 (95%CI: 0.026; 0.170). The intracranial ORR in patients with brain metastases at baseline is also improved with lorlatinib (N=78) i.e. 65.8% (95%CI: 48.6; 80.4) vs 20.0 % (95%CI: 9.1; 35.6) with crizotinib. The intracranial DOR was improved with lorlatinib (NE (95%CI: NE, NE) vs 9.4 months (95%CI: 6.0, 11.1), n=33) and 72% of the patients (n = 18) in the lorlatinib arm had a duration response of ≥12 months.

The treatment effect of lorlatinib according to PFS by BIRC is consistent across important **subgroups** regardless of the presence of brain metastases at baseline, gender, age and smoking status.

3.3. Uncertainties and limitations about favourable effects

OS data are immature but considering the prognosis of the treated disease in the first-line setting (median OS with crizotinib is ~57 months), this is acceptable for now. The MAH will provide updated OS data as part of the final clinical study report for the pivotal Study B7461006 (CROWN) by 30 June 2025 (Annex II condition).

Since an updated OS analysis will not be available until 2025, PFS2 data will be presented in the context of the next annual renewal (Recommendation).

3.4. Unfavourable effects

In the pivotal study 1006, all patients had **adverse events** and ~97% of the AEs from lorlatinib were treatment-related.

For the pooled population, the overall frequencies of AEs, grade 3 (52.1%) and grade 4 AEs (12.4%) is in line with the pivotal 1006 study. The most common AEs of any grade in the pooled were also overall consistent to the frequencies observed in the pivotal study.

Adverse events of special interest with lorlatinib consists of hypercholesterolemia, hypertriglyceridemia, oedema, weight gain and CNS-related effects. **CNS-related effects** are common with lorlatinib and was the main dose-limiting toxicity in the phase 1 study. Cognitive effects occurred more frequently in the lorlatinib arm than in the crizotinib arm (21.5% vs 5.6%) and grade 3 AEs occurred in the lorlatinib arm only (2.9%); there were no Grade 4 AEs. Mood effects were also more frequent in the lorlatinib arm than in the crizotinib arm (16.1% vs 4.9%) and there were 2 Grade 3 AEs, both in the lorlatinib arm. Speech effects AEs occurred only with lorlatinib (4.7%), but only one grade 3 event and no discontinuations. AEs of psychotic effects also occurred in the lorlatinib arm only (3.4%), but no grade 3 or 4 events were observed.

Peripheral neuropathy was frequent in any grade (43.7%) and considered treatment-related in 30.3% of the patients of the pooled population. However, grade 3 AEs occurred at a low frequency (2.7%) and only 1 treatment-related event led to permanent treatment discontinuation.

There were two **new safety findings** with lorlatinib, hypertension and hyperglycaemia. Hypertension was one and it is noted that treatment-related cases were rare (2%). This is a known class effect of other ALK-inhibitors. Hyperglycaemia was also a new safety finding and although this was also observed in the crizotinib arm, the event is more frequent overall (10.1%) and as a treatment-related event (5.4%) with lorlatinib. Five patients experienced a grade 3 event.

Serious adverse events (SAES) were observed in a similar number of patients in both arms of the pivotal 1006 study (34.2% vs 27.5%) and this corresponded to 39.5% in the pooled population. The most common SAEs observed in the pooled population was disease progression (6.3%), pneumonia (4.4%) and dyspnoea (2.9%).

Deaths due to treatment toxicity were rare (1.3%, 2 patients in the pivotal study) and patients most frequently **died** due to disease progression, both in the pivotal 1006 study (11.4%) and in the pooled population (30%). The two treatment-related deaths from lorlatinib were cardiac failure and respiratory failure.

Discontinuations due to AEs in the pooled population were 9.2%, of which 4.2% of the events were considered treatment-related. Grade 3 events of cognitive effects and peripheral neuropathy were the most frequent events to led to discontinuation.

3.5. Uncertainties and limitations about unfavourable effects

There are no major uncertainties or limitations about the unfavourable effects.

Effects Table

Table 93. Effects Table for lorlatinib for treatment of ALK+ advanced NSCLC previously not treated with an ALK inhibitor, Study 1006 (data cut-off: 20 March 2020)

Effect	Short description	Unit	Treatment Lorlatinib N=149	Control Crizotinib N=147	Uncertainties / Strength of evidence	Ref
Favourable Effects						
PFS by BIRC	Progression-free survival	Months 95%CI	NE NE; NE	9.3 7.6; 11.1	HR 0.28 0.191; 0.413	
OS	Overall survival	Months 95%CI	NE NE; NE	NE NE; NE	HR 0.72 0.414, 1.249 OS data is immature (only 17% events)	
ORR	Overall response rate	% 95%CI	75.8 68.2, 82.5	57.8 49.4, 65.9		
DOR	Duration of response	Months	NE NE; NE	11.0 9.0, 12.9		
Unfavourable Effects						
Gr 3-4	AE	%	72.5	55.7		
SAEs		%	34.2	27.5		
AEs leading to permanent treatment discontinuation		%	6.7	9.2		

Abbreviations: BIRC: Blinded Independent Review Committee; NE: Not estimable; AE: Adverse event; SAEs: Serious AEs; Gr.: grade; disc: leading to

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The target population of ALK inhibitor-naïve advanced ALK-positive NSCLC have other effective treatment options with alectinib, ceritinib, and brigatinib, which prolong PFS and have CNS anti-tumour effects. Although most patients derive clinical benefit from these treatments, emergence of resistance mechanisms, including ALK-mutations, continues to be a treatment challenge. Therefore, there is an unmet medical need for additional ALK TKIs and lorlatinib is designed to meet this need.

Lorlatinib has received conditional MA in the 2L setting for patients who progress on second-generation ALK-TKIs. Data in support of the CMA were derived from a single-arm, uncontrolled trial demonstrating therapeutic activity of lorlatinib in patients previously treated with alectinib, ceritinib or brigatinib as either 1st or subsequent line of treatment. The extent of the benefit with lorlatinib in the second-line indication after a second-generation ALK-TKI still requires confirmation to be provided in the context of the ongoing study B7461027 (SOB). However, the data from the current variation are considered to fulfil the requirement of the second specific obligation to the CMA (CROWN study).

There was a clinically meaningful improvement of the primary efficacy endpoint of **PFS by BIRC** with a median not estimable (95%CI: NE, NE) for lorlatinib versus 9.3 months (95%CI: 7.6, 11.1) in the crizotinib arm, **HR 0.28** (95%CI: 0.191, 0.413). The KM curves clearly separate after 4 months of therapy corresponding to the markedly fewer PFS events with lorlatinib. PFS by INV results were in line

and supportive. Although OS data is immature with only 17% events, considering the prognosis of the treated disease in the first-line setting (median OS with crizotinib is ~57 months), this is acceptable.

The overall **response rate** with lorlatinib was also clinically significantly improved with lorlatinib. There was also a clinically significant longer **duration of response** by BIRC with lorlatinib vs crizotinib (NE versus 11.0 months) and it is noted that 30% of the patients in the lorlatinib arm had a duration of response of ≥18 months.

Efficacy in the brain was clearly improved with lorlatinib, which is best demonstrated by the prolonged time to intracranial progression by BIRC in the ITT population (HR 0.07) and the intracranial ORR in patients with brain metastases at baseline i.e. 65.8% vs 20.0 % with crizotinib. Additionally, the treatment effect of lorlatinib according to PFS by BIRC is consistent across important subgroups regardless of presence of brain metastases at baseline, gender, age and smoking status.

Since OS data are immature, the MAH will submit final OS data of the Phase III CROWN study (B7461006) as an Annex II condition (PAES) and PFS2 data in the context of the next annual renewal (Recommendation).

Moreover, the ongoing study B7461027 (SOB) should be conducted as planned with recruitment of approximately 70 patients in the second-line setting post a second-generation ALK-TKI. The clinical study report will be submitted by 30 June 2024.

Overall, it can be concluded that treatment with lorlatinib has shown a statistically and clinically meaningful improvement of efficacy in terms of PFS, response rate and duration of response compared to crizotinib in the treatment of adult patients with ALK-positive advanced NSCLC not previously treated with an ALK inhibitor. In addition, lorlatinib also prevents intracranial progression of disease and produced more and longer clinically relevant intracranial responses in patients with brain metastases at baseline compared to crizotinib. This improved efficacy is balanced against the safety profile of lorlatinib, even though there were **2 new safety findings** in the pivotal study (hypertension and hyperglycaemia) and that lorlatinib causes more toxicity than crizotinib regarding hypercholesterolemia, hypertriglyceridemia, oedema, peripheral neuropathy and CNS-related effects. Since these AEs were mostly of low-grade and manageable, the markedly improved efficacy outweighs these risks with lorlatinib.

3.6.2. Balance of benefits and risks

The benefit-risk balance in the treatment of adult patients with ALK-positive advanced NSCLC not previously treated with an ALK inhibitor is positive. Further clarifications are still needed in patients previously treated with a second-generation ALK-TKI (SOB).

The safety profile of monotherapy with lorlatinib in the targeted population is considered acceptable.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Lorviqua monotherapy in the treatment of adult patients with ALK-positive advanced NSCLC not previously treated with an ALK inhibitor is positive and submission of the results of Study 1006 fulfilled the respective specific obligation. However, since OS data are immature, the MAH will submit final OS data of the Phase III CROWN study (B7461006) as an Annex II condition (PAES).

The B/R in patients previously treated with ALK inhibitors still requires confirmation and the clinical study report of study B7461027 will be submitted by 30 June 2024 (SOB).

In addition, the MAH should update the RMP as requested by the next given opportunity.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from the phase III randomised CROWN (1006) study listed as a specific obligation (SOB) in the Annex II; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated accordingly. Version 4.1 of the RMP has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to include minor editorial changes in the PI.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it is deleted from the Annex II:

Description	**Due date**
In order to further confirm the efficacy and safety of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the phase III study CROWN (1006) comparing lorlatinib versus crizotinib for the first-line treatment of advanced ALK-positive NSCLC. The clinical study report will be submitted by:	31 December 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of lorlatinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor, the MAH will submit the results including overall survival (OS) data of the Phase III CROWN study (B7461006) comparing lorlatinib versus crizotinib for that same setting. The clinical study report will be submitted by:	30 June 2025

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK TKI therapy, the MAH should conduct a single-arm study investigating patients in that same setting (B7461027) and submit the clinical study report by:	30 June 2024

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Lorviqua-H-C-004646-II-0015’.