28 February 2019
EMA/CHMP/182840/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lorviqua

International non-proprietary name: lorlatinib

Procedure No. EMEA/H/C/004646/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AAG	α1-acid glycoprotein
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIFA	Italian Medicine Agency
AJCC	American Joint Committee for Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{24}	area under the plasma concentration-time profile from time 0 to 24 hours
AUC_{tau}	area under the plasma concentration versus time interval from time zero through the dosing interval
AV	atrioventricular
BA	bioavailability
BBB	blood-brain barrier
BCS	biopharmaceutics classification system
BE	bioequivalence
BID	twice a day
BOR	Best Overall Response
BTD	Breakthrough Therapy Designation
cfDNA	circulating free deoxyribonucleic acid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	clearance
CLI	single-dose clearance
CM	Carcinomatous meningitis
CMA	Conditional Marketing Authorisation
C_{max}	mean peak plasma concentration
CNA	circulating nucleic acid
CNS	central nervous system
CO	Clinical Overview
CQA	critical quality attribute
CRM	continual reassessment method
CR	complete response
CSF	cerebrospinal fluid
CSR	clinical study report
CTD	Common Technical Document
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DoE	design of experiments
DOR	duration of response
IC DOR	Intracranial duration of response
DMA	Danish Medicine Agency
EC	European Commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EML4	echinoderm microtubule-associated protein-like 4
EOP1	End-of-Phase 1
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

E-R	exposure response
EU	European Union
EXP	expansion
FAL	Final Advice Letter
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
GC	gas chromatography
GCP	Good Clinical Practice
hPXR	human Pregnane X Receptor
hCAR	human constitutive androstane receptor
HDL	high density lipoprotein
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
HSA	human serum albumin
IC	intracranial
IC ORR	intracranial objective response rate
IC_{50}	50% inhibitive concentration
ICH	International Council for Harmonisation
ICR	Independent Central Review
IHC	immunohistochemistry
ILD	interstitial lung disease
IR	infrared
ITT	intention-to-treat
IV	intravenous
IU	international units
KRAS	Kirsten rat sarcoma viral oncogene homologue
LC	liquid chromatography
LM	Leptomeningeal disease
LDPE	low density polyethylene
LDL	low density lipoprotein
LIC	Lead-in Cohort
LOAEL	lowest-observed-adverse-effect level
LVEF	left ventricular ejection fraction
MAA	Marketing Authorization Application
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MDZ	midazolam
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCA	non-compartmental analysis
NDA	New Drug Application
NE	not estimable
NOAEL	no-observed-adverse-effect-level
MNT	not more than
NR	not reached
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
Ph. Eur	European Pharmacopoeia
PK	pharmacokinetic(s)
PMAR	Pharmacokinetic Modeling Analysis Report
popPK	population pharmacokinetics
PR	partial response
PRO	patient reported outcome
PS	Performance Status
PT	Preferred Term
PXRD	powder X-ray diffractometer
QbD	quality by design
QC	Quality control

QD	once daily
QLQ-LC13	Quality of Life Questionnaire Lung Cancer 13
QoL	Quality of Life
QTc	QT interval corrected for heart rate
QTTP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RH	relative humidity
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
SA	scientific advice
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TAMC	Total aerobic microbial count
TDI	time-dependent inhibition
TDOSE	total daily dose
TKI	tyrosine kinase inhibitor
T_{max}	time to peak concentration
TQT	thorough QT
TTR	time to tumour response
TYMC	total combined yeasts/moulds count
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UV	ultraviolet
V_{ss}	steady-state volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 9 January 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Lorviqua, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA / Committee for Medicinal Products for Human Use (CHMP) on 15 September 2016.

The applicant applied for the following indication: Lorviqua monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs), except for patients treated with crizotinib as the only ALK-TKI.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA/60972/201717 on the granting of a class 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 applicant 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.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance lorlatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved 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:

- An open-label, non-comparative Phase 1b/2 study: Adequacy of the approach to the primary efficacy analysis whereby data is pooled across different ALK-positive NSCLC cohorts; whether the pooled efficacy data generated from the study could be used to support a conditional Marketing Authorisation application.
- 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.
- Pharmacokinetic (PK) and clinical pharmacology studies: Adequacy of plan and timing of study submission in relation Marketing Authorisation Application (MAA).
- Regulatory approach and submission strategy: Adequacy of the Phase 3 study to support MAA, and suitability for use as confirmatory study to convert CMA to full MA.

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: Daniela Melchiorri

The application was received by the EMA on	9 January 2018
The procedure started on	1 February 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	24 April 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	26 April 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 May 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 May 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 August 2018
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	

A GCP inspection at two investigator sites (in Australia and Italy) and at the sponsor site in the USA was performed between 16 April 2018 and 22 June 2018. The outcome of the inspection carried out was issued on:	30 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 September 2018
The CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation sent to the applicant on	18 October 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 January 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	29 January 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lorviqua on	28 February 2019

2. Scientific discussion

2.1. Problem statement

Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some patients with ALK-positive NSCLC will not respond to treatment (intrinsic resistance), and other patients who initially experience clinical benefit will later develop resistance (acquired resistance). Next-generation ALK-TKIs such as ceritinib, alectinib, and brigatinib have been developed to address crizotinib treatment failure. However, ALK-positive NSCLC remains an incurable disease, as patients ultimately develop resistance to second-generation ALK-TKIs, including but not limited to emergence of brain metastases. Therefore, there is a need for additional ALK-TKIs, in patients whose disease has progressed on a second-generation ALK-TKI, which can overcome resistance mutations and with central nervous system (CNS) penetration.

2.1.1. Disease or condition

Lorviqua (lorlatinib) is intended as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with one or more ALK TKIs, except for patients treated with crizotinib as the only ALK-TKI.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Lung cancer is one of the most common cancers in the world (1.8 million new cases in 2012), 12.9% of all new cancers worldwide[1]. In Europe, the age standardised predicted mortality rate for lung cancer was 35.98 per 100,000 men and 14.24 per 100,000 women as of 2015.

About 85%–90% of lung cancers are constituted by NSCLCs, and ALK-positive NSCLC represents approximately 4%–5% of all NSCLC patients in both Caucasian and Asian populations, which represents potentially 40,000 new cases worldwide each year.

2.1.3. 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

[1] Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.0, Estimated Cancer Incidence, Mortality and Prevalence Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2012. Available from: http://globocan.iarc.fr
[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.

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].

2.1.4. Clinical presentation, diagnosis and stage

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.

2.1.5. Management

While the standard treatment algorithm for unselected NSCLC patients has historically involved front-line treatment with chemotherapy, recent clinical studies have demonstrated that patients with ALK-positive locally advanced or metastatic NSCLC respond well to treatment with the ALK inhibitor crizotinib.

The approval of crizotinib was based on results from 2 single-arm studies[7]. Crizotinib is a first-generation ALK-TKI is indicated for the treatment of ALK-positive advanced NSCLC (hereafter referred to as ALK-positive NSCLC). Crizotinib significantly prolonged progression-free survival (PFS) in previously untreated patients with ALK-positive advanced non-squamous NSCLC when compared with standard platinum-based chemotherapy regimens.

Resistance due to the emergence of various ALK kinase domain mutations and the activation of bypass resistance mechanisms, continues to present a treatment challenge with the use of ALK-TKIs. ALK resistant mutations following treatment with a second-generation ALK-TKI have also been observed in the clinic. Among them, ALKG1202R and ALKI1171T missense mutations are common resistance mutations after ceritinib and alectinib treatment, respectively[8].

Among patients whose disease has progressed on second-generation TKIs used either in the first- or second-line setting, chemotherapy would be the fall back standard of care. Outcomes with chemotherapy have been modest. In a randomised Phase 3 trial of ceritinib vs chemotherapy (docetaxel or pemetrexed) in patients with ALK-positive NSCLC who had been previously treated with chemotherapy and crizotinib, chemotherapy had an objective response rate (ORR) of 6.9% and median PFS of 1.6 months, as determined by blinded independent central review (ICR). Chemotherapy also has a limited intracranial (IC) ORR even in a treatment-naïve setting. In a randomised Phase 3 study of first-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged NSCLC, the

[6] Camidge D, Doebele RC. Treating ALK-positive lung cancer-early successes and future challenges. Nat Rev Clin Oncol. 2012;9(5):268-77.
[7] Xalkori. crizotinib EPAR.
[8] Ou SH, Azada M, Hsiang DJ, et al. Next-generation sequencing reveals a novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib. J Thorac Oncol 2014;9(4):549-53.

platinum doublet was reported to have an IC ORR by ICR of 21.2% (95% confidence interval [CI]: 11.1, 34.7).

Unmet medical need

Because there are no agents approved that confer substantial benefit for ALK-positive advanced NSCLC previously treated with 2 or more ALK-TKIs, there is a substantial unmet medical need in this treatment setting. Of note, this is a clinical situation that is similar to that in patients whose disease progressed after treatment with a second-generation ALK-TKI when used as the only ALK-TKI. Thus, additional drugs are needed to overcome resistance mechanisms, to impact patient outcomes through improved response rates and PFS, and to have significant antitumor activity against CNS metastases.

Chemotherapy would provide another treatment option in patients whose disease progressed after treatment with a second-generation ALK-TKI (either as the only ALK-TKI or when used after crizotinib). Because there are no published clinical data available on the antitumor activity of chemotherapy in this particular setting, the best approximation for the efficacy of chemotherapy would be patients previously treated with a platinum doublet and crizotinib. Data in this setting have been reported for the chemotherapy control arms of the alectinib Phase 3 ALUR trial and the ceritinib Phase 3 ASCEND-5 trial. In the ALUR trial, the ORR for single-agent chemotherapy was 11.4%, and there were no IC responses and median PFS was 1.4 months (95% CI not reported). In the ASCEND-5 trial, the ORR for single-agent chemotherapy was 6.9% with an IC ORR of 5.0% and a median PFS of 1.6 months (95%CI: 1.4, 2.8).

About the product

Lorlatinib is a selective, adenosine triphosphate (ATP) -competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases.

In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays. Lorlatinib demonstrated marked anti-tumour activity in mice bearing tumour xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two (2) of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib was also capable of penetrating the blood-brain barrier. Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALK^{L1196M} brain tumour implants. The applicant applied for the following 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 treated with one or more ALK tyrosine kinase inhibitors (TKIs), except for patients treated with crizotinib as the only ALK TKI."

The recommended indication for approval is:

Lorlatinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (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 recommended dose is 100 mg lorlatinib taken orally once daily.

Duration of treatment

Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.

Delayed or missed doses

If a dose of lorlatinib 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.

Table 1: Recommended lorlatinib dose modifications for adverse reactions

Adverse reaction[a]	**Lorlatinib dosing**
Hypercholesterolaemia or hypertriglyceridaemia	
Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L) OR Mild hypertriglyceridaemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) Moderate hypertriglyceridaemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	Introduce or modify lipid-lowering therapy[b] in accordance with respective prescribing information; continue lorlatinib at same dose.
Severe hypercholesterolaemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 501 and 1,000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy;[b] if currently on lipid-lowering therapy, increase the dose of this therapy[b] in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b] or increase the dose of this therapy[a] in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximising lipid-lowering therapy[b] in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur despite maximal lipid-lowering therapy[b] in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.
Central nervous system effects (changes in cognition, mood or speech)	
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention	Permanently discontinue lorlatinib.

Adverse reaction[a]	Lorlatinib dosing
indicated	
Lipase/Amylase increase	
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
Interstitial lung disease (ILD)/Pneumonitis	
Grade 1: Mild OR Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
PR interval prolongation/Atrioventricular (AV) block	
First-degree AV block: Asymptomatic	Continue lorlatinib at the same dose without interruption. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.
First-degree AV block: Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume lorlatinib at 1 reduced dose level.
Second-degree AV block Asymptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does not show second degree AV block, resume lorlatinib at 1 reduced dose level.
Second-degree AV block Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second degree AV block resolve or if patients revert to asymptomatic first degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV block	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib at 1 reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
Other adverse reactions	
Grade 1: Mild OR Grade 2: Moderate	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3: Severe	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.

Abbreviations: AV=atrioventricular; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; NCI=National Cancer Institute; ULN=upper limit of normal.

[a] Grade categories are based on NCI CTCAE classifications.

[b] Lipid-lowering therapy may include: HMG CoA reductase inhibitor, nicotinic acid, fibric acid, or ethyl esters of omega-3 fatty acids.

Type of Application and aspects on development

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

The applicant claims that in pivotal Study B7461001 (also called study 1001), lorlatinib demonstrated clinically meaningful benefit in patients with ALK-positive NSCLC who previously received a range of treatments with prior ALK-TKIs and/or chemotherapy regimens, with tumour responses that were rapid, deep, and durable.

Importantly, lorlatinib also had activity against brain metastases and exhibited antitumor activity across a variety of ALK kinase domain resistance mutations, including the difficult-to-treat G1202R/G1202del mutations. Lorlatinib also evoked responses in tumours resistant to prior ALK-TKIs that did not contain detectable ALK resistance mutations.

Lorlatinib was generally tolerable, as AEs were primarily mild to moderate in severity and manageable by dosing interruption, dose reduction, and/or standard supportive medical therapy, as the rate of permanent treatment discontinuations associated with AEs was low without any treatment-related deaths. The safety profiles between the overall safety population and subgroups of baseline demographics (age, race, gender) were similar.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant claims that the confirmatory data will be provided with data from Study B7461006, an ongoing Phase 3, randomised, open-label trial of the safety and efficacy of lorlatinib and crizotinib for first-line treatment of subjects with advanced ALK-positive NSCLC. Study B7461006 is a global study with total of 280 subjects planned for enrolment. The First Patient First Dose was in May 2017, study enrolment is on schedule and planned to be completed by 4Q2018 with clinical study report expected by 31 December 2021.

- Unmet medical needs will be addressed

The applicant claims that the clinical benefit of lorlatinib in patients with ALK-positive advanced NSCLC previously treated with one or more ALK-TKIs was shown by the results of Study 1001 as evidenced by rapid, deep, and durable responses, also across subgroups of baseline demographics (age, race, gender) and ECOG PS.

Because there are no agents approved that confer substantial benefit for patients who have been previously treated with 2 or more ALK-TKIs, there is a substantial unmet need in this setting. Of note, this is a clinical situation that is similar to that in patients whose disease progressed after treatment with a second-generation ALK-TKI when used as the only ALK-TKI.

In contrast to the poor outcome with immune checkpoint inhibitors or chemotherapy, the ORR for lorlatinib after a second-generation ALK-TKI is compelling.

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

In addition to the systemic response, lorlatinib also exhibited rapid, deep, and durable intracranial responses consistent with its ability to cross the blood-brain barrier (BBB). Lorlatinib has the potential to fulfil an important unmet medical need in this heavily pre-treated patient population.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant claims that despite the introduction of effective ALK-TKIs over the past several years, ALK-positive NSCLC is a serious, life-threatening disease that remains incurable.

There is a high unmet medical need in patients for whom treatment with second-generation ALK-TKIs

such as alectinib or ceritinib has failed, because available treatment options are not effective and no therapies exist that would be specifically indicated in that setting.

Consequently, new drugs are needed to overcome ALK-TKI resistance mechanisms and to enhance patient outcomes.

Overall, the safety, efficacy, and PK data make lorlatinib a useful therapeutic option that should be made available to the public immediately. Based on the current timeline projections, waiting for randomised data from Phase 3 Study B7461006 may translate into a 1- to 3-year delay in the availability of lorlatinib in the EU for patients with ALK-positive advanced NSCLC who have progressed after second generation ALK inhibitor.

2.2. Quality aspects

2.2.1. Introduction

The finished product Lorviqua is presented as film-coated tablets in 2 strengths containing 25 mg and 100 mg lorlatinib as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, calcium hydrogen phosphate, sodium starch glycollate, and magnesium stearate.

Film-coating: hypromellose, lactose monohydrate, macrogol, triacetin, titanium dioxide (E171), iron oxide black (E172), iron oxide red (E172).

The product is available in OPA/Al/PVC blisters with aluminium foil backing as described in Section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of lorlatinib is (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4,8-methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile corresponding to the molecular formula $C_{21}H_{19}FN_6O_2$. It has a relative molecular mass of 406.41 daltons and the following structure:

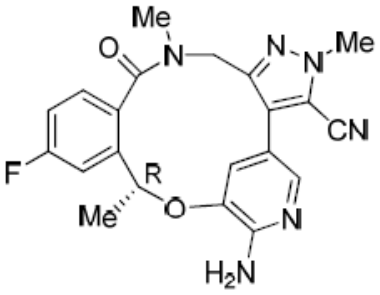


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of IR spectroscopy, mass spectroscopy, nuclear magnetic resonance spectroscopy, X-Ray diffraction, ultraviolet/visible (UV/Vis) spectrum, and specific optical rotation. The solid state properties of the active substance were measured by X-Ray diffraction.

Lorlatinib is a non-hygroscopic white to off white powder. The aqueous solubility of lorlatinib is high at low pH (0.1 N HCl) and decreases with increasing pH. It has very low solubility above pH 4.5. It is classified as a BCS class 4 substance with low solubility and low permeability. Due to the low solubility of lorlatinib, the substance is milled and a requirement for particle size is included in the active substance specification.

The active substance exhibits stereoisomerism due to the presence of one chiral centre, giving 2 possible stereoisomers. For lorlatinib, the absolute configuration at the 10-position is the R-optical isomer.

Lorlatinib shows polymorphism.

Manufacture, characterisation and process controls

The active substance is synthesised in 4 main steps using commercially available well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. An impurity risk assessment for mutagenicity according to International Council for Harmonisation (ICH) M7 guideline has been performed for all actual and potential impurities. No mutagenicity impurities were detected. An overall risk assessment for elemental impurities in accordance with ICH Q3D guideline is presented.

Elements of quality by design (QbD) (enhanced approach) have been applied during the development of the manufacturing process of the active substance, in order to gain manufacturing process knowledge and to define operating ranges.

Specification

The active substance specification includes tests for appearance (visual), identification (IR, HPLC, PXRD), assay (HPLC), residual solvents (GC), impurities (HPLC), particle size (laser light diffraction), water content (Ph. Eur.), and residue on ignition (Ph. Eur.).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data of active substance stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, degradation products, water content, solid form, particle size, and microbial quality. With the exception of the chiral purity method, the analytical methods used in the primary stability program are the same as the release methods.

There were no trends observed during the stability studies at any of the storage conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. As demonstrated by the photostability in packaging, the current packaging configuration, double antistatic low density polyethylene (LDPE) bags in high density polyethylene (HDPE) drum, adequately protects the active substance; therefore an additional light restriction is not required.

Samples of the active substance were subjected to forced degradation conditions. Overall, lorlatinib is stable under various stressed conditions. No significant degradation was observed.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months with no recommendations on the storage temperature in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is formulated as immediate-release film coated tablets in 2 strengths (25 mg and 100 mg). The 25 mg tablet is presented as a round, light pink film-coated tablet debossed with "Pfizer" in one side and "25" and "LLN" on the other side. The 100 mg tablet is presented as an oval, dark pink film-coated tablet debossed with "Pfizer" on one side and "LLN 100" on the other side.

The formulation and process development of lorlatinib immediate-release film-coated tablets focused on the quality attributes defined in a Quality Target Product Profile (QTPP).

Lorlatinib is categorised as a BCS Class IV active substance (low solubility and low permeability) according to the Biopharmaceutics Classification System. Lorlatinib solubility is pH dependent, with solubility being highest under low pH gastric conditions in the fasted state. As such the impact of active substance particle size was an important consideration during finished product development.

The selection of excipients for the commercial tablet formulations was based on the evaluation of the compatibility of the active substance with platform formulations using an accelerated stability program. Accelerated stability studies comparing coated tablets and uncoated tablet found no impact on stability from film-coating. Supporting development data and registration stability studies showed that the excipients selected are suitable to enable the finished product to achieve acceptable stability. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except Opadry II which complies with internal standards. However, the CHMP recommends submitting an appropriate variation application to establish or adopt a colour reference as part of the Opadry appearance acceptance criteria or alternatively develop an identity test that can distinguish between the two Opadry material types (Tan and Lavender). There are no novel excipients used in the finished product formulation. The list of excipients is included in Section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product has been formulated as an immediate release film-coated tablet for oral administration. Bioequivalence study was performed showing bioequivalence between 25 mg lorlatinib used in Phase 2 clinical tablet and the proposed commercial 25 mg and 100 mg lorlatinib tablets. There were considered bioequivalent.

In vitro dissolution testing was performed to demonstrate the *in vitro* dissolution performance of the proposed commercial lorlatinib tablet strengths and the Phase 2 clinical tablet. The data are shown that there was no difference between the dissolution profiles of the formulations tested.

A risk based approach was taken during the development of the commercial manufacturing process to guide the design of experiments and to ensure that final finished products of acceptable quality and stability are consistently produced. A risk assessment was conducted, which identified potential relationships between manufacturing process parameters finished product quality attributes.

The primary packaging is OPA/Al/PVC foil blisters with aluminium foil backing. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Lorlatinib 25 mg and 100 mg immediate release film-coated tablets are manufactured using a conventional dry granulation process which consists of 8 main steps: de-agglomeration, blending, intragranular lubricant blending, dry granulation (roller compaction and milling), extra-granular lubricant blending, tableting, film-coating and packaging.

The manufacturing process for lorlatinib immediate release 25 mg and 100 mg film-coated tablets uses conventional manufacturing techniques and equipment. The in-process controls are adequate for this type of pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (LC, UV/DAD), assay (LC), degradation products (LC), dissolution (LC), content uniformity (LC), microbial limits (Ph. Eur.)

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches per strength of finished product stored in commercial packaging system for up to 18 months under long term conditions (25 ºC/60% RH and 30°C/75 % RH) and for up to 6 months under accelerated conditions (40 ºC/75% RH) according to the ICH guidelines were provided.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbial purity.

The long-term and accelerated stability studies have demonstrated that the finished has acceptable stability at the proposed storage condition in the proposed commercial packaging configurations.

In addition, one batch per strength packed in HDPE bottles and aluminum foil lidding was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in appearance, assay, water content and dissolution. The degradation product increased under light exposure. No increase was observed in the control samples. Formation of this degradant is controlled by the protective packaging configurations used.

Based on available stability data, the proposed shelf-life of 24 months when stored in OPA/Al/PVC blisters with aluminium foil backing without special storage conditions as stated in the SmPC (Section 6.3) is acceptable**.**

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To submit an appropriate variation application to establish or adopt a colour reference as part of the Opadry appearance acceptance criteria or alternatively develop an identity test that can distinguish between the 2 Opadry material types (Tan and Lavender).

2.3. Non-clinical aspects

2.3.1. Introduction

Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the ALK and ROS1 receptor tyrosine kinase (RTK) that also potently inhibits ALK kinase domain mutations responsible for resistance to ALK inhibitors. Oncogenic fusions of *ALK* and *ROS1* define 2 distinct subsets of human lung adenocarcinoma patients and play essential roles in regulation of tumour cell survival, growth and metastasis (Soda et al, 2007; Bergethon et al, 2012).

2.3.2. Pharmacology

Lorlatinib has been studied in a variety of *in vitro* and *in vivo* studies to determine activity by assessing inhibition of ALK or ROS1 tyrosine kinase activity, kinase selectivity, antitumor efficacy, PK/PD relationships, and mechanism of action. Lorlatinib was evaluated in *in vitro*, *ex vivo*, and *in vivo* safety pharmacology studies to identify potential effects on the cardiovascular, respiratory, and CNSs.

Primary pharmacodynamic studies

In vitro studies

Inhibition of wild-type ALK, wild-type ROS1, and ALK mutant kinase activity in a biochemical enzyme assay (Study PF-06463922_12Mar13_174542)

Recombinant proteins of human ALK and ROS1 kinase domains, including various clinically relevant ALK kinase domain mutants, were used to determine lorlatinib potency against RTK targets in biochemical enzyme assays.

Table 2: Biochemical potencies (Ki) of Lorlatinib for Target Kinases in Recombinant Enzyme Assays

Recombinant Enzyme Assays	K_i, GMean (GCI95)[a]						K_i Ratio Crizotinib/ Lorlatinib[b]
	Lorlatinib			Crizotinib			
Recombinant human ALK wild-type and ALK mutant kinase domains	**nM (range)**	**ng/mL**	**n**	**nM (range)**	**ng/mL**	**n**	
Wild-type ALK	<0.2	<0.08	3	0.72 (0.65-0.80)	0.3	127	>4
ALK^{L1196M}	0.7 (0.4-1.3)	0.3	3	8.1 (7.6-8.7)	3.6	143	12
ALK^{G1269A}	0.9 (0.3-3.0)	0.4	2	20.1 (17.6-23.1)	9.1	4	22
ALK^{F1174L}	<0.1	<0.04	1	0.82 (0.74-0.90)	0.4	3	>8
ALK^{C1156Y}	<0.1	<0.04	1	0.6 (0.1-3.3)	0.3	3	>6
ALK^{L1152R}	<0.1	<0.04	1	2.2 (1.3-3.6)	1	3	>22
$ALK^{1151Tins}$	0.1	0.04	1	2.2	1	1	22
ALK^{S1206Y}	0.2	0.08	1	1.3	0.6	1	7
Recombinant human ROS1 wild-type kinase domain							
Wild-type ROS1	<0.005	<0.002	2	0.12 (0.08-0.19)	0.06	3	>24

K_i = Inhibition constant; GMean = geometric mean; GCI95 = Geometric confidence level.
a. K_i values are geometric means with a geometric confidence 95% interval for n independent measurements.
b. K_i ratio was calculated based on GMean (in nM) of lorlatinib divided by crizotinib Ki.

Inhibition of Wild-type ALK and ALK^{I171T} Kinase Activity in a Biochemical Enzyme Assay

Lorlatinib inhibited recombinant wild-type ALK and ALK^{I1171T} kinase domain in an ATP-competitive enzymatic kinase assay resulting in K_i values of <0.1 nM and 0.25 nM, respectively (Study PF-06463922_29Mar16_055600).

Table 3: Inhibition Constants, Ki and Kiapp (1 mM ATP), for Pre-activated Recombinant Wild-type ALK and ALKI1171T with Lorlatinib and Crizotinib in Biochemical Assays

Compound	K_i, nM			K_i^{app} (1 mM ATP), nM		
	WT	I1171T	n	WT	I1171T	n
Lorlatinib	<0.1	0.25 ± 0.01	2	0.65 ± 0.03	7.8 ± 0.1	2
Crizotinib	0.73 ± 0.01	1.03 ± 0.02	2	8.3 ± 0.2	30.4 ± 0.7	2

The enzymes were preactivated and tested in microfluidic mobility-shift assays. Inhibition constants, Ki (with standard errors, n = 2), were derived using a competitive inhibition equation and experimentally determined ATP K_m (97 and 35 μM for wild-type and ALK^{I1171T}, respectively). ATP = Adenosine triphosphate; K_i = Inhibition constant; K_i^{app} = Apparent inhibition constant; n = number of replicates; WT = Wild type.

Biochemical Profile of Lorlatinib Major Metabolite, PF-06895751

The major metabolite of lorlatinib, PF-06895751, was inactive against wild-type ALK in a biochemical assay at 10, 1 and 0.1 μM doses using a K_m-level of ATP (Study PF-06463922_21Jul17_025806). The lorlatinib metabolite was also inactive against ROS1 and a diverse panel of 40 other kinases at 1 μM.

Kinase Selectivity of Lorlatinib in Biochemical and Cell-based Assays (Study PF-06463922_12Mar13_174542)

To investigate kinase selectivity of lorlatinib relative to its target kinases, ALK and ROS1, lorlatinib was evaluated in biochemical kinase screening assays against a panel of 206 recombinant kinases.

Eleven (11) kinases were identified for which lorlatinib exhibited activity and showed selectivity margins of less than 100x compared to the target ALK^{L1196M}.

The selectivity of lorlatinib was further evaluated in a panel of cell-based assays for selected kinases that were identified as potential relevant hits in biochemical assays.

Table 4: Kinase Selectivity of lorlatinib in Cell-based Assays

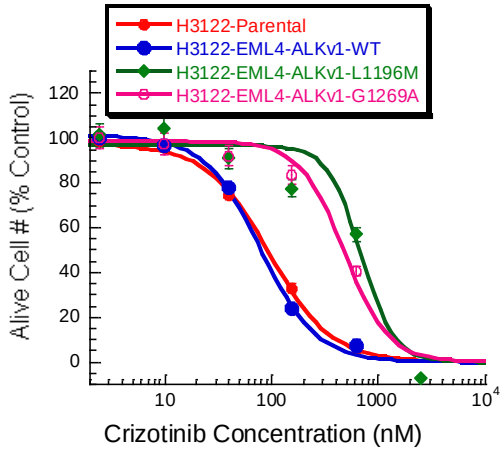
In vitro Cellular Activity Against Non-Target Kinases		Mean Cell IC50 [b]		Selectivity vs ALK-L1196M[c]
Cells	Phosphorylation Target Assayed	nM	ng/mL	
NIH3T3-EML4-$ALKv1^{L1196M}$	Engineered EML4-$ALKv1^{L1196M}$ phosphorylation	21	8.5	1
TrkA-PAE	NGF-stimulated TrkA phosphorylation	>10000	>4064	476
TrkB-PAE	BDNF-stimulated TrkB phosphorylation	229	93	11
A549	EGF-stimulated wild-type EGFR phosphorylation	>10000	>4064	>476
PC9	Endogenous $EGFR^{E746\text{-}A750\ Del}$ phosphorylation	>10000	>4064	>476
NCI-H3255	Endogenous $EGFR^{L858R}$ phosphorylation	>10000	>4064	>476
NCI-H1975	Endogenous $EGFR^{L858R/T790M}$ phosphorylation	>10000	>4064	>476

ALK = Anaplastic lymphoma kinase; BDNF = Brain-derived neurotrophic factor; EGF = Epidermal growth factor; EGFR = EGF receptor; IC50 = 50% inhibitory concentration; NGF = Nerve growth factor; TrkA = Tropomyosin receptor kinase A; TrkB = Tropomyosin receptor kinase B; PAE = Porcine aortic endothelial cells.
a. Reported are either IC50 values at the Km-level of ATP or Ki (where shown).
b. RTK phosphorylation was determined by using ELISA capture methods.
c. Ratio of 476 does not match the study report due to a rounding error in the original report.

Lorlatinib Inhibition of Phosphorylation of ALK and ROS Variants

To confirm inhibition of target kinases in cell lines, the ability of lorlatinib to inhibit the phosphorylation of ALK fusion variants, clinically relevant crizotinib resistant ALK mutants, and ROS1 fusion variants

were evaluated by capture enzyme-linked immunosorbent assay (ELISA) or Western Blot analysis and 50% inhibitive concentration (IC_{50}) values were determined (Study PF-06463922_12Mar13_174542).



HC3122- Parental (endogenous EML4-ALKv1 expression) and HC3122 cells expressing exogenous EML4-ALKv1, EML4-ALKv1^{L1196M}, and EML4-ALKv1^{G11269A} were treated with designated concentrations of crizotinib for 72 hours. The effect of crizotinib on cell proliferation was determined by utilizing a commercially available CellTiter-Glo® Assay kit (Promega).

Figure 2: Acquired Resistance to Crizotinib in H3122-EML4-ALK^{L1196M} and H3122-EML4-ALK^{G1269A} Models

Clinically relevant mutations of EML4-ALK following ALK inhibitor treatment include L1196M, G1269A, F1174L, C1156Y, L1152R, G1202R, S1206Y, 1151Tins, and I1171T. In engineered NIH3T3 cell lines expressing EML4-ALKv1 mutations, lorlatinib inhibited ALK phosphorylation.

Table 5: Lorlatinib potency against ALK fusion variants and ALK fusion mutations in cells (ALK Phosphorylation)

Cell-based ALK phosphorylation (Y1604) ELISA Assay[a]	IC_{50} (Mean ± SEM)				IC_{50} Ratio Crizotinib/ Lorlatinib
	Lorlatinib		Crizotinib		
	nM	n	nM	n	
Endogenous cell lines expressing:					
EML4-ALKv1 in H3122 cells	2.4 ± 0.3	3	87 ± 8.9	29	36
EML4-ALKv3a/b in H2228 cells	1.3 ± 0.4	3	206 ± 41	3	158
NCI-H3122 engineered cells expressing:					
H3122-EML4-ALKv1^{L1196M}	11 ± 0.3	7	535 ± 73	6	49
H3122-EML4-ALKv1^{G1269A}	17 ± 1.9	3	504 ± 135	3	30
NIH3T3 engineered cells expressing:					
EML4-ALKv1	1.5 ± 0.4	5	80 ± 37	101	53
EML4-ALKv2	1.4 ± 0.1	2	96 ± 3.7	2	69
EML4-ALKv3a	0.9 ± <0.1	2	55 ± 2.8	2	61
EML4-ALKv3b	1.0 ± <0.1	2	76 ± 13	2	76
KIF5B-ALK	0.5 ± 0.2	3	29 ± 6.4	3	58
EML4-ALKv1^{L1196M}	21 ± 2.3	5	843 ± 382	101	40
EML4-ALKv1^{G1269A}	15 ± 8.5	2	605 ± 90	4	40
EML4-ALKv1^{F1174L}	0.2 ± <0.1	2	165 ± 36	4	825
EML4-ALKv1^{C1156Y}	1.6 ± 1.4	2	478 ± 153	4	299
EML4-ALKv1^{L1152R}	9 ± 7	2	1026 ± 71	4	114
EML4-ALKv1^{G1202R}	65 ± 23	4	1148 ± 471	4	18
EML4-ALKv1^{1151Tins}	46 ± 0.7	2	3039 ± 39	2	66
EML4-ALKv1^{S1206Y}	4.2	1	626	1	149
EML4-ALKv1^{I1171T}	7.1 ± 2.0	3	240 ± 68	3	34

ELISA = Enzyme-linked immunosorbent assay; IC_{50} = 50% inhibitory concentration; n = Number of replicates; SEM = Standard error of the mean.
a. The cells were treated with lorlatinib, crizotinib, or vehicle in the serum free media for 1 hour, and lysed by using the Cell Lysis Buffer (Cell Signaling Technologies). The ALK-tyrosine 1604 (Y1604) phosphorylation in cell lysates was determined utilizing a commercially available PathScan® Phospho-ALK Chemiluminescent Sandwich ELISA Kit (Cell Signaling Technologies). IC_{50} values were calculated by concentration-response curve fitting utilizing a four-parameter analytical method.
Sources: Study PF-06463922_12Mar13_174542 and Study PF-06463922_29Mar16_055600.

In the panel of NIH3T3-ROS1 cell lines engineered to express ROS1 fusion proteins, lorlatinib inhibited ROS1 kinase activity with IC_{50} values ranging from 0.23 nM to 1.30 nM.

Lorlatinib Inhibition of Cell Proliferation (Study PF-06463922_12Mar13_174542)

Lorlatinib was evaluated for its ability to inhibit ALK fusion or mutant ALK fusion dependent cancer cell growth in a panel of human NSCLC cells that harbour ALK fusion proteins.

Table 6: Effect of lorlatinib on ALK Fusion or ROS1 Fusion Dependent Phenotypes

Cell-based Functional Assays		IC_{50} (Mean ± STD)				IC_{50} Ratio Crizotinib/ Lorlatinib
		Lorlatinib		Crizotinib		
		nM	n	nM	n	
Cell line	**ALK or ROS1 Fusion**					
	ALK fusion driven cell proliferation[a]					
H3122	Endogenous EML4-ALK v1	2.4 ± 0.3	4	108 ± 29	4	45
H2228	Endogenous EML4-ALK v3a/b	1.3 ± 0.1	3	118 ± 14	3	91
H3122	Engineered EML4-ALK $v1^{L1196M}$	30 ± 7	3	838 ± 154	3	28
H3122	Engineered EML4-ALK $v1^{G1269A}$	30 ± 16	4	623 ± 251	4	21
Ba/F3	Engineered EML4-$ALKv1^{I1171T}$	14 ± 12	5	225 ± 148	5	16
	ALK fusion driven cell apoptosis[b]					
H3122	Endogenous EML4-ALK v1	4.9 ± 0.2	3	149 ± 8	3	30
H3122	Engineered EML4-ALK $v1^{L1196M}$	29 ± 5.7	3	1520 ± 372	3	52
H3122	Engineered[c] EML4-ALK $v1^{G1269A}$	28 ± 4.9	3	1526 ± 291	3	55
	ROS1 fusion driven cell proliferation					
HCC78	Endogenous SLC34A2-ROS1	2.6 ± 3	3	41 ± 14	3	16
BaF3	Engineered CD74-ROS1(s)	0.6 ± 0.5	4	5.9 ± 4.4	4	10

IC_{50} = 50% inhibitory concentration; n = Number of replicates; STD = Standard deviation.
a. Cell proliferation was determined by utilizing a commercially available CellTiter-Glo® Assay kit (Promega).
b. Cell apoptosis was determined by using a commercially available Caspase-Glo® 3/7 Assay kit (Promega).
c. Corrected typo where incorrect mutant number was written in study report.
Sources: Study PF-06463922_12Mar13_174542 and Study PF-06463922_29Mar16_055600.

In vivo studies

Summary of in vivo primary pharmacodynamic studies

Study Reference /Study Type	Species (Strain)	Dose (mg/kg) Route	Results
PF-06463922_12Mar13_174736 Inhibition of ALK Phosphorilation in ALKv1, ALK^{L1196M}, ALK^{G1269A} Xenofraft Tumours	Human lung adenocarcinoma xenograft model nu/nu or anthymic mouse implanted with H3122 cells expressing active EML4-ALKv1, EML4-$ALKv1^{L1196M}$ and EML4-$ALKv1^{G1269A}$ fusion protein	0.06 to 40 mg/kg/day 6 to 14 days PO BID or subcutaneous pump infusion	PF-06463922 dose-dependently inhibited ALK activity in the ALK fusion driven tumour xenograft models. **EC_{50}s of PF-06463922 against ALK phosphorylation in tumours:** ALK in H3122 model = 4.4 nM ALK^{L1196M} in H3122-EML4-ALK^{L1196M} model = 36 nM (BID study) ALK^{L1196M} in H3122-EML4-ALK^{L1196M} model = 66 nM (SC infusion pump study) ALK^{G1269A} in H3122-EML4-ALK^{G1269A} model = 31 nM
PF-06463922_29Mar16_055600 Inhibition of ALK Phosphorilation in, ALK^{I1171T} Xenofraft Tumours	Lung adenocarcinoma xenograft model anthymic mouse implanted with NIH3T3 cells expressing active EML4-$ALKv1^{I1171T}$	0.3, 1 and 3 mg/kg/day for 9 days Subcutaneous pump infusion	ALK^{I1171T} in H3122-EML4-ALK^{1171T} model = 6.4 nM

Study Reference /Study Type	Species (Strain)	Dose (mg/kg) Route	Results
PF-06463922_22 Jun17_020236 Inhibition of ALK Phosphorilation in, ALK^{G1202R} Xenofraft Tumours	Lung adenocarcinoma xenograft model nu/nu mouse implanted with NIH3T3 cells expressing active EML4-$ALKv1^{G1202R}$	0.75, 2.5, 7.5, 20, or 25 mg/kg/day for 6 days Subcutaneous pump infusion	ALK^{G1202R} in H3122-EML4-ALK^{G1202R} model = 190 nM
PF-06463922_12Mar13_174736 Antitumor activity Xenofraft Tumours	Human lung adenocarcinoma xenograft model nu/nu or anthymic mouse implanted with H3122 cells expressing active EML4-ALKv1, EML4-$ALKv1^{L1196M}$ and EML4-$ALKv1^{G1269A}$ fusion protein	0.06 to 40 mg/kg/day 12 to 13 days PO BID or subcutaneous pump infusion	PF-06463922 dose-dependently inhibited tumour growth and induced tumour regression in ALK fusion driven tumour xenograft models. H3122 model: 59% regression at 3 mg/kg/day SC infusion; H3122-EML4-$ALKv1^{L1196M}$ model: 63% regression at 20 mg/kg/day PO BID; 57% regression at 15 mg/kg/day SC infusion; H3122-EML4-$ALKv1^{G1269A}$ model: 59% regression at 25 mg/kg/day SC infusion **PF-06463922 plasma concentration to achieve tumour stasis:** H3122 model = 6.5 nM H3122-EML4-$ALKv1^{L1196M}$ model (PO, BID) = 51 nM H3122-EML4-$ALKv1^{L1196M}$ model (SC infusion) = 68 nM H3122-EML4-$ALKv1^{G1269A}$ model = 54 nM
PF-06463922_29Mar16_055600 Antitumor activity Xenofraft Tumours	Human lung adenocarcinoma xenograft model anthymic mouse implanted with NIH3T3 cells expressing active EML4-$ALKv1^{I1171T}$	0.3, 1 and 3mg/kg/day for 9 days Subcutaneous pump infusion	Dose dependent antitumor efficacy of PF-06463922 and correlation to inhibition of EML4-ALK^{I1171T} phosphorylation observed. ALK^{I1171T} phosphorylation (100% inhibition) and antitumor efficacy (50% regression) achieved in the 3 mg/kg/day dose group with a mean unbound plasma Cav of 118 nM. **PF-06463922 plasma concentration to achieve tumour stasis:** NIH3T3-EML4-ALK^{I1171T} model = 19 nM.
PF-06463922_22 Jun17_020236 Antitumor activity Xenofraft Tumours	Lung adenocarcinoma xenograft model nu/nu mouse implanted with NIH3T3 cells expressing active EML4-$ALKv1^{G1202R}$	0.75, 2.5, 7.5, 20, or 25 mg/kg/day for 6 days Subcutaneous pump infusion	Dose dependent antitumor efficacy of PF-06463922 and correlation to inhibition of EML4-ALK^{G1202R} phosphorylation observed. At 2.5 mg/kg/day, 71% TGI and tumour regression of 34%, 76%, and 77% at the 7.5, 20, and 25 mg/kg/day, respectively. EC_{50} for tumour growth inhibition was 165 nM which correlated with tumour stasis concentration.

Study Reference /Study Type	Species (Strain)	Dose (mg/kg) Route	Results
PF-06463922_12 Mar 13_174736 Antitumor activity Xenofraft Tumours	Lung adenocarcinoma xenograft model anthymic mouse implanted with NIH3T3 cells expressing active ROS1 fusion protein	0.02 to 6 mg/kg/day for 9 days PO BID	PF-06463922 dose-dependently inhibited tumour growth and induced tumour regression (85% regression at 6 mg/kg/day) in ROS1 fusion driven tumour xenograft model. **PF-06463922 plasma concentration to achieve tumour stasis:** NIH3T3-CD74-ROS1 model = 5.6 nM.
PF-06463922_12 Mar 13_174736 Antitumor activity in Brain Xenofraft Tumours	Human lung adenocarcinoma xenograft model anthymic mouse implanted with H3122 cells expressing active EML4-ALKv1, EML4-ALKv1^{L1196M} fusion protein	6 mg/kg/day in h3122-luciferase model ;5, 10 and 20 mg/kg in H3122-EML4-ALK^{L1196M} luciferase model Subcutaneous pump infusion	Lorlatinib reduced tumour burden at 6 mg/kg/day in H3122-luciferase and at 5, 10, and 20 mg/kg/day in H3122-EML4-ALK^{L1196M}-luciferase model (with plasma exposure levels ranging from 215 nM to 571 nM of free drug).

- **Functional Biomarker Analysis in the H3122-EML4-ALKv1^{L1196M} and NIH3T3-CD74-ROS1 Tumour Models (Study PF-06463922_12Mar13_174736).**

Significant dose-dependent induction of caspase 3 levels was observed at 3 and 10 mg/kg BID groups (doses that showed significant antitumor efficacy) coupled with an upregulation of pre-apoptosis protein BIM. In addition, a dose-dependent inhibition of Ki67 was also observed in the 3 and 10 mg/kg treatment groups. Marked dose-dependent inhibition of phosphorylated ALK, ERK, AKT, and STAT3 was observed at dose levels of 1, 3, and 10 mg/kg/day at 1-hour and 3-hour time points post dose following 4-days of lorlatinib treatment (PO, BID). Similar effects with these markers were also observed following 1 hour of lorlatinib treatment in cells, with the exception that AKT (S473) inhibition was less significant than in tumour tissues. Furthermore, a significant and dose dependent down-regulation of cell cycle protein cyclin D1 and transcription regulator Myc was observed in the 3 and 10 mg/kg/day groups in the H3122-EML4-ALKv1^{L1196M} model corresponding to inhibition of cell proliferation (Ki67 and cell viability), induction of apoptosis (caspase 3), and significant antitumor efficacy.

Secondary pharmacodynamic studies

In the assessment of secondary pharmacology, lorlatinib was profiled *in vitro* against a broad panel of receptors, enzymes, transporters, and ion channels in a wide ligand screening panel at concentrations up to 10 μM. Less than 50% inhibition of binding or enzymatic activity was observed against most profiled targets with the exception of the following enzymes: acetylcholinesterase (73.0% inhibition), AurA/Aur2 kinase (87.0% inhibition), EGFR (73.6% inhibition), and Lck (53.4% inhibition), with the enzymatic 50% inhibitory concentration (IC_{50}) values for these activities determined to be >7000x the enzymatic IC_{50} value for the target ALKL^{1196M} (0.7 nM, 0.3 ng/mL).

The kinase selectivity profile of lorlatinib was also evaluated in a broad biochemical kinase panel of 206 recombinant kinases. Eleven (11) kinases were identified for which lorlatinib exhibited activity and showed selectivity margins of less than 100x compared to the target ALKL1196M.

There was no binding or enzymatic activity at 10 μM for the metabolite PF-06895751.

Safety pharmacology programme

Lorlatinib was evaluated in *in vitro*, *ex vivo*, and/or *in vivo* safety pharmacology studies to identify potential effects on the cardiovascular, respiratory, and CNS.

- *Cardiovascular Effects*

In vitro, lorlatinib inhibited hERG (IC_{50}=82,489 ng/ml) and calcium currents (IC_{50} = 17,871 ng/ml), ICs_{50} that correspond to 350x and 76x the human clinical exposure at 100 mg once daily (C_{max} = 236 ng/ml), respectively. Inhibition of the sodium current was not observed at doses ≤100 µM.

Antagonist effect on calcium channel was not observed in the isolated rat aorta model where lorlatinib did not produce vasoconstriction in aortic rings at ≤30 µM.

Ex vivo, lorlatinib induced an increase in PR interval in a concentration-dependent manner from 1 µM (406 ng/ml) to 30 µM (12,193 ng/ml). There were no effects on any other parameters evaluated such as dP/dt (contractility), left ventricular pressure, coronary perfusion pressure, QRS and QT intervals.

The *in vivo* study has been conducted in conscious animals. Oral administration of lorlatinib induced an increase in systolic, diastolic and mean blood pressure, an initial decrease and later increase in heart rate in rat at 10 and 30 mg/kg. No exposure measures were conducted in this study. In a previous single-dose rat toxicokinetic study, the administration of lorlatinib at 10 and 30 mg/kg resulted in unbound AUC_{24} values of 4700 and 16,200 ng·h/ml, respectively, and unbound C_{max} values of 524 and 1640 ng/ml, respectively. In dog, oral administration of lorlatinib at 15 mg/kg/day induced an increase in heart rate and decrease systolic blood pressure, PR and QRS interval prolongation and increase fractional shortening with unbound mean C_{max} and AUC_{24} values of 519 ng/ml and 6690 ng·h/ml, respectively. No cardiovascular changes were observed at doses of 2 mg/kg/day with associated unbound mean C_{max} and AUC_{24} values of 68 ng/ml and 890 ng·h/ml, respectively.

PF-06895751, a major human circulating metabolite of lorlatinib, did not inhibit hERG potassium ion channels with an IC_{50} >300 µM (55,260 ng/ml).

- *Neurofunctional Effects*

Lorlatinib was shown to be a brain penetrable compound, with measurable concentrations in the brain and CSF in the rat, dog, and human.

Lorlatinib caused a significant reduction in amplitude of long term potentiation in hippocampal brain slices, a measure that is widely considered to be one of the cellular mechanisms that underlie learning and memory formation. This effect was observed at 1 µM (406 ng/mL), a concentration above the cell-based TrkB IC_{50} of 93 ng/mL whereas the effect was not observed at 0.1 µM (41 ng/ml).

In a contextual renewal model, lower memory recall scores were observed at ≥3 mg/kg/day following a single dose of lorlatinib. The unbound brain concentrations of lorlatinib (137 and 511 ng/g[4]) at 10 and 30 mg/kg doses, respectively, exceeded both the wild-type cell-based ALK IC_{50} of 0.6 ng/ml (primary pharmacology) and was similar to the cell-based TrkB IC_{50} of 93 ng/ml (secondary pharmacology). At 3 mg/kg, variability in the pharmacologic sensitivity was identified between studies, with the unbound brain concentrations of lorlatinib (24.6 to 31.4 ng/g) below the cell based TrkB IC_{50}. No effects were observed on cue-induced renewal responding or total number of nose pokes, other measurements of cognitive function, or indirect measures of activity.

In addition, after 14 days of lorlatinib administration to rats, on Day 3 and 13, functional effects were observed such as, abnormal behaviour (i.e. teeth chattering), involuntary movements (i.e. retropulsion and trembling), reduced handling reactivity, decreased arousal, abnormal gait, and reduced reflex responses (i.e. uncoordinated air righting-reflex, and reduced extensor thrust response). There were

no lorlatinib-related FOB findings at ≤20 mg/kg/day. No functional observational effects were identified in the pivotal toxicity studies following 4 and 13 weeks of dosing. There were no microscopic findings observed in the CNS in any of the studies conducted in rats or dogs, although non-adverse lower brain weights were observed in rats after 13 weeks of lorlatinib administration. The no-observed-adverse-effect-level (NOAEL) in rats, 15 mg/kg/day with an associated unbound AUC_{24} exposure of 13,600 (males) and 39700 ng•h/ml (females) following 13 weeks of lorlatinib administration, provide a margin of 7.1x the unbound human steady-state AUC exposure (1920 ng·h/ml) at the recommended dose of 100 mg QD.

- *Respiratory Effects*

Lorlatinib was administered to male rats (6/group) at single doses of 0 (vehicle), 10, 30, or 100 mg/kg. Statistically significantly lower mean tidal volumes were observed at doses ≥30 mg/kg. There were no significant changes in respiratory rate or minute volume at ≤100 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies with lorlatinib have been submitted (see non-clinical discussion).

Pharmacokinetics

The non-clinical pharmacokinetic/toxicokinetic, absorption, distribution, metabolism, and excretion (ADME) properties of lorlatinib (PF-06463922) were evaluated *in vivo* in rats and dogs and to a lesser extent in rabbits using oral and/or intravenous (IV) routes of administration. *In vitro* studies were also conducted to assess plasma protein binding of lorlatinib, partitioning of lorlatinib into red blood cells, hepatic uptake properties by transporters, drug metabolism of lorlatinib, and to assess the effects of lorlatinib on selected cytochrome P450 (CYP) enzymes, uridine diphosphate glucuronosyltransferase (UGT) enzymes, and selected efflux and uptake transporter activities.

An LC-MS/MS method has been developed for quantification of lorlatinib in rat, rabbit and dog plasma. This method appears to be sufficiently validated for the TK studies. Furthermore, a non-validated LC-MS/MS method has been used to measure lorlatinib concentrations in brain and CSF for both rats and dogs. An LC MS/MS method was also developed and validated for quantification of the metabolite, PF-06895751 in both rat and dog plasma to be used in the 13-week toxicity studies. The applied analytical methods are considered appropriate and validated for their purpose.

Absorption

In rats and dogs, following intravenous (IV) administration, lorlatinib exhibited low plasma clearance (CL) of 15.5 ml/min/kg in rats and 9 ml/min/kg in dogs, and a volume of distribution (Vss) of 2.66 L/kg in rats and 2.8 L/kg in dogs, which exceeded total body water, suggesting extensive distribution to tissues. Oral bioavailability was high (>100% in rats and 96.6% in dogs).

The toxicokinetics of lorlatinib were evaluated as part of oral repeat-dose toxicity studies in rats and dogs, EFD studies in rats and rabbits, and in support of phototoxicity evaluation.

The systemic exposure to lorlatinib increased with increasing dose over the dose range evaluated in the toxicology studies.

PF-06895751 (or M8) was a major pharmacologically inactive metabolite in human plasma that was also observed in rat and dog plasma following oral administration of 13-week repeat doses of lorlatinib. However, the unbound plasma area under the concentration-time curve (AUC) of PF-06895751 in rat

and dog plasma following oral administration of repeat doses of lorlatinib was <4% of that observed in humans after oral administration of multiple doses of lorlatinib (100 mg once daily [QD]).

Lorlatinib was not a substrate for P-gp or BCRP, and these efflux mechanisms are expected to have minimal effect on the absorption of lorlatinib.

Distribution

[^{14}C]Lorlatinib-derived radioactivity was well distributed to most tissues and organs in male pigmented Long Evans rats, and was consistent with a Vss for lorlatinib that exceeded total body water. The uptake and retention of [^{14}C]lorlatinib-derived radioactivity was particularly prominent in the pigmented uveal tract. Tissues with the highest C_{max} values for radioequivalents were observed for the uveal tract, liver, intervertebral discs, adrenal gland, and Harderian gland. Radioactivity concentrations were observed for up to 24 hours post-dose in non-circumventricular CNS tissues protected by the blood-brain barrier. In the vast majority of tissues, the elimination of [^{14}C]lorlatinib-derived radioactivity was complete by 96 hours post-dose. However, the QWBA shows a high AUC_{last} and a slow $t_{½}$ (more than 10 days) in some tissues like the eyes, the kidneys and the thyroid after a single oral dose of 10 mg/kg. However, a rapid decline in lorlatinib concentration was seen during the first 48 hours pose dose, followed by a slow terminal $t_{½}$ in these tissues.

Lorlatinib can cross the BBB and distribute to the CNS tissues in rats and dogs. In addition, quantifiable lorlatinib concentrations were also observed in brain and CSF samples obtained at necropsy in the 4-week toxicity study in rats and dogs.

In HEK293 cells transfected with OATP1B1 or OATP1B3, lorlatinib was not a substrate for either of these hepatic uptake transporters.

Lorlatinib and its major pharmacologically inactive metabolite (M8, PF-06895751) in humans showed moderate binding to proteins in mouse, rat, rabbit, dog, and human plasma.

In vitro, lorlatinib showed similar partitioning between the blood cells and plasma compartments for mouse, rat, rabbit, dog, and human.

Placental transfer of lorlatinib was not studied.

Metabolism

In vivo

After oral administration, the major primary metabolic pathways of [^{14}C]lorlatinib in rats and humans involved oxidation and glucuronidation, while oxidation was mainly involved in dogs. Although the glucuronidation pathway for lorlatinib was observed in both rats and humans, the positions of the glucuronide conjugates on the lorlatinib molecule differed between rats (M1b) and humans (M1a).

Similarity in the oxidative metabolic pathways and the presence of the major human circulating metabolite (M8) supports the selection of rats and dogs as the non-clinical species for toxicology evaluations.

Lorlatinib (PF-06463922) and pyrazole N-desmethyl lorlatinib (M2a, PF-06648706) were the major circulating entities in rat and dog plasma.

In human plasma, lorlatinib was the most abundant drug-related component, representing 44.4% of plasma AUC of the circulating radioactivity. The major circulating metabolite for lorlatinib in humans was a cleaved product of lorlatinib (PF-06895751, M8), which likely was formed via multiple biotransformation steps and accounted for 21% of circulating radioactivity. This metabolite constituted a disproportionate circulating metabolite as the unbound plasma AUC in humans (854 ng•h/ml) following oral administration of multiple 100 mg QD doses of lorlatinib (CSR; Study B7461001)

exceeded those observed in rats (32.1 ng•h/ml [male], 9.32 ng•h/ml [female]) and dogs (20.1 ng•h/ml) at the highest doses tested in the 13-week toxicity studies.

In vitro

The *in vitro* metabolism of lorlatinib in liver microsomes and hepatocytes was generally low across the evaluated species (mouse, rat, rabbit, dog, monkey, and human).

CYP-mediated metabolism contributed approximately 67% to the clearance for lorlatinib based on parent drug disappearance, with ~33% of the clearance derived from non-CYP mediated process.

Lorlatinib was mainly metabolised by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP1A2, CYP3A5, and UGT1A3. Formation of PF-06895751 likely involved, at least in part, CYP3A4/5 as administration of itraconazole with lorlatinib to humans reduced the plasma AUC for this metabolite compared to lorlatinib alone.

In *in vitro* studies, CYP3A4 was consistently identified to contribute to the formation of M6. Formation of M2a was mediated mainly by CYP3A4 and CYP3A5, with minor contributions from CYP2C8, CYP2C19, and CYP1A2.

Glucuronidation of lorlatinib constituted a major clearance pathway in humans, with the glucuronide conjugate (M1a, PF-06924938) comprising a mean of ~13.5% of dose in excreta (10.9% in urine, 2.6% in faeces). Results from *in vitro* evaluations using HLM and recombinant human (rh)UGT enzymes indicated that UGT1A4 was the primary enzyme mediating the glucuronidation of lorlatinib to form M1a, with minor contribution from UGT1A3.

Excretion

Following oral administration of [^{14}C]lorlatinib, the primary route of elimination of radioactivity was via the faeces in rats and dogs, whereas in humans, elimination involved both the urinary (47% dose recovered) and faecal routes (40.9% dose recovered). Excretion in milk was not tested.

Pharmacokinetic drug interactions

Lorlatinib and cytochromes

In vitro, lorlatinib demonstrated little or no reversible or time dependent inhibition (TDI) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 enzyme activities (half maximal inhibitory concentration [IC_{50}] >100 µM) except for CYP2C9 where IC_{50} for reversible inhibition was 44 µM and for CYP3A4/5 where IC_{50} were 23, 10 and 22 µM for testosterone 6β-hydroxylation, midazolam 1'-hydroxylation, and nifedipine oxidation, respectively.

Although *in vitro*, lorlatinib showed reversible inhibition and TDI towards CYP3A4/5, in human hepatocytes, lorlatinib has also been shown to induce CYP3A4 and to activate human pregnane X receptor (hPXR).

PF-06895751, the major circulating metabolite of lorlatinib in humans, showed little or no reversible inhibition and no TDI for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at concentrations up to 100 µM. PF-06895751 showed weak TDI for CYP3A4/5.

In human hepatocytes, lorlatinib caused a dose-dependent induction of CYP3A4 at concentrations ≥0.1 µM, and the same for dose-dependent induction of CYP3A4/5 activity (midazolam 1' hydroxylation) at concentration up to 3 or 10 µM and it also caused activation of the hPXR in a dose-dependent manner over the concentration range of 0.01 to 100 µM, with the EC_{50} and the E_{max} of 2.76 and 13-fold, respectively, comparable to those observed with rifampin (2.76 µM and 13-fold, respectively).

Treatment of human hepatocytes with lorlatinib caused ≥2-fold dose-dependent induction of CYP2B6 mRNA and enzymatic activity (bupropion hydroxylation) at concentrations of ≥0.5 µM. In addition, lorlatinib (0.01-50 µM) also caused dose-dependent hCAR1 activation up to 6.46-fold, while the positive controls phenobarbital (3.1 to 750 µM) and CITCO (0.005 to 20 µM) showed dose-dependent activation of up to 3.05 and 22.46-fold.

In vitro, lorlatinib showed an increase (≥2-fold) in CYP1A2 mRNA in 1 of 3 lots of human hepatocytes at concentrations ≥50 µM, but no induction of the enzymatic activity in all 3 lots. The lowest concentration associated with no induction of CYP1A2 messenger ribonucleic acid (mRNA) (30 µM) exceeded the 50x unbound C_{max} ($C_{max,u}$) value (~24 µM).

In vitro, PF 06895751 showed a low potential to cause induction of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Lorlatinib and UGTs (UDP-glucoronyl transferase)

In vitro studies indicated a low likelihood of inhibitory DDI by lorlatinib with UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 but the IC_{50} value obtained for inhibition of UGT1A1 (46 µM) indicates there may be a potential for lorlatinib to inhibit UGT1A1. PF-06895751 demonstrated little or no reversible inhibition of UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 (IC_{50} >100 µM) in HLM with or without the addition of 2% BSA.

Lorlatinib and protein transporters

Lorlatinib showed a low potential to cause DDI by inhibiting BCRP (systemically), OAT1, OCT2 and MATE2K, but has the potential to inhibit P-gp (systemically and GI tract), BCRP (GI tract), OATP1B1, OATP1B3, OCT1, OAT3, and MATE1 at clinically relevant concentrations. Since lorlatinib is an activator of hPXR *in vitro*, which regulates the expression of P-gp (Urquhart et al., 2007), the net effect of lorlatinib on P-gp activity *in vivo* is not known.

In vitro, PF-06895751 did not inhibit the activities of Pgp and BCRP mediated efflux of respective substrates at concentrations up to 268 µM, OATP1B1, OATP1B3 or OCT1 at concentrations up to 50 or 100 µM and OAT1, OAT3, OCT2, MATE1, or MATE2K at concentrations up to 50 or 100 µM.

2.3.3. Toxicology

The oral route of administration was selected for these studies since it is the intended route of clinical exposure. Rats and dogs were dosed twice daily (BID), approximately 6 or 7 hours apart to ensure appropriate exposure in a 24-hour period and was also supportive of the continuous daily dosing planned in the clinic. Due to a gender difference in exposure observed in rats, doses in the 4- and 13-week rat toxicity studies were twice as high in male as in female animals, in an attempt to achieve comparable systemic exposures.

Most of the pivotal toxicity studies were conducted using the free base of lorlatinib (PF-06463922, anhydrous form); however, the genotoxicity studies and some of the pivotal and non-pivotal and investigational studies used the acetic acid solvate form of lorlatinib (PF-06463922-14), and the 14-day non-pivotal toxicity study in dogs and electro-retinography study in rats used the hydrochloride salt form of lorlatinib (PF-06463922-01). The free base form of lorlatinib represents the form that will be commercially available for clinical use.

Single dose toxicity

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
PF-06463922 Non- GLP	Rat/3M	0, 10, 30, 100 mg/kg Oral gavage	MTD: 100 mg/kg/day	**100 mg/kg**: Reduced activity, pancreas (minimal degeneration of islet cells, ↑ vacuolation, single cell necrosis)
PF-06463922 Non-GLP	Dog/1M and 1F	25, 50, 100 mg/kg Oral gavage	MTD: 100 mg/kg/day	**100 mg/kg**: reduced body weight, emesis, watery faeces, Increased WBC, Increased neutrophil, Increased monocyte

Repeat dose toxicity

Lorlatinib was administered to rats and dogs in toxicity studies up to 13 weeks in duration with BID dosing. Moribundity preceded by clinical signs of intolerance was observed in repeat-dose toxicity studies at ≥30 mg/kg/day in rats and ≥25 mg/kg/day in dogs where systemic exposure exceeded exposure at clinically relevant doses.

The main target organs:

- Inflammation was observed in the skin and cervix of rats and the lung, trachea, skin, lymph nodes and/or the oral cavity including mandibular bone of dogs in repeat-dose studies of ≥4 weeks in duration and was associated with moribundity in dogs during the 13-week repeat-dose toxicity study. Inflammation in multiple tissues was associated higher WBC counts, fibrinogen, and/or globulin and lower albumin in rats and dogs. The inflammatory response in tissues and associated changes in clinical pathology parameters were partially to completely reversible following a 4-week non-dosing period in both rats and dogs.

-Pancreas: acinar atrophy with decreased zymogen granules and occasional single cell necrosis, and/or islet angiectasis. The incidence and severity of the pancreatic findings were dose-related and often correlated with elevations of amylase and lipase.

-Hepatobiliary system: Bile duct hyperplasia associated with elevations in liver enzymes (ALT, AST, ALP, GLDH, and/or GGT) was observed in rats and dogs. Increases in sinusoidal Kupffer cell pigmentation and mild haemorrhage in the mucosa of the gallbladder was also observed after 13 weeks of dosing in dogs. Findings in the liver included higher liver weights in rats with microscopic observations of hepatocellular hypertrophy and/or increased sinusoidal cellularity; higher liver weights with no microscopic correlates was observed in dogs. The bile duct hyperplasia was considered adverse when associated with increased bilirubin or presence of icterus in rats and when at moderate severity in dogs.

-Male reproductive organs: seminiferous tubule degeneration with associated secondary effects and/or glandular atrophy of the prostate were observed in rats and dogs in repeat-dose toxicity studies ≥2 weeks in duration. Partial or complete reversibility of the effects was demonstrated.

-Cardiovascular system: changes in blood pressure and heart rate and associated secondary effects on cardiac parameters of lorlatinib were identified in telemetered rats and dogs in single- and/or repeat-dose studies. Higher heart weights with no microscopic correlates were observed in rats after 4 weeks of dosing; higher heart weights associated with minimally increased cellularity of Anichkov cells was identified after 13 weeks of dosing. These changes likely reflect a compensatory response to hemodynamic changes and not a direct effect on cardiac tissue. Lorlatinib administration to dogs

resulted in ECG changes with increases in PR intervals considered to be a direct effect of lorlatinib; other changes were considered secondary to increased heart rate.

-Gastrointestinal tract: Clinical signs of gastrointestinal effects (emesis and/or abnormal faeces), stomach (erosions and/or ulceration), and intestinal macroscopic/microscopic findings (non-adverse single cell necrosis, villous atrophy, crypt hyperplasia, epithelial degeneration, and/or subacute inflammation) were observed in rats and/or dogs. Partial or complete reversibility of the effects was demonstrated.

-Peripheral nerves: Axonal degeneration was observed in rats at ≥4 weeks of dosing. Dysregulation of BDNF-TrkB signalling through TrkB inhibition might be a potential mechanism of the observed axon degeneration. Complete reversibility of axon degeneration in rats.

-CNS: No functional observational effects were identified in the pivotal toxicity studies following 4 and 13 weeks of dosing. Functional observational battery effects after 14 days of lorlatinib administration to rats included abnormal behaviour (i.e. teeth chattering), involuntary movements (i.e. retropulsion and trembling), reduced handling reactivity, decreased arousal, abnormal gait, and reduced reflex responses (i.e. uncoordinated air righting-reflex, and reduced extensor thrust response) at 60 mg/kg/day. No functional observational effects were identified in the pivotal toxicity studies following 4 and 13 weeks of dosing at doses up to 30 mg/kg/day, despite achieving comparable systemic exposures as the 60 mg/kg/day in the 14-day study. There were no microscopic findings observed in the CNS in any of the studies conducted in rats or dogs, although non-adverse lower brain weights were observed in rats after 13 weeks of lorlatinib administration. The potential for an effect on cognitive function was suggested from an *ex vivo* hippocampal brain slice assay and an exploratory *in vivo* contextual renewal model in rats.

-Kidney: Renal changes including glomerulopathy, arterial degeneration/necrosis, increased incidence and/or severity of tubular basophilia and pigmentation, and hyaline casts were observed in rats following 13 weeks of dosing, and correlated with urinalysis changes. Alterations in renal biomarkers without microscopic correlates were observed in rats at 4 weeks. The renal changes in rats were partially or completely reversible.

-Haematolymphopoietic system: Alterations in the cellularity of the spleen, lymph nodes, and/or thymus with associated haematological changes were identified in rats and dogs following ≥2 and ≥4 weeks of lorlatinib administration, respectively. The haematolymphopoietic findings were not considered adverse due to limited severity and/or adaptive nature of the changes. Partial or complete reversibility was demonstrated.

-Body weight changes: Lorlatinib administration caused dose-related non-adverse higher body weight and body weight gain that correlated with higher food consumption in rats after ≤13 weeks of lorlatinib administration. Similar lorlatinib-related effects did not occur in dogs.

-Hyperlipidaemia (cholesterol and triglycerides) was observed in rats and dogs following ≥2 weeks lorlatinib administration. The finding of increased food consumption, body weight gain, and cholesterol after lorlatinib administration were likely due to off-target inhibition of TrkB.

Other non-adverse findings observed inconsistently in rats and/or dogs after ≥4 weeks of lorlatinib administration included minimal to moderate mammary gland atrophy (male rats), minimal secretory depletion in the salivary (rats), and changes in adrenal gland weight (decreased in rats and increased in dogs), minimal electrolyte imbalances (rats and dogs), uterine atrophy (rats), and minimal decreases in brain weight (rats).

The NOAELs were identified as 8/4 (M/F) mg/kg/day in rats and 7 mg/kg/day in dogs, with associated unbound AUC_{24} exposures of 6240/7820 ng•h/ml and 2980 ng•h/ml, respectively, following 13 weeks

of lorlatinib administration. The NOAELs in rats and dogs provide margins of 3.3x (male)/4.1x (female) and 1.6x, respectively, the unbound human steady-state AUC exposure of 1920 ng•h/mL at the recommended dose of 100 mg QD. However, it seems that the NOAELs following 13 weeks of BID dosing in rats and dogs were not well established given the toxicities observed at those doses.

The exposure of the main metabolite of lorlatinib (PF-06895751, M8) were obtained from 13-week repeat-dose toxicity studies in rats and dogs. However, the unbound plasma area under the concentration-time curve (AUC) of PF-06895751 in rat and dog plasma following oral administration of repeat doses of lorlatinib was <4% of that observed in humans after oral administration of multiple doses of lorlatinib (100 mg once daily [QD]).

Genotoxicity

Lorlatinib was tested in a conventional genotoxicity battery. It was identified as an aneugen, but not a mutagen or clastogen following genetic toxicity assessments. Significant increases in micronucleus formation were detected *in vitro* in TK6 cells following 4 hours of lorlatinib treatment at concentrations ≥293 µg/mL with or without metabolic activation. Lorlatinib induced significant increases in micronucleus formation at 100 mg/kg/day but not at ≤30 mg/kg/day following 2 days of administration in rats. Centromere analysis in the *in vitro* micronucleus assay determined that positive micronucleus results (*in vitro* and *in vivo*) were due to an aneugenic mechanism. As it is widely accepted that aneugens induce their effects by a threshold mechanism, a NOEL was established for micronucleus formation *in vivo* at 30 mg/kg/day in male and female rats, with associated unbound AUC24 values of 17,700 (males) and 45,500 ng•h/ml (females) providing margins of 9.2x (males) and 24x (females) the unbound human steady-state AUC exposure of 1920 ng•h/ml, at the clinical dose of 100 mg QD.

PF-06895751, the major human metabolite of lorlatinib was not mutagenic in the bacterial reverse mutation assay when tested up to 5000 µg/plate and did not cause micronucleus formation in an *in vitro* micronucleus assay.

Carcinogenicity

No carcinogenicity studies with lorlatinib were submitted (see non-clinical discussion).

Reproduction Toxicity

No fertility studies were performed. Effects on male reproductive organs (testes, epididymis, and/or prostate) were observed in rats and dogs in repeat-dose toxicity studies after ≥2 weeks of lorlatinib administration. Seminiferous tubular degeneration and/or atrophy in the testes, and epididymal changes (inflammation and/or vacuolation) were observed in the rat and dog. In the prostate, minimal to mild glandular atrophy was observed at 25 mg/kg/day in dogs. These changes correlated with lower testes, epididymis and prostate weights in dogs. Partial or complete reversibility of the effects on male reproductive system was demonstrated following a 4-week non-dosing recovery period after 4 or 13 weeks of lorlatinib administration to rats and dogs.

Preliminary GLP embryo-foetal development studies were conducted in rats and rabbits. Because embryo-foetal toxicity and developmental abnormalities were observed in the preliminary studies, pivotal studies were not conducted.

Lorlatinib-related maternal toxicity and developmental toxicities including lower embryo-foetal viability, lower embryo-foetal viability, lower mean foetal body weights, and/or foetal malformations (including

rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate, and dilation of ventricles of the brain) were observed in rats and rabbits. There were no animal to human exposure margins for lorlatinib at the developmental lowest-observed-adverse-effect level (LOAEL) in the rat (1 mg/kg/day) and the developmental NOAEL in the rabbit (1 mg/kg/day). No pre- and postnatal studies were performed.

Toxicokinetic data

Toxicokinetic data have been obtained from repeat-dose toxicity of Lorlatinib in rats and dogs. Likewise, the exposure of the main metabolite of lorlatinib (PF-06895751, M8) has been obtained from 13-week repeat-dose toxicity studies in rats and dogs.

Table 7: Animal exposure in the pivotal repeat-dose toxicity studies with Lorlatinib

Study ID	Daily Dose (mg/kg)	Unbound AUC (ng.h/mL)		Unbound C_{max} (ng/mL)		Unbound Exposure Margin[b]	
		♂	♀	♂	♀	♂	♀
Wistar Rats 4-week with 4-week recovery 12GR341	2/1[a](1/0.5)	1120	1740	92.7	110	0.6	0.9
	8/4 [a] (4/2 BID)	4850	5700	382	292	2.5	3.0
	30/15 [a] (15/7.5 BID)	25200	20800	1940	1440	13	11
Wistar Rats 13-week with 4 week recovery (8001588)	2/1[a](1/0.5)	1190	1750	97.6	118	0.6	0.9
	8/4 [a] (4/2 BID)	**6240**	**7820**	442	451	**3.3**	**4.1**
	15/15 [a] (7.5/7.5 BID)	13600	39700	915	2000	7.1	21
Dogs 4-week with 4-week recovery 12GR342	2 (1BID)	1160		101		0.6	
	7 (3.5 BID)	3130		278		1.6	
	25 (12.5 BID)	11500		1110		6.0	
Dogs 13-week (8001589)	2 (1BID)	809		91.3		0.4	
	7 (3.5 BID)	**2980**		330		**1.6**	
	25 (12.5 BID)	8900		1030		4.6	

[a] Doses are for males/females
[b] The unbound human steady-state AUC exposure of 1920 ngh/mL at the recommended dose of 100mg QD.
NOAEL in bold

Table 8: Mean Plasma TK Parameters of PF-06895751 (M8) in Rats and Dogs Given Oral Repeat Doses of Lorlatinib

Week	Dose (mg/kg/day)	N/Sex	T_{max} (h)	C_{max} (ng/mL)		AUC_{24} (ng•h/mL)	
				Total	Unbound[b]	Total	Unbound[a]
13-Week Study in Rats (8001588 [16LJ022])							
4	2	3/M	NR	NR	NC	NR	NC
	8	3/M	6.7	3.57	0.750	47.0	9.87
	15	3/M	6.7	8.75	1.84	153	32.1
	1	3/F	NR	NR	NC	NR	NC
	4	3/F	7.0	3.08	0.647	NR	NC
	15	3/F	5.7	4.01	0.842	44.4	9.32
13-Week Study in Dogs (8001589 [16LJ023])							
4	2	3/M + 3/F	NR	NR	NC	NR	NC
	7	3/M + 3/F	4.5	4.31	0.496	63.7	7.33
	25	3/M + 3/F	4.2	10.9	1.25	175	20.1

AUC_{24} = Area under the concentration-time curve from 0 to 24 hours after dosing; BLQ = Below the limit of quantitation; C_{max} = Maximum observed plasma concentration; F = Female; f_u = Fraction unbound; GD = Gestation day; M = Male; N = Number of animals; NC = Not calculated; NR = Not reported; T_{max} = Time to reach C_{max}.
a. C_{max} or AUC unbound = C_{max} or AUC (total) × 0.210/0.115 (mean f_u in rat/dog plasma, respectively; Study YDP067/136).

Local Tolerance

Administration of lorlatinib was not associated with vascular or perivascular irritation at the doses tested and was not considered to cause local irritation.

Other toxicity studies

Immunotoxicity

A dedicated immunotoxicity study has not been performed. Potential immunotoxic effects of lorlatinib were addressed in the repeat-dose toxicity studies.

Mechanistic studies

Metabolic and Lipid Profile Studies

Lorlatinib administration was associated with increases in body weight and body weight gain with correlated increases in food consumption in rats and elevations in cholesterol and/or triglycerides in rats and dogs at ≥2 weeks in duration.

Mechanistic studies 7 days to 4 weeks in duration were conducted in rats to further evaluate the time course of effects on fractionated lipid profiles and the potential mechanism associated with the body weight and food consumption changes.

CNS Toxicity

The potential for CNS effects and impairment of cognitive function was suggested from the ex vivo hippocampal brain slice model, the rat contextual renewal model, and FOB assessments in repeat-dose toxicity studies. Clinical signs of CNS effects were observed and animals with higher exposure to lorlatinib were more likely to exhibit a higher incidence of CNS effects.

Phototoxicity

The NOEL for phototoxicity in rats provided a margin of 17x, the unbound human steady-state AUC exposure of 1920 ng•h/ml at the recommended dose of 100 mg once daily (QD).

Metabolites

No separate non-clinical evaluation of metabolites has been conducted.

In vitro bacterial reverse mutation and micronucleus assays were conducted with the major human circulating metabolite (PF-06895751) of lorlatinib (see Genotoxicity).

Impurities

Four impurities (PF-06752166, PF-06876367, PF-06744689 and PF-06856050) are specified above 0.15%, the level of qualification in the drug substance. These impurities were tested in a 4-week repeat-dose toxicity study in rats. The adverse effects in this impurity qualification study were consistent with those observed in the other repeat-dose toxicity studies.

According to the guideline ICH Q3A, genotoxicity studies have to be conducted. An *in vitro* bacterial reverse mutation assay that demonstrates that PF-06744689 impurities is not mutagenic, clastogenic or aneugenic with a lower NOAEL than lorlatinib has been submitted. PF-06752166, PF-06876367 and PF-06856050 have been assessed in 2 validated and complimentary in silico systems with additional expert analysis in accordance with ICH M7 guidance and are predicted to be not mutagenic (Class 4).

PF-06856050 and PF-06752166 share structural features and SARAH hypothesis with the parent and were thus qualified by Ames negative test of the parent. PF-06752166 is qualified by Ames negative tests of PF-06668559, PF-06841215, and parent which share the same structural features and Sarah hypotheses as this impurity.

2.3.4. Ecotoxicity/environmental risk assessment

In the Phase 1 screening environmental risk assessment, the $PEC_{surfacewater}$ for lorlatinib was calculated as 0.005 µg/L, using a refined Fpen for the target patient population.

Lorlatinib $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, lorlatinib is not expected to pose a risk to the environment.

Table 9: Summary of main study results

Substance (INN/Invented Name): Lorlatinib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …**? (Other Concern)**	2.23 (pH=5) 2.47 (pH=7) 2.45 (pH=9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase 1			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ refined (e.g. prevalence)	0.005	µg/L	<0.01 threshold

2.3.5. Discussion on non-clinical aspects

In vitro and *in vivo* pharmacodynamics evaluation of lorlatinib demonstrated that lorlatinib is a potent inhibitor of wild-type ALK, wild-type ROS1, and several ALK mutant kinase activity. Comparing to crizotinib, lorlatinib had significantly enhanced potency against ALK mutations. Primary *in vivo* pharmacodynamics of lorlatinib were evaluated in human xenograft tumour models in athymic mice. Subcutaneous xenograft models tested for ALK and ROS fusions including secondary ALK mutations. An orthotopic brain metastasis model was also used. The *in vivo* pharmacodynamics studies with lorlatinib showed significant and dose dependent antitumor activity against a broad range of mutations. The safety pharmacology studies conducted revealed a cardiovascular safety signal in *in vitro*, ex vivo and in *in vivo* studies. Furthermore, lorlatinib appears to affect memory recall in the rat at clinically relevant exposure levels.

Single dose pharmacokinetics and bioavailability of lorlatinib were evaluated in rats and beagle dogs after administration of a single oral dose. Lorlatinib appears to be readily absorbed with a very high bioavailability in both rats and dogs. Repeated dose pharmacokinetics of lorlatinib were evaluated in rats, dogs and rabbits. Repeated dose studies in male and female rats showed dose proportionality. However, a sex-related difference in exposure was seen. Neither dogs nor rabbits showed these sex-related differences.

Lorlatinib appears to be distributed in all tissues, which is consistent with the Vss being higher than total body water and thereby reflecting distribution to tissue including distribution to CNS.

The rat and dog were selected as the rodent and non-rodent species, respectively, for general toxicity studies because they demonstrated the ability to assess potential toxicities from both primary and secondary pharmacological targets, exposure profiles were sufficient, and there was representation of major metabolism pathways observed in humans.

The single dose toxicity studies in rats and dogs were not GLP compliant. This is accepted, as there are GLP compliant repeated dose toxicity studies that cover this part of the toxicity evaluation.

The main toxicities observed were inflammation across multiple tissues (skin and cervix of rats and lung, trachea, skin, lymph nodes and/or the oral cavity including mandibular bone of dogs; associated with increases in white blood cells, fibrinogen, and/or globulin and decreases in albumin) and changes in the pancreas (with increases in amylase and lipase), hepatobiliary system (with increases in liver enzymes), male reproductive system, cardiovascular system, kidneys and gastrointestinal tract, peripheral nerves and the CNS (potential for cognitive functional impairment) (at dose equivalent to human clinical exposure at the recommended posology. Changes in blood pressure and heart rate, and QRS complex and PR interval were also observed in animals after acute dosing (approximately 2.6 times the human clinical exposure at 100 mg after a single dose based on C_{max}). All target organ findings with the exception of hepatic bile duct hyperplasia were partially to fully reversible (see Section 5.3 of the SmPC).

Lorlatinib is not mutagenic but is aneugenic *in vitro* and *in vivo* with a no observed effect level for aneugenicity approximately 16.5 times human clinical exposure at 100 mg based on AUC. No carcinogenicity studies were conducted with lorlatinib which is acceptable in line with ICH S9 guideline.

Seminiferous tubular degeneration and/or atrophy in the testes, and epididymal changes (inflammation and/or vacuolation) were observed in the rat and dog. In the prostate, minimal to mild glandular atrophy was observed in dogs at dose equivalent to human clinical exposure at the recommended posology). The effects on male reproductive organs were partially to fully reversible.

In embryo foetal toxicity studies, conducted in rats and rabbits, respectively, increased embryolethality and lower foetal body weights and malformations were observed. Foetal morphologic abnormalities included rotated limbs, supernumerary digits, gastroschisis, malformed kidneys, domed head, high arched palate, and dilation of ventricles of the brain. The exposure at the lowest doses with embryo foetal effects in animals was equivalent to the human clinical exposure at 100 mg, based on AUC (see Section 5.3 of the SmPC).

Lorlatinib is not expected to result in phototoxicity in the eyes or skin upon UV radiation exposure after repeat dosing.

The Environmental Risk Assessment of the medicinal product lorlatinib, was realised according to the "Guideline on the Environmental Risk Assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr1, 2006) and considering the Questions and Answers document on it (EMEA 2011).

In the Phase 1 screening environmental risk assessment, the $PEC_{surfacewater}$ for lorlatinib was calculated as 0.005 µg/L, using a refined Fpen for the target patient population. The refined $PEC_{surfacewater}$ is lower than the 0.01 µg/L action limit for continuing to a Phase 2 Tier A assessment.

The octanol-water partition coefficient (Kow) was estimated using a validated and recognised method "Shake Flask Method" according to the OECD 107. The log Pow values for lorlatinib are 2.23, 2.47 and 2.45 at pHs 5, 7 and 9, respectively, which are below the trigger value of 4.5 for conducting a PBT assessment.

2.3.6. Conclusion on the non-clinical aspects

The non-clinical data submitted are considered acceptable and support the use of lorlatinib in the intended indication.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the applicant.

The applicant 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

Overview of Clinical Studies Including Subjects Who Received Lorlatinib and Were Evaluable for Pharmacokinetics

Protocol No. Study Status	Study Design	Treatment Groups (Formulation)	Number of subjects	Sampling	PK Analysis	Demographics	Study start (FSFV)/ Study end (LSLV)
HEALTHY SUBJECT STUDIES							
Mass Balance Study							
B7461004 Completed	Phase 1, open-label, single-dose, single-center study to evaluate the mass balance and PK of lorlatinib	100 mg lorlatinib containing approximately 100 μCi of [^{14}C]lorlatinib, fasted (Bulk powder for preparation of an oral solution at the clinic)	6 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 6 M Age range: 27-44 years Race: 6 W	30 September 2015/ 04 November 2015
Bioavailability and Bioequivalence Studies							
B7461005 Completed	Phase 1, randomized, open-label, 3-period, 6-sequence, crossover Relative BA study	Treatment A (Reference): 1 × 100 mg lorlatinib tablet, fasted (Acetic acid solvate immediate-release tablet) Treatment B (test): 1 × 100 mg lorlatinib tablet, fasted (Anhydrous free-base extemporaneous immediate-release tablet) Treatment C (test): 1 × 100 mg lorlatinib tablet, fasted (Maleate salt extemporaneous immediate-release tablet)	20 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 20 M Mean age (SD): 39.4 (9.0) Age range: 25-55 years Race: 4 W/9 B/7 O	05 March 2015/ 13 May 2015

Overview of Clinical Studies Including Subjects Who Received Lorlatinib and Were Evaluable for Pharmacokinetics

Protocol No. Study Status	Study Design	Treatment Groups (Formulation)	Number of subjects	Sampling	PK Analysis	Demographics	Study start (FSFV)/ Study end (LSLV)
B7461007 Completed	Phase 1, open label, single-dose, randomized, 2-period, 2-treatment, 2-sequence, crossover Absolute BA study	Treatment A (Reference): 50 mg lorlatinib, fasted (IV solution for injection) Treatment B (Test): 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base immediate-release tablet)	11 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 11 M Mean age (SD): 37.6 (10.3) Range: 24-52 Race: 1 W/4 B/ 1 A/5 O	13 June 2016/ 02 September 2016
B7461008 Completed	Phase 1, randomized, open-label, 4-period, 4 treatment, 4-sequence, crossover food-effect, antacid-effect, and BA study	Treatment A: 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base immediate-release tablets) Treatment B: 100 mg lorlatinib (4 × 25 mg tablets), fed (Anhydrous free-base immediate-release tablets) Treatment C: 20 mg QD rabeprazole from D1-D5 100 mg lorlatinib (4 × 25 mg lorlatinib tablets) on D6, fasted (Anhydrous free-base immediate-release tablets) Treatment D: 100 mg lorlatinib, fasted (Oral solution, 100 mL of a 1 mg/mL solution)	27 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 1 F/26 M Mean age (SD): 35.9 (10.3) Age range: 20-55 years Race: 21 W/6 B	01 December 2015/ 11 April 2016

Overview of Clinical Studies Including Subjects Who Received Lorlatinib and Were Evaluable for Pharmacokinetics

Protocol No. Study Status	Study Design	Treatment Groups (Formulation)	Number of subjects	Sampling	PK Analysis	Demographics	Study start (FSFV)/ Study end (LSLV)
B7461016 Completed	Phase 1, randomized, single-dose, open label, 4-period, 4-treatment, 4-sequence, crossover BE study	Treatment A (Reference): 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base [Form 7] immediate-release tablets) Treatment B (Test Formulation 1): 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base [Form 7] commercial immediate-release tablets) Treatment C (Test Formulation 2): 100 mg lorlatinib (2 × 50 mg tablets), fasted (Anhydrous free-base [Form 7] commercial immediate-release tablets) Treatment D (Test Formulation 3): 100 mg lorlatinib (1 × 100 mg tablet), fasted (Anhydrous free-base [Form 7] commercial immediate-release tablets)	20 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 20 M Mean age (SD): 42.2 (9.46) years Age range: 25-54 years Race: 19 W/1 B	08 November 2016/ 06 February 2017
Drug-interaction Studies							
B7461011 Completed	Phase 1, open-label, 2-period, 2-treatment, fixed-sequence, crossover study to estimate the effect of multiple dose rifampin on the single dose PK of lorlatinib in HVs	Treatment A (Reference): Day 1 of Period 1: single dose of 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base immediate-release tablets) Treatment B (Test): Day 1 to Day 12 of Period 2: Rifampin 600 mg QD Day 8 of Period 2: 100 mg lorlatinib (4 × 25 mg tablets), fasted (Anhydrous free-base immediate-release tablets)	12 **healthy** subjects	Full PK profile	NCA and popPK analysis	Sex: 1 F/11 M Mean age (SD): 36.5 (11.1) Age range: 21-55 years Race: 6 B/2 W/4 O	06 July 2016/ 06 October 2016
B7461012 Completed	Phase 1, open-label, fixed sequence, 2-period study to investigate the effect of multiple doses of itraconazole on the PK of single dose lorlatinib	Period 1 (Reference): Day 1: 50, 75 or 100 mg lorlatinib, fasted (Anhydrous free-base immediate-release 25 mg tablets) Period 2 (Test): Days 1-11: Itraconazole 200 mg QD; Day 5: 50, 75 or 100 mg lorlatinib, fasted (Anhydrous free-base immediate-release 25-mg tablets)	16 **healthy** subjects	Full PK profiles	NCA	Sex: 16 M Mean age (SD): 34.1 (10.6) Age range: 20-54 years Race: 1 B/12 W/3 O	16 August 2016/03 May 2017

Overview of Clinical Studies Including Subjects Who Received Lorlatinib and Were Evaluable for Pharmacokinetics

Protocol No. Study Status	Study Design	Treatment Groups (Formulation)	Number of subjects	Sampling	PK Analysis	Demographics	Study start (FSFV)/ Study end (LSLV)
Patient Study							
B7461001 Ongoing	**Phase 1 portion:** To assess safety and tolerability of lorlatinib as a single agent at increasing dose levels in patients with ALK-positive or ROS1-positive advanced NSCLC in order to estimate the MTD and select RP2D.	**Phase 1**: Escalating doses of 10, 25, 50, 75, 100, 150, 200 mg QD and 35, 75 and 100 mg BID, fed or fasted (Acetic acid solvate 5-mg, 25 mg and 100-mg tablets)	**Phase 1**: 55[b] **ALK-positive or ROS1-positive advanced NSCLC**	Full PK and sparse PK profiles	NCA and popPK analysis	**Phase 1** Sex: 32 F/22 M Mean age (SD): 51.9 (12.8) Age range: 27-82 years Race: 3 B/37 W/7 A/1 O/6 unspecified	08 January 2014 Ongoing, enrollment complete as of 15 March 2017, the data cutoff date for the interim clinical study report)
	Phase 2 portion: To evaluate overall (intra- and extracranial) and intracranial antitumor activity of single-agent lorlatinib at RP2D in patients with ALK-positive advanced NSCLC or ROS1-positive advanced NSCLC. **Japan LIC[a]:** To evaluate the safety and PK of lorlatinib in Japanese patients treated at a previously tested dose in Phase 1 (Japan Sites only).	**Phase 2**: 100 mg QD, regardless of food (Anhydrous free-base immediate-release 4 x 25 mg tablets) **Japan LIC**: 100 mg QD, regardless of food (Anhydrous free-base immediate-release 4 x 25 mg tablets)	**Phase 2**: 276[c] (patients with ALK-positive NSCLC or ROS1-positive advanced NSCLC) **Japan LIC**: 3	Full PK and sparse PK profiles	NCA and popPK analysis	**Phase 2** Sex: 157 F /118 M Mean age (SD): 53.6 (12.1) Age range: 19-85 years Race: 132 W/3 B/103 A/12 O/25 unspecified **Japan LIC**: Sex: 2 F/1 M Age range: 39-51 years Race: Asian	

a. Japan LIC was considered separate from Phase 1 and Phase 2 in terms of efficacy and safety evaluations; however PK data for the LIC patients and Phase 2 patients were summarized together.
b. Study B7461001 enrolled 55 patients in Phase 1, however only 54 patients received the treatment. Therefore, all other numbers reported in this table are based on total 54 patients.
c. Study B7461001 enrolled 276 patients in Phase 2, however only 275 patients received the treatment. Therefore, all other numbers reported in this table are based on total 275 patients.

2.4.2. Pharmacokinetics

The majority of clinical studies conducted with lorlatinib enrolled healthy volunteers. Study B7461001 (Phase 1/2) was conducted in patients.

Methods

Bioanalytical methods using LC-MS/MS for the quantitative determination of lorlatinib in plasma, urine and CSF, for cortisol and 6β-hydroxycortisol in urine and for rifampin, desacetyl rifampin, midazolam, cholesterol and 4β-hydroxycholesterol in plasma were developed and validated at contract laboratories. LC-MS/MS methods for quantification of PF-06895751 (major human metabolite of lorlatinib) in plasma was developed and validated at Pfizer PDM (Groton, USA). Validations were conducted in compliance with current guidelines on bioanalytical method validation.

PK parameters for lorlatinib and its metabolite PF-06895751 (M8) were derived from concentration vs time data, and estimated by non-compartmental methods. Plasma concentrations vs time data were modelled using a nonlinear mixed effects population analysis approach in NONlinear Mixed Effects Modeling (NONMEM).

Evaluation and qualification of models

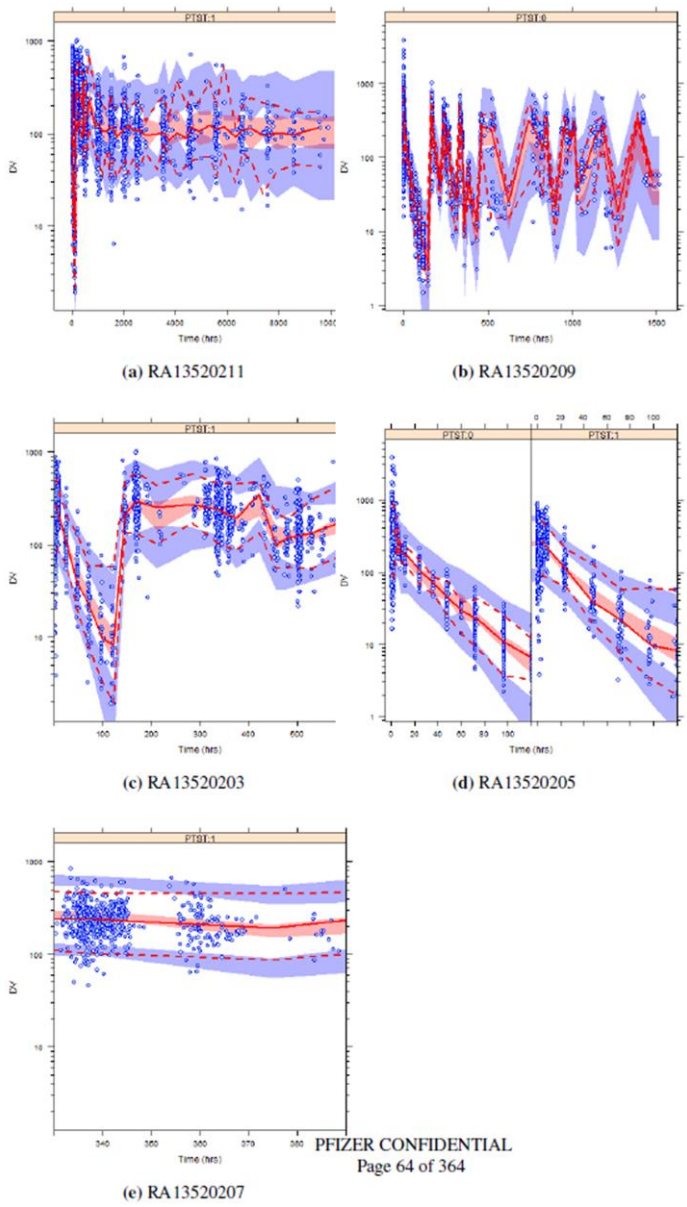
The Pop PK population included data from 425 subjects (healthy volunteers and patients). Out of this data pool, 27 data points were excluded with a stated reason.

Table 10: Covariates considered in the population PK analysis

PK Parameters	Covariates
CL	AGE, SEX, PTST, CYP2C19, CYP3A5, CYP2C9, TDOSE, RACE, BALB, BALK, BBIL, BTG, BHGRADE, BRGRADE, WNCL, BALT
V_2	AGE, SEX, BRGRADE, BTG, RACE, WNCL
k_a	FOOD, PSCI, PPI
Relative F	FOOD, PSCI, PPI, TDOSE, BHGRADE, BRGRADE, WNCL, BALT, CYP2C19, CYP3A5, CYP2C9

Source: Module 5, Section 5.3.3.5, PMAR-681, Table 4.
CL=clearance, which is comprised of an initial clearance after single dose and a time dependent induced clearance; V 2=volume of distribution of central compartment; k_a=Rate constant of absorption; F=absolute bioavailability; BWT= baseline body weight; BALT=baseline alanine aminotransferase; BALB=baseline albumin; BBIL=baseline total bilirubin; BTG=baseline triglycerides; BALK=baseline alkaline phosphatase; BHGRADE=baseline hepatic impairment as assessed by NCI criteria method (normal [A], mild [B1], mild [B2], and moderate [C]); BRGRADE=baseline renal impairment as assessed by K/DOQI staging (normal [A], mild [B], moderate [C], severe [D]); CYP2C19=CYP2C19 phenotype (poor, intermediate, extensive, or ultra metabolizer); CYP3A5=CYP3A5 phenotype (poor, intermediate, extensive, or ultra metabolizer); PK=pharmacokinetic; PPI=rabeprazole or no rabeprazole co-administration; PSCI=formulation (acetic acid solvate, free base, or IV solution); FOOD=fasted or fed; PTST=healthy volunteer or patient; RACE=Race (White, Black, Asian, or Other); TDOSE=total daily dose; WNCL=baseline standardized creatinine clearance.

Covariate data from triglycerides and CYP phenotype had >10% missing. Covariate data collected in the 7 studies with healthy subjects for triglycerides had 29.4% missing data and phenotype CYP2C19, CYP2C9 and CYP3A5 data had 35% missing data. The category for ultra-rapid metabolisers was represented for CYP2C19 (n=7). All other categories were represented by at least 5 subjects.



ePharmacology artifact IDs are shown in subfigure labels.
TAFD was reset on Period 1 Day 1 and thus the first 120 hours represents a pooling of Day -7 and Period 1 Day 1. Shaded areas represent a simulation based 90% prediction interval of the 5th, 50th, and 95th percentile of the simulated data. Red lines represent the 5th, 50th, and 95th percentile of the observed data. Figure 9a All Patient Data, Figure 9b All healthy volunteer data, Figure 9c First 600 hours (patients only), Figure 9d First 120 hours (both patients and healthy volunteers), and Figure 9e Day 15 of Cycle 1 (patients only).
DV=dependent variable or observed concentrations; hr=hour; PTST=patient status, 0 for healthy volunteer, 1 for patients; TAFD=time after first dose.

Figure 3: Prediction- and variability-corrected visual predictive check of final model

The final model was a 2-compartment model, with mixed first order and, zero-order absorption and a time-dependent induction of clearance. The VPCs for the final model were acceptable. The shrinkage on final parameters was high (>30%) for almost all PK parameters, which could have profound impact on the sequential PK/PD analyses. Sensitivity analysis of PPI-use on ka showed impact of PPI-use on exposure expressed as C_{max}, but not AUC. This is in line with the results from study 1008 indicating a 30% reduction on C_{max} after PPI-use with no impact on AUC.

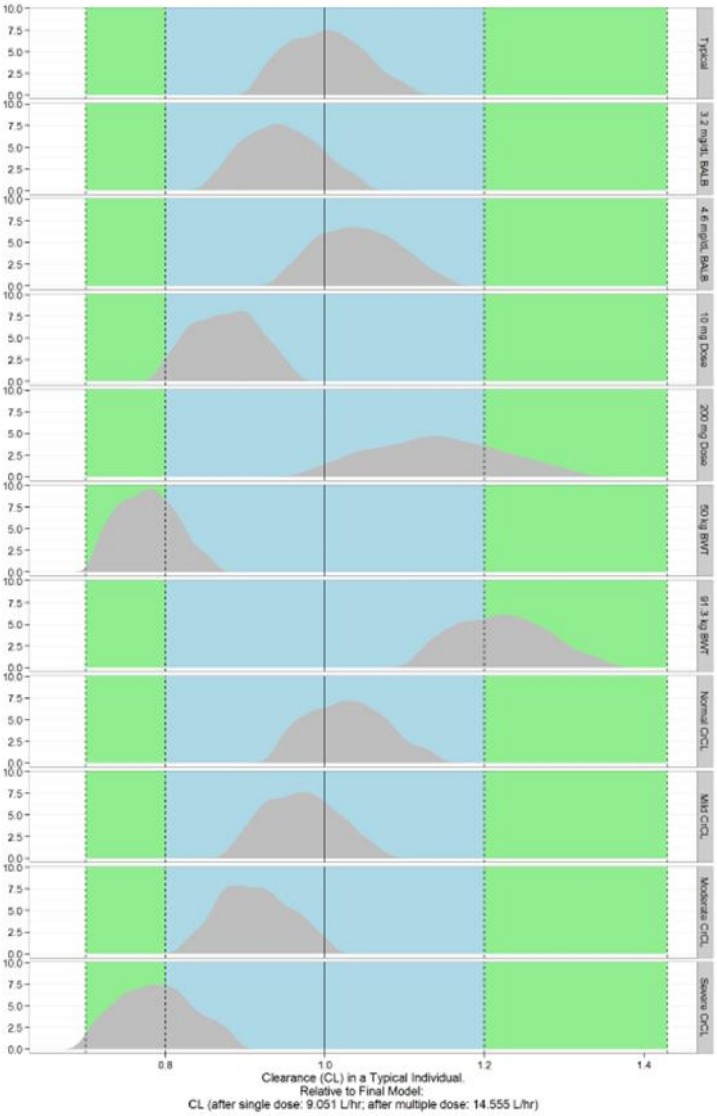
Table 11: Final model final parameter estimates

	Model Results			Bootstrap Results	
Parameter	Value	RSE(%)	Shrinkage(%)	Mean	95% Confidence Interval
$\theta_{CLI\ (L/h)}$	9.035	6.860	-	9.088	(8.0115 - 10.0609)
$\theta_{V_2\ (L)}$	120.511	10.764	-	120.618	(103.3633 - 137.6947)
$\theta_{ka\ (h^{-1})}$	3.113	12.063	-	3.128	(2.3125 - 3.9145)
$\theta_{Q\ (L/h)}$	22.002	8.515	-	22.491	(17.6495 - 26.3563)
$\theta_{V_3\ (L)}$	154.905	5.314	-	156.640	(134.2215 - 175.6205)
θ_{IND}	0.020	10.787	-	0.027	(-0.2136 - 0.2535)
$\theta_{D1\ (h)}$	1.148	5.200	-	1.149	(1.0344 - 1.2611)
θ_{F}	0.759	7.169	-	0.764	(0.6728 - 0.8462)
$\theta_{CLMX\ (L/h)}$	14.472	6.860	-	14.584	(12.7286 - 16.2186)
$\theta_{Res.\ Error\ for\ IV}$	0.115	14.929	-	0.110	(0.0811 - 0.1487)
$\theta_{Res.\ Error\ for\ PO}$	0.438	3.485	-	0.437	(0.4090 - 0.4670)
$\theta_{BALB\ on\ CL}$	0.067	37.112	-	0.069	(0.0214 - 0.1122)
$\theta_{TDOSE\ on\ CL}$	0.001	55.719	-	0.001	(0.0004 - 0.0023)
$\theta_{WNCL\ on\ CL}$	0.235	20.164	-	0.240	(0.1457 - 0.3238)
$\theta_{PPI\ on\ k_a}$	-0.675	-11.020	-	-0.664	(-0.8508 - -0.4986)
IIV	Value	CV(%)	Shrinkage(%)	Mean	CI
ω^2_{CL}	0.030	17.201	23.212	0.030	(0.0159 - 0.0433)
$\omega_{F}\omega_{CLMX\ (L/h)}$	-0.006	7.460	-	-0.005	(-0.0173 - 0.0061)
ω^2_{F}	0.022	14.964	40.174	0.023	(0.0027 - 0.0420)
$\omega^2_{V_2}$	0.086	29.268	52.835	0.085	(0.0430 - 0.1284)
$\omega_{V_2}\omega_{V_3}$	-0.017	12.881	-	-0.017	(-0.0492 - 0.0160)
$\omega^2_{V_3}$	0.101	31.742	53.123	0.099	(0.0513 - 0.1502)
ω^2_{ka}	2.329	152.626	45.113	2.345	(1.5982 - 3.0608)
OFV	-2588.508	-	-	-2640.454	(-3277.2723 - -1899.7429)

ePharmacology artifact ID RA13523032. Line 1 substituted.
The mean and 95% Confidence Intervals are generated from a bootsrap run of 1000 resampled datasets
BALB=baseline albumin; CV= Coefficient of Variation; CI=Confidence Interval; Res Err= Residual Error; CLI=initial clearance; D1=zero order duration of absorption; F=bioavailability; h=hour; IIV=inter-individual variability; IND=rate constant of induction; ka=rate constant of absorption; L=liter; OFV=objective function value; PO=oral; PPI=proton pump inhibitor use; RSE=Relative Standard Error; TDOSE=total daily dose (mg); V_2=central volume of distribution; V_3=peripheral volume of distribution; WNCL=baseline standardized creatinine clearance.

The sensitivity analysis of various covariate effects on CL showed impact from body weight (BWT), TDOSE and WNCL, but within the extended boundary range of 70-142.9%. This boundary range was chosen as the area of no effect, based on results of the DDI study with itraconazole which resulted in a lorlatinib exposure increase of 42%.

The sensitivity analysis of BWT influence on CL showed a clear effect where clearance increased with body weight. Body weights in the studied Pop PK population ranged from 31.8 to 155.5 kg and exceeded the 10^{th} and 90^{th} percentiles interval.



ePharmacology artifact ID RA13536082.
Typical individual defined as a 70 kg individual with no PPI use, baseline standardized creatinine clearance of 100 mL/min, baseline albumin of 4 mg/dL, and dosed at 100 mg
The blue ribbon represents 80-125% of the typical individual. The green ribbon represents 70-142.9% of the typical individual.
The renal impairment staging with CrCL is defined by the KDOQI renal impairment guidelines.
BALB=basline albumin; BWT=baseline body weight; CrCL=baseline standardized creatinine clearance.

Figure 4: Sensitivity analysis with lorlatinib clearance

The final popPK model was used in sequential PK/PD analyses, to evaluate E-R relationships for efficacy and safety endpoints.

Statistical methods

Results were presented using descriptive statistics. Data were analysed after log-transformation using linear mixed effect statistical methods and the ratio of adjusted mean differences (test/reference) and associated 90% CIs were calculated for evaluation of effect.

Absorption

Lorlatinib is categorised as a BCS Class IV drug substance with pH-dependent solubility (10 mg/ml at pH <2 and 0.1 mg/ml at pH 7.7).

Median time to peak concentration, T_{max}, was 1.2 hours following a single 100 mg dose and 2.0 hours following multiple daily doses of 100 mg lorlatinib in cancer patients. (Study 1001, Phase 2 and Japan LIC).

Co-administration of agents that can affect gastric pH may potentially alter drug absorption, hence 100 mg lorlatinib with concomitant treatment of rabeprazole was investigated in healthy subjects (study 1008). PK results are presented in Table 12 showed a 30% decrease in C_{max} with no impact on lorlatinib AUC.

The potential for efflux transporters P-gp and BCRP to transport lorlatinib was investigated *in vitro* in transfected MDCKII cells with positive controls and the results indicated lorlatinib was not a substrate.

Bioavailability

Bioavailability of lorlatinib was studied in healthy volunteers in study 1005, 1007 and 1008.

Comparison of IV versus oral tablets in study 1007, showed the mean absolute bioavailability for lorlatinib is 80.8% (Table 12). There was no difference in the exposure of the major metabolite PF-06895751 after oral administration of lorlatinib compared to IV.

Table 12: Statistical summary of treatment comparison for lorlatinib pharmacokinetic parameters; Study 1007

	Adjusted Geometric Means			
Parameter (Units)	Reference Lorlatinib 50 mg Intravenous	Test Lorlatinib 4 × 25 mg Oral Tablets	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf}(dn) (ng•hr/mL)	5189	4191[b]	80.78	(75.73, 86.16)
AUC_{last}(dn) (ng•hr/mL)	5028	4106[b]	81.65	(76.56, 87.08)

Source: Module 5, Section 5.3.1.1, Study 1007 CSR In-text Table 14.
Values had been back-transformed from the log scale.
The mixed effects model included sequence, period and treatment as fixed effects and subject within sequence as a random effect.
AUC_{inf}=area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last}=area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; CI=confidence interval; CSR=clinical study report; dn=dose normalized; hr=hour(s).
The ratios (and 90% CIs) were expressed as percentages.
Values were normalized to 50 mg intravenous dose.

At 100 mg once daily, the geometric mean (% coefficient of variation [CV]) peak plasma concentration was 577 (42) ng/ml and the AUC_{24} was 5,650 (39) ng·h/ml in patients with cancer. The geometric mean (% CV) oral clearance was 17.7 (39) L/h (Study 1001, Phase 2 and Japan LIC).

Table 13: Pharmacokinetic parameters of lorlatinib at steady state in patients with ALK-positive or ROS-1 positive NSCLC (study 1001) following administration of lorlatinib multiple oral doses (100 mg QD)

Cohort	Visit	N, n[a], n[b]	AUC_{tau} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	CL/F (L/hr)	R_{ac}	R_{ss}
1001 Phase 1	CID15	16, 15, 14	5121 (30)	550 (32)	1.1 (1.0-4.0)	19.5 (30)	1.07 ± 0.31	0.660 ±0.186
1001 Phase 2 and Japan LIC	C1D15	22, 20, 14	5650 (39)	577 (42)	2.0 (0.5-22.7)	17.7 (39)	1.08 ± 0.43	0.658 ± 0.286

Source: Module 5, Section 5.3.5.2, Study 1001, Table 14.4.4.4.1.1.1, Table 14.4.4.4.1.2.1.
Pharmacokinetic parameters are defined in Table 3.
Geometric mean (geometric %CV) for AUC_{tau}, C_{max}, and CL/F; arithmetic mean ± SD for R_{ac} and R_{ss}; median (range) for T_{max}
%CV=percent coefficient of variation; C=Cycle; D=Day; Japan LIC=Japanese patient only Lead-in Cohort; N=number of subjects in the treatment group; n[a]=number of subjects for whom R_{ac} could be determined, n[b]=number of subjects for whom R_{ss} could be determined; NSCLC=non-small-cell lung cancer; QD=once daily; SD=standard deviation.

Different oral formulations of lorlatinib were used throughout the development programme: Form 1 maleate salt formulation, Form 3 acetic acid solvate formulation and Form 7 anhydrous free base that was selected as commercial form of the drug substance.

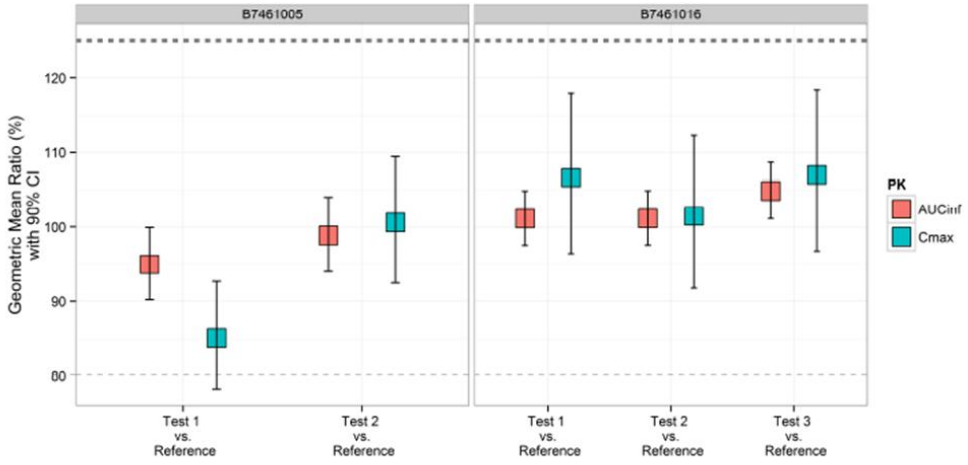
Formulations used in healthy subjects and in the main efficacy study in patients were compared in studies 1005 and 1016. Results indicated no clinically relevant exposure differences. For study 1005, it is of note, the geometric mean ratio of free base formulation compared to acetic acid solvate for C_{max} was 85.13% with a 90%CI: 78.22-92.65, slightly below BE acceptance criteria of 80-125%.

Table 14: Overview of biopharmaceutics studies of lorlatinib

Study Number	Study Design/Objective	Study Populationa	Formulation
1005	Relative bioavailability study	20 healthy subjects	1) Acetate solvate immediate-release Phase 1 clinical image tablet 2) Anhydrous free-base extemporaneous immediate-release tablet 3) Maleate salt extemporaneous immediate-release tablet
1007	Absolute bioavailability study	11 healthy subjects	1) IV solution for injection 2) PO: Anhydrous free-base immediate-release clinical image tablet
1008	Food-effect, antacid effect, and bioavailability study	27 healthy subjects	1) Anhydrous free-base immediate-release clinical image tablet 2) Oral solution
1016	Bioequivalence study	20 healthy subjects	1) Anhydrous free-base immediate-release clinical image tablet 2) Anhydrous free-base immediate-release commercial image tablet

Source: SBS Table 1 and SBS Table 2.
Abbreviations: IV=intravenous; PO=per os (orally); SBS=Summary of Biopharmaceutics and Associated Analytical Methods.
a. Number of subjects who received lorlatinib.

Bioequivalence was shown between the free base clinical reference formulation and different strengths of the commercial image tablet in study 1016 (Figure 5).



Source: SBS, Appendix 2.
B7461005: The reference (treatment A) is the acetic acid solvate reference formulation, Test 1 (treatment B) is the anhydrous free base clinical image formulation, and Test 2 (Treatment C) is the maleate formulation.
B7461016: Reference is the anhydrous free base clinical formulation, Test 1 refers to 4 × 25 mg of the commercial image tablets, Test 2 is 2 × 50 mg of the commercial image tablets, and Test 3 is 1 × 100 mg of the commercial image tablets.
AUC_{inf}=area under the concentration time curve from time 0 to infinity; C_{max}=maximum-observed plasma concentration; 90% CI=90% confidence interval; ID=identification; PK=pharmacokinetic(s); SBS=summary of biopharmaceutics; vs.=versus.

Figure 5: Bridging of lorlatinib clinical trial formulations with relative bioavailability and bioequivalence studies 1005 and 1016

Influence of food

The influence of food was investigated in 6 patients in study 1001 and in 24 healthy subjects in study 1008 (results presented in Table 15). Results indicated T_{max} was slightly prolonged in the fed state compared to the fasted in both study groups.

Table 15: Summary of plasma PF-06463922 PK parameter values following single oral doses

Parameter (units)	Parameter Summary Statistics[a] by Treatment: PF-06463922 100 mg tablets	PF-06463922 100 mg tablets with High Fat Meal	PF-06463922 100 mg tablets + Rabeprazole 20 mg	PF-06463922 100 mg Oral Solution
N, n	24, 24	23, 23	23, 23	24, 24
AUC_{inf} (ng•hr/mL)	8712 (24)	8779 (24)	8629 (24)	9359 (24)
AUC_{last} (ng•hr/mL)	8191 (21)	8262 (22)	8011 (21)	8789 (21)
C_{max} (ng/mL)	547.8 (20)	488.5 (26)	383.0 (28)	704.7 (22)
T_{max} (hr)	1.50 (0.500-2.02)	2.00 (1.00-6.00)	2.00 (1.50-6.00)	1.00 (0.500-1.50)
$t_{½}$ (hr)	24.2 ± 5.22	23.7 ± 6.04	25.6 ± 6.42	24.1 ± 5.36
CL/F (L/hr)	11.48 (24)	11.40 (24)	11.58 (24)	10.69 (24)
V_z/F (L)	390.6 (20)	378.2 (22)	414.5 (21)	361.1 (19)

Source: Table 14.4.3.1
PK Parameters are defined in Table 7.
Abbreviations: %CV = percent coefficient of variation; N = Number of subjects in the treatment group; n = Number of subjects contributing to the summary statistics (see Table 16.2.5.5.1.2 supporting data for k_{el} and $t_{½}$); PK = pharmacokinetics.
a Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (± SD) for $t_{½}$.

Distribution

The apparent volume of distribution of lorlatinib (V_z/F) was large and indicated extensive distribution into tissues (Table 15). The volume of distribution of the major metabolite PF-06895751 was not given.

In vitro binding to human plasma proteins was 66% (fu of 0.340). For human serum albumin (HSA) and for α1-acid glycoprotein (AAG), fu was 0.474, and 0.620 respectively. Concentration dependency was not studied. The concentration investigated was >C_{max} after multiple doses of lorlatinib 100 mg QD and within the dose proportional exposure range after QD 10 mg - 200 mg lorlatinib. Protein binding of PF-06895751 was moderate with a fu of 0.207 in human plasma. With a Cb/Cp of 0.99, lorlatinib distributes equally to whole blood and plasma. The blood-plasma ratio of the major metabolite was not determined.

The ability of lorlatinib to cross the BBB was evaluated in Study 1001. CSF concentrations and time-matched plasma concentrations of lorlatinib were available for 4 patients from Phase 1 and 1 patient from Phase 2 and Japan LIC. Mean CSF/free plasma ratios were 0.7481 and 0.6791, respectively, for Phase 1 (n=4) and Phase 2 and Japan LIC (n=1) patients. Therefore, lorlatinib can cross the BBB following oral administration. CSF samples from treated patients were not analysed for PF-06895751.

Elimination

Excretion

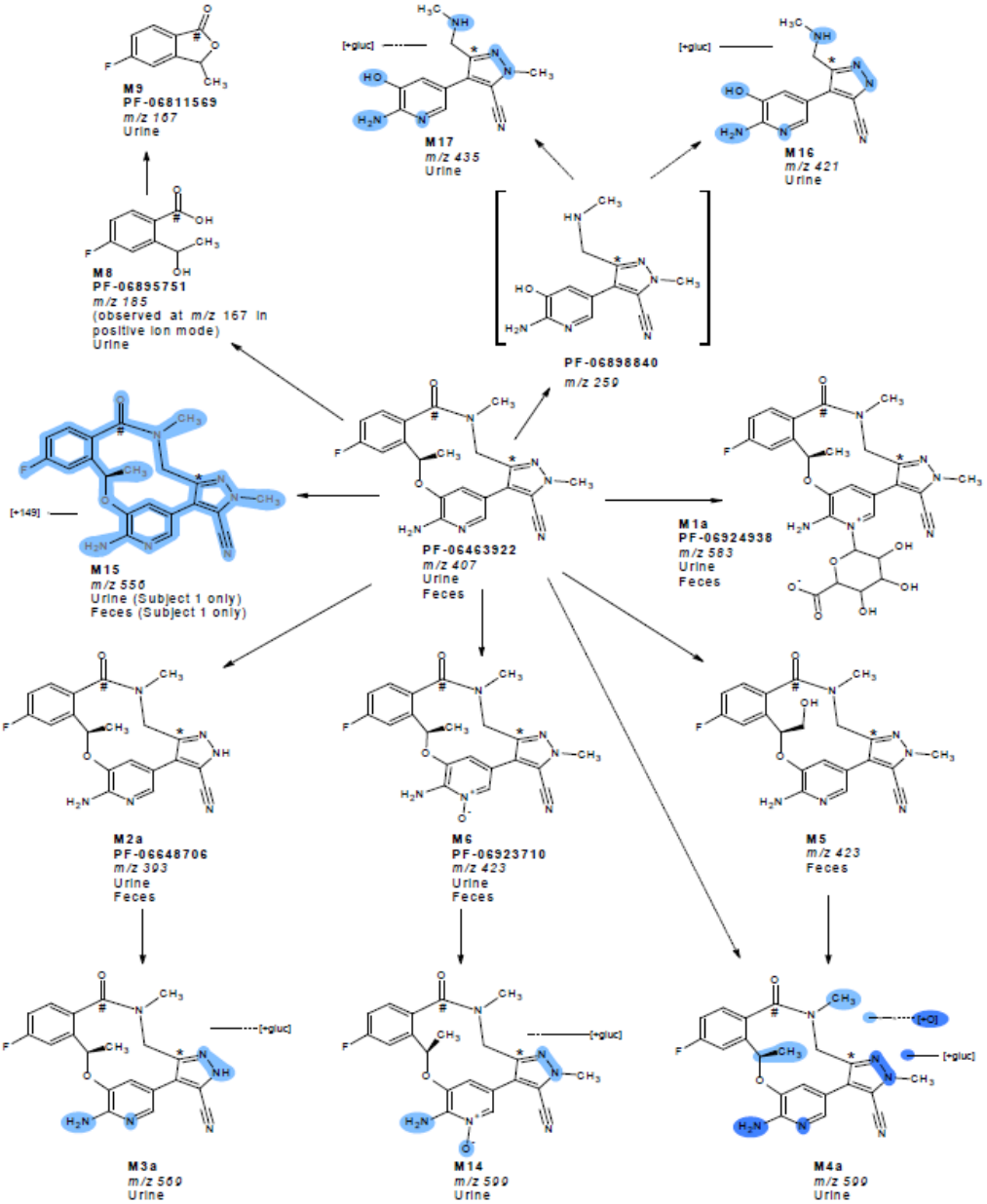
In cancer patients the plasma half-life of lorlatinib after a single 100 mg dose was 23.6 hours (Study 1001, Phase 2 and Japan LIC). The plasma half-life of lorlatinib ranged from 20.9 to 25.5 hr across studies and was close to tau (QD dosing). Despite the long half-life, no accumulation of lorlatinib occurred after multiple doses of the planned intended daily dose of 100 mg.

In the human mass balance study (Study 1004) following oral administration of a 100 mg radiolabelled dose of lorlatinib, the urinary excretion of unchanged lorlatinib was found to be a minor route of elimination with less than 1% of the administered parent drug. In plasma and faeces, lorlatinib accounted for 44.4% and 9.1% of total radioactivity respectively.

Metabolism

In the mass balance study, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in faeces, with an overall recovery of radioactivity in excreta of 88.6%. Radioactivity corresponding to 64% of the dose was identified (estimated including metabolites observed in single subjects). In plasma, a benzoic acid metabolite of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib was observed as a major metabolite (PF-06895751), accounting for 21% of the circulating radioactivity. A follow-up study (B7461017) with a different site of radiolabelling has been completed.

The major human metabolite PF-06895751 was not detected in the rat or dog ADME study. PF-06895751 was detected in plasma after repeat-dose administration of lorlatinib in the 13-week rat and dog toxicity studies, at levels 30-40 fold below the mean steady-state exposure in humans achieved after 100 mg QD lorlatinib. The observed exposure of PF-06895751 in humans is not covered by non-clinical safety studies.



Source: Section 16.2.5.10.6
Position of ^{14}C radiolabel in Study B7461004 (#) and in Study B74641017 (*) indicated.
PF-06898840 is a proposed intermediate; this component was not identified in the plasma or the excreta.
Highlighted regions represent the proposed sites of metabolism.

Figure 6: Proposed biotransformation pathways of lorlatinib in human excreta

Inter-conversion

Results from Study 1001 (n=6) indicated that no considerable chiral inversion of lorlatinib occurred in plasma.

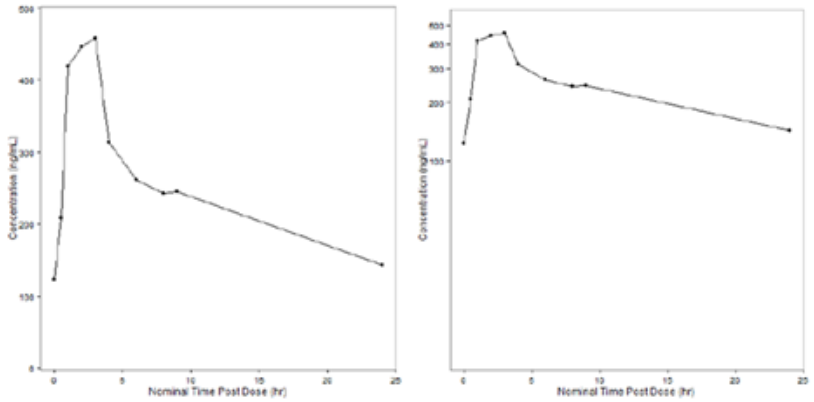
Pharmacokinetics of metabolites

The metabolite PF-06895751 was considered pharmacological inactive after CEREP screening. There was inhibition of binding to GABAA1 of 30.9% at 10 µM, which is considered to be a weak to moderate effect. The tested concentration was above the maximum observed plasma concentration of PF-06895751 in a patient (761 ng/mL at Cycle 10).

Table 16: PK parameters of lorlatinib metabolite, PF-06895751, in healthy subjects (studies 1007, 1011 and 1012) by study and treatment arm following administration of a single oral dose (100 mg) of lorlatinib

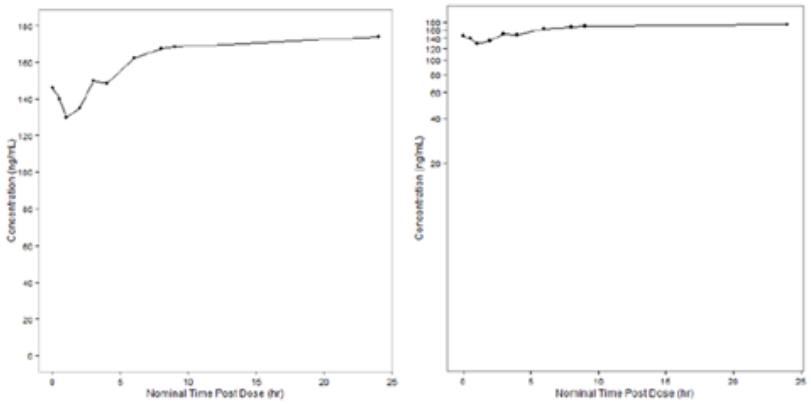
Study No./ Data Set	Lorlatinib Formulation; Fasted/Fed Condition	N, n	Lorlatinib PK Parameter Summary Statistics[a] for a 100-mg Single Oral Dose					
			AUC_{inf} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)	MR Ratio AUC_{inf}	MR Ratio C_{max}
Healthy Subjects								
1007	Anhydrous free-base immediate-release tablets; Fasted	11, 10	4399 (23)	47.0 (38)	24.0 (12.1-48.0)	32.8 ± 6.1	1.19 (38)	0.207 (34)
1011	Anhydrous free-base immediate-release tablets; Fasted	12, 10	4453 (38)	59.0 (29)	30.1 (24.0-36.1)	29.1 ± 7.5	1.17 (25)	0.209 (29)
1012	Anhydrous free-base immediate-release tablets; Fasted	12, 12	3721 (34)	51.7 (38)	24.0 (12.0-48.0)	29.6 ± 6.7	1.12 (54)	0.276 (49)

Source: Module 5, Section 5.3.1.1, Study 1007 CSR, In-text Table 15; Module 5, Section 5.3.3.4, Study 1011 CSR, In-text Table 16; Module 5, Section 5.3.1.4, Study 1012 CSR, In-text Table 15.
Pharmacokinetic parameters are defined in Table 3.
Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean ± SD for $t_{½}$.
%CV=percent coefficient of variation; hr=hour(s); Japan LIC=Japanese patient only Lead-in Cohort; N=number of subjects in the treatment group and contributing to the summaries; n=number of subjects with reportable AUC_{inf}, $t_{½}$ and MR Ratio AUC_{inf} values; PK=pharmacokinetic(s); SD=standard deviation.



Source: ePharm Artifact IDs 13307219 and 13307745.

Figure 7: Linear and semi-log plots of median plasma concentration-time profiles of lorlatinib following administration of multiple oral 100 mg doses of lorlatinib in patients with non-small cell lung cancer (study 1001)



Source: ePharm Artifact IDs 13307218 and 13307743.

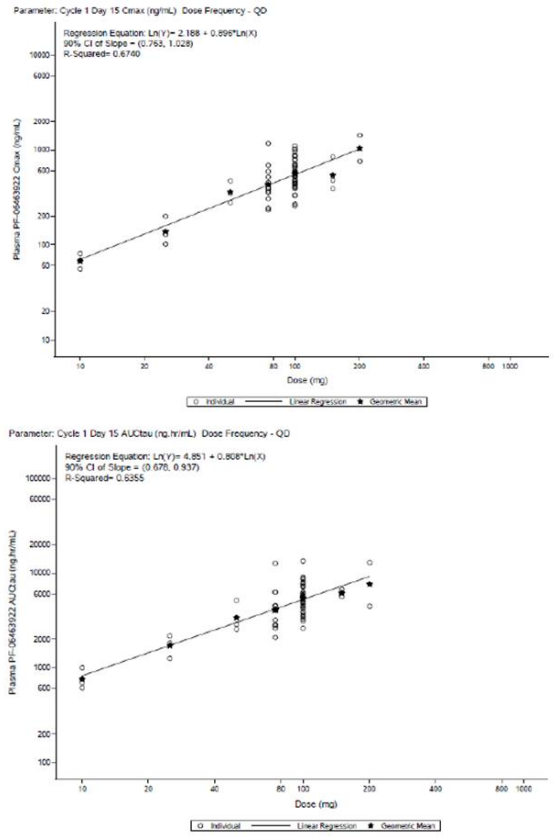
Figure 8: Linear and semi-log plots of median plasma concentration-time profiles of PF-06895751 following administration of multiple oral 100 mg doses of lorlatinib in patients with non-small cell lung cancer (study 1001)

The exposure profile of lorlatinib 100 mg QD displayed in Figure 7 indicates that steady-state was reached at Cycle 1, Day 15 in contrast to the plasma profile for PF-06895751 which indicates that steady-state was not reached (Figure 8) at Cycle 1, Day 15. After a single 100 mg dose of lorlatinib, T_{max} for PF-06895751 was ≥24 hours and the elimination seemed effective from 40 hours post-dose.

Consequences of possible genetic polymorphism

The Pop PK model indicated that polymorphisms of the phenotypes for CYP3A5, CYP2C9 and CYP2C19 evaluated as poor, intermediate, extensive or ultra metabolisers (data from the 7 healthy subject studies) did not have significant impact on lorlatinib exposure. Ultra-rapid metabolisers were represented for CYP2C19. No data were collected from ultra-rapid metabolisers of CYP2C9. None of the investigated phenotypes represented major routes of elimination.

Dose proportionality and time dependencies



Source: Appendix 2, Module 5.3.5.3, SCP Supporting Figures: Figure 14.4.4.4.3.3 and Figure 14.4.4.4.3.4.
Pharmacokinetic parameters are defined in Table 3.
AUC_{tau}=AUC_{24} for QD dosing; PF-06463922=lorlatinib; QD=once daily.

Figure 9: Log-Log plots of individual and geometric mean C_{max} and AUC_{tau} values of lorlatinib as a function of dose following administration of multiple QD doses of lorlatinib (Cycle 1 Day 15) (study 1001)

Data indicate a dose proportional increase in lorlatinib exposure expressed as C_{max} and AUC_{tau} over the investigated dose range of 10-200 mg QD, after single and multiple doses. Lorlatinib AUC_{tau} seemed to increase less than dose-proportionally after 15 doses.

The accumulation ratio for lorlatinib at steady-state was <1 even though the half-life was close to tau and indicated auto-induction of metabolising enzymes. This is in line with the increased metabolic ratio (AUC_{tau}) of PF-06895751 to lorlatinib of 1.8 observed on Cycle 1, Day 15 after 100 mg QD.

Intra- and inter-individual variability

The inter-individual variability (CV%) after a single oral dose of 100 mg QD lorlatinib in healthy subjects across studies 1004, 1005, 1007, 1008, 1011, 1012 and 1016 ranged from 18-38% and 18-37%, for Cmax and AUCinf respectively. Intra-individual variability between first and last dose evaluated in Study 1001, Phase 2 in patients, (N=19/22) was based on geometric mean after 100 mg QD and the %CV ranged from 36-39% and 40-42% for AUC_{tau} and C_{max}, respectively. Inter- and intra-individual variability of lorlatinib PK appear to be moderate. The variability was slightly higher in patients after multiple doses compared to healthy subjects.

Pharmacokinetics in target population

PK was evaluated in patients after single and multiple doses of lorlatinib after dose escalation and after long-term administration of 100 mg QD (4x25 mg). The PK profile of lorlatinib after single dose was comparable in both healthy subject and patients. Steady-state was reached after 15 days of dosing, which was longer than expected from $t_{½}$, but in line with the lack of accumulation and increased CL/F after multiple doses. This effect caused by auto-induction was also indicated by ratios of 4β-hydroxycholesterol/cholesterol and 6β-hydroxycortisol/cortisol that reached a maximum within 8 days.

Table 17: PK parameters of lorlatinib at steady state in patients with ALK-positive or ROS1-positive NSCLC (study 1001) following administration of multiple oral doses of lorlatinib (100 mg QD)

Cohort	Visit	N, n[a], n[b]	AUC_{tau} (ng•hr/mL)	C_{max} (ng/mL)	T_{max}* (hr)	CL/F (L/hr)	R_{ac}	R_{ss}
1001 Phase 1	C1D15	16, 15, 14	5121 (30)	550 (32)	1.1 (1.0-4.0)	19.5 (30)	1.07 ± 0.31	0.660 ±0.186
1001 Phase 2 and Japan LIC	C1D15	22, 20, 14	5650 (39)	577 (42)	2.0 (0.5-22.7)	17.7 (39)	1.08 ± 0.43	0.658 ± 0.286

Source: Module 5, Section 5.3.5.2, Study 1001, Table 14.4.4.1.1.1, Table 14.4.4.1.2.1.
Pharmacokinetic parameters are defined in Table 3.
Geometric mean (geometric %CV) for AUC_{tau}, C_{max}, and CL/F; arithmetic mean ± SD for R_{ac} and R_{ss}; median (range) for T_{max}
%CV=percent coefficient of variation; C=Cycle; D=Day; Japan LIC=Japanese patient only Lead-in Cohort; N=number of subjects in the treatment group; n[a]=number of subjects for whom R_{ac} could be determined, n[b]=number of subjects for whom R_{ss} could be determined; NSCLC=non-small-cell lung cancer; QD=once daily; SD=standard deviation.

Special populations

Renal impairment

Clearance was notably reduced in one patient with severe renal impairment. Renal function assessed as baseline creatinine clearance (WNCL), was found to be a statistically significant covariate affecting lorlatinib clearance in Pop PK analysis.

Table 18: Lorlatinib initial clearance summarized by baseline K/DOQI renal impairment stage for healthy volunteers and patients dosed at 100 mg

Basline Renal Impairment	n	Baseline CrCL (mL/min) Median (Range)	Baseline CrCL (mL/min) Mean ± SD	Baseline Standardized CrCL (mL/min) Median (Range)	Baseline Standardized CrCL Mean ± SD	Lorlatinib Single Dose Clearance (L/hr) Median (Range)	Lorlatinib Single Dose Clearance (L/hr) Mean ± SD
A (Normal)	226	115.78 (90.23-235.39)	120.12 ± 23.36	111.78 (64.40-458.06)	116.27 ± 33.87	9.80 (6.35-17.09)	9.84 ± 1.63
B (Mild)	120	76.11 (60.53-89.98)	76.59 ± 8.58	88.02 (53.50-156.48)	90.45 ± 21.13	8.04 (5.84-11.42)	8.17 ± 1.17
C (Moderate)	45	53.59 (31.58-59.93)	52.04 ± 6.61	68.00 (46.40-107.58)	69.50 ± 13.68	7.22 (5.38-9.87)	7.16 ± 1.01
D (Severe)	1	24.54	24.54	36.82	36.82	4.81	4.81
All	392	96.96 (24.54-235.39)	98.74 ± 31.95	101.03 (36.82-458.06)	102.79 ± 33.28	8.88 (4.81-17.09)	9.01 ± 1.77

ePharmacology artifact ID RA13519111.
CrCL=Cockcroft-Gault calculated creatinine clearance; hr=hour; L=liter; mg=milligram; n=number of patients; K/DOQI=Kidney Disease Outcome Quality Initiative; Stdev=standard deviation.

Table 19: Lorlatinib single-dose and steady state clearance summarized by baseline renal function with K/DOQI classification at 100 mg QD

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

Source: Module 5, Section 5.3.3.5, PMAR-681, Table 15 and Table 16.
CrCL=Cockcroft-Gault calculated creatinine clearance; hr=hour; n=number of patients; K/DOQI=Kidney Disease Outcome Quality Initiative; QD=once daily; SD=standard deviation.
a. The lorlatinib steady state clearance reported are the individual clearance estimates for each patient in Study 1001 at Cycle 1 Day 15, after multiple dosing.

Hepatic impairment

Impact of hepatic impairment on lorlatinib exposure has not been formally studied. Results from the patient study (Study 1001) and the human mass-balance study (Study 1004) indicate that lorlatinib elimination primarily occurred via hepatobiliary elimination.

Table 20: Lorlatinib steady state clearance summarized by baseline NCI hepatic impairment stage for B7461001 patients dosed at 100 mg QD

Basline Hepatic Impairment	n	Lorlatinib Steady State Clearance (L/hr) Median (Range)	Lorlatinib Steady State Clearance (L/hr) Mean ± SD
A (Normal)	236	13.39 (7.68-23.09)	13.78 ± 2.55
B1 (Mild)	36	13.15 (8.79-20.15)	13.71 ± 2.98
B2 (Mild)	6	12.56 (11.56-19.05)	14.08 ± 3.16
All	278	13.31 (7.68-23.09)	13.78 ± 2.61

ePharmacology artifact ID RA13519110.
The lorlatinib steady state clearance reported are the individual clearance estimates for each individual at Cycle 1 Day 15, after multiple dosing.
hr=hour; L=liter; mg=milligram; n=number of patients; NCI=National Cancer Institute; Stdev=standard deviation.

Gender

In the Pop PK analysis, gender did not affect lorlatinib PK, in contrast to pre-clinical findings where gender had marked effect on exposure. Both genders were represented in the clinical PK studies. Women represented 57% of the studied patient Pop PK population. The studies in healthy subjects were predominantly performed in males.

Race

Race was evaluated as Asian vs non-Asian in selected patients from Study 1001. No clinically relevant differences were observed. Race was also tested as a covariate in Pop PK analysis and did not have significant effect on PK parameters. Half of the subjects in the clinical studies were white.

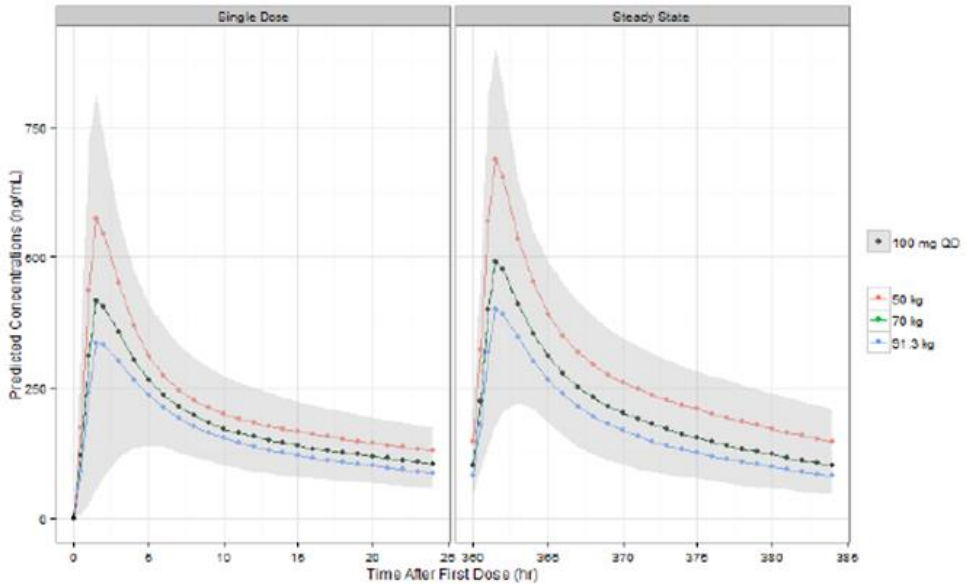
Table 21: Statistical summary of treatment comparison for lorlatinib PK parameters in Asian vs. non-Asians patients by visit (Phase 2 and Japan LIC)

Parameter (units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Asian[b] (Test) vs. Non-Asian (Reference) (Lead In Day -7)				
AUC_{inf} (ng•hr/mL)	9590	8717	110.02	(80.48, 150.40)
C_{max} (ng/mL)	907.2	595.2	152.40	(116.21, 199.86)
Asian[b] (Test) vs. Non-Asian (Reference) (Cycle 1 Day 15)				
AUC_{tau} (ng•hr/mL)	5946	5369	110.74	(83.71, 146.49)
C_{max} (ng/mL)	644.8	515.5	125.07	(93.71, 166.93)

Source: Table 14.4.4.1.2.3.1 and 14.4.4.1.2.3.2
Abbreviation: CI=confidence interval.
Pharmacokinetic parameters are defined in Table 4.
a. The ratios (and 90% CIs) are expressed as percentages.
b. Asian subjects included Japanese patients

Weight

Sensitivity analysis of body weight influence on clearance showed that clearance increased with body weight. The sensitivity analysis simulating the concentrations following 100 mg QD administration with body weights at the 10th and 90th percentile extremes (corresponding to 50 and 91.3 kg) indicated no clinically relevant effect on exposure. Body weights in the studied Pop PK population ranged from 31.8 to 155.5 kg.



Source: Module 5, Section 5.3.3.5, PMAR-681, Figure 13.
The shaded gray ribbon represents the 95% prediction interval for a typical 70 kg White male with no PPI use, a baseline albumin of 4 mg/dL, and dosed at 100 mg. 50 and 91.3 kg are the 10th and 90th percentile body weights, of pooled healthy subjects and subjects. All covariates other than weight are set at the typical values.
hr=hour; PPI=proton-pump inhibitor; QD=once daily.

Figure 10: Simulated body weight effect on lorlatinib PK

Elderly

In the studied Pop PK population (age 19 to 85), age did not seem to affect lorlatinib PK. Elderly ≥65 years were all cancer patients from Study 1001, and represented approximately 14% of the studied Pop PK population.

Age distribution of patients with PK data in Study B7461001

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK data - Study B7461001	45/334	16/334	1/334

Children

Lorlatinib PK was not studied in children. Lorlatinib is currently proposed indicated in adults only.

Pharmacokinetic interaction studies

In vitro

The potential for lorlatinib to cause DDI was investigated *in vitro*. The results indicated lorlatinib could induce CYP3A4, CYP2B6, activate hPXR and hCAR1 and inhibit CYP3A4/5, CYP2C9, UGT1A1, P-gp, BCRP (GI tract), OATP1B1, OATP1B3, OCT1, OAT3 and MATE1 at clinically relevant concentrations.

The DDI effects identified in the in-vitro studies with possible clinical impact were further investigated in-vivo or in relevant cell lines (transporter studies). DDI caused by the major metabolite PF-06895751 was tested in-vitro over a large range of concentrations. Interactions were found to be unlikely at the clinically relevant concentrations achieved after 100 mg QD Lorlatinib in patients.

Interaction study with CYP3A4/5 inhibitor (Study 1012)

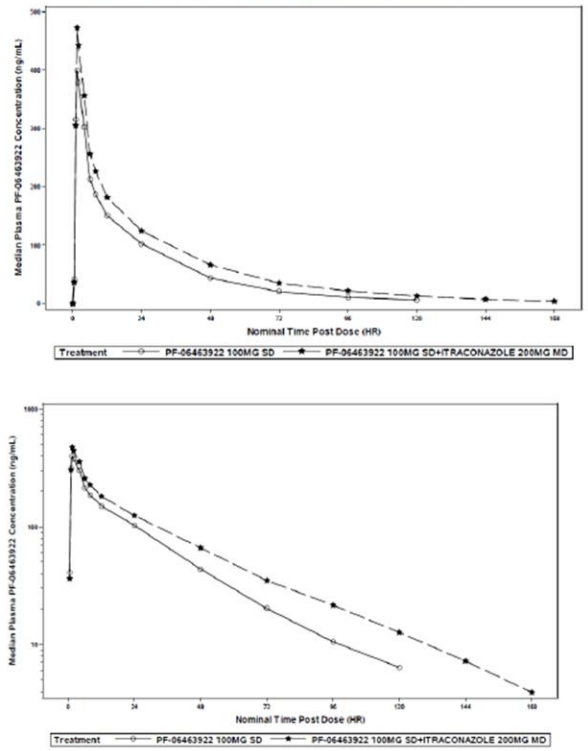
The effect of a single oral dose of lorlatinib (50 mg, 75 mg, and 100 mg) with and without 200 mg once daily itraconazole was evaluated in a 2-way crossover study in 16 healthy volunteers. Lorlatinib AUC_{inf} increased by 42% and C_{max} by 24%.

Table 22: Statistical summary of treatment comparison for PF-06463922 (100 mg) PK parameters with and without itraconazole

Parameters (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test PF-06463922 100 mg Single Dose + Itraconazole 200 mg Multiple Dose	Reference PF-06463922 100 mg Single Dose		
AUC_{inf} (ng·h/mL)	10400	7338	141.79	(128.71, 156.21)
AUC_{last} (ng·h/mL)	10180	7119	142.94	(130.02, 157.15)
C_{max} (ng/mL)	514.4	413.6	124.39	(110.20, 140.41)

Source: Table 14.4.3.3
Parameters are defined in Table 5.
Abbreviations: CI=confidence interval.
a. The ratios (and 90% CIs) are expressed as percentages.

Figure 10. Median Plasma Lorlatinib Concentration-Time Profiles Following a Single Oral 100 mg Dose of Lorlatinib Alone and in Combination with Multiple Oral 200 mg QD Doses of Itraconazole, Study 1012



Source: Module 5, Section 5.3.3.4, Study 1012 CSR, In-text Figure 1.
Upper and lower panels are linear and semi-logarithmic scales, respectively.
Corresponding mean plots Figures 14.4.2.2.1.3 and 14.4.2.2.1.4.
HR=hour(s); MD=multiple dose; PF-06463922=lorlatinib; QD=once daily; SD=single dose.

Interaction study with CYP3A4/5 inducer (Study 1011)

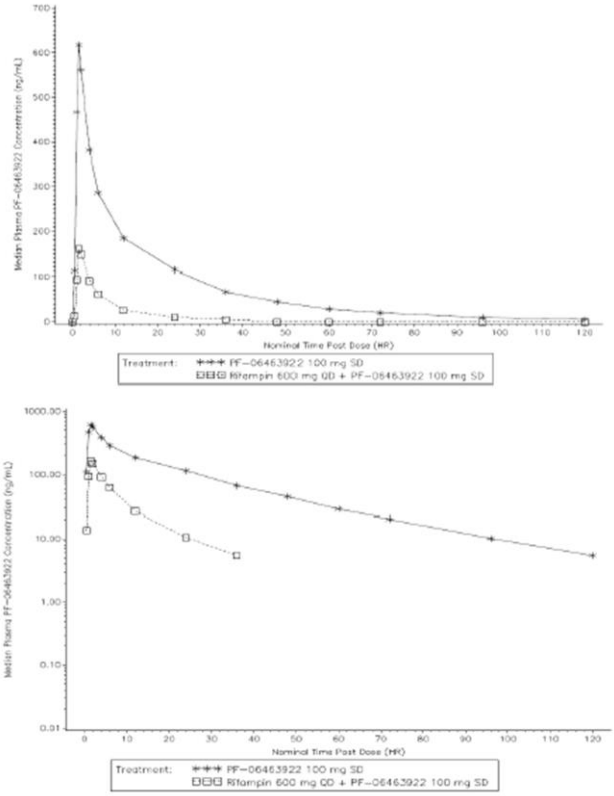
Co-administration of 600 mg QD rifampin decreased lorlatinib exposure expressed as AUC_{inf} and C_{max} by 85% and 76%, respectively and led to elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in all subjects, hence concomitant use of strong CYP3A4/5 inducers with lorlatinib are contraindicated. The Applicant advices concomitant use of moderate CYP3A4/5 inducers with lorlatinib should be avoided. The metabolic ratio of PF-06895751 increased from 1.2 to 5.5 for AUC_{inf} and from 0.21 to 1.1 for C_{max}, following co-administration of lorlatinib and rifampin.

Table 15. Statistical Summary of Treatment Comparison for PF-06463922 Pharmacokinetic Parameters

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test Rifampin 600 mg QD + PF-06463922 100 mg SD	Reference PF-06463922 100 mg SD		
AUC_{inf} (ng•hr/mL)	1292	8766	14.74	(12.78, 17.01)
AUC_{last} (ng•hr/mL)	1200	8597	13.96	(12.09, 16.12)
C_{max} (ng/mL)	148.4	621.4	23.88	(21.58, 26.43)

Source: Table 14.4.3.3
Rifampin was only given from Day 1 to Day 9 in Period 2 to all subjects (versus protocol specified rifampin dosing from Day 1 to Day 12). Additionally, Subject 10011007 discontinued from study during Period 2 and did not take rifampin dose on Day 9 onwards. Values had been back-transformed from the log scale.
Pharmacokinetic parameters are defined in Table 7.
Abbreviations: CI = confidence interval; hr = hour(s); QD = once a day; SD = single dose.
a. The ratios (and 90% CIs) are expressed as percentages.

Figure 6. Median Plasma Lorlatinib Concentration-Time Profiles Following a Single Oral 100 mg Dose of Lorlatinib Alone and in Combination with Multiple Oral 600 mg QD Doses of Rifampin; Study 1011



Source: Module 5, Section 5.3.3.4, Study 1011 CSR, In-text Figure 1.
Upper and lower panels are linear and semi-logarithmic scales, respectively.
Time post dose referred to time post lorlatinib dose in each period.
Rifampin was only given from Day 1 to Day 9 in Period 2 to all subjects (vs protocol specified rifampin dosing from Day 1 to Day 12). Additionally, Subject 10011007 discontinued from study during Period 2 and did not take rifampin dose on Day 9.
HR=hour(s); PF-06463922=lorlatinib; QD=once a day; SD=single dose.

Interaction study with CYP3A4/5 substrate (Study 1001, Phase 1)

The effect on midazolam exposure after co-administration with lorlatinib, was estimated to be decreases of AUC_{inf} of 61% and 62% after 25 and 150 mg QD lorlatinib dosing and decreases in C_{max} of 40% and 50% after 25 mg and 150 mg QD lorlatinib dosing, respectively, compared to midazolam dosed alone. Co-administration with CYP3A4/5 substrates should be avoided. The study demonstrated that lorlatinib induced a reduction in oral midazolam exposure (AUC) which classifies lorlatinib as a moderate CYP3A inducer.

Time-dependent CYP3A4/5 inhibition towards midazolam was demonstrated *in vitro*.

Table 23: Descriptive summary of plasma midazolam PK parameters following a single oral 2 mg dose alone and in presence of lorlatinib (25 mg QD or 150 mg QD)

	Parameter Summary Statistics[a] by Treatment			
	Day -7 Lead In (Alone)		Cycle 1 Day 15 (With Lorlatinib)	
Parameter [Units]	25 mg QD PF-06463922	150 mg QD PF-06463922	25 mg QD PF-06463922	150 mg QD PF-06463922
N, n	3, 3	3, 2	3, 3	3, 3
AUC_{inf} [ng•hr/mL]	54.53 (43)	(42.2, 46.8)	21.32 (18)	16.09 (29)
AUC_{last} [ng•hr/mL]	51.30 (47)	36.49 (20)	20.43 (18)	14.44 (25)
C_{max} [ng/mL]	16.06 (42)	11.56 (48)	9.697 (40)	5.734 (43)
T_{max} [hr]	0.500 (0.500-1.00)	0.500 (0.500-0.500)	0.500 (0.500-1.00)	0.500 (0.500-0.533)
$t_{½}$ [hr]	4.620 ± 1.933	(2.35, 7.89)	3.343 ± 2.036	5.257 ± 5.064
CL/F [L/hr]	36.68 (43)	(42.7, 47.4)	93.86 (18)	124.2 (29)
Vz/F [L]	229.0 (7)	(161, 486)	404.4 (51)	702.2 (100)

Source: Table 14.4.4.3.1.1

On Lead-in Day-7, the treatment was a 2 mg dose of midazolam and the exposure parameters were reported for midazolam alone before any doses of lorlatinib were given. On Cycle1 Day15, the exposures reported were of 2 mg dose of midazolam after 15 days of continuous lorlatinib dosing at the respective dose levels.

Abbreviations: N=number of patients contributing to the summary statistics; n = Number of patients where $t_{½}$, AUCinf, CL/F and Vz/F could be determined. Parameters are defined in Table 4.

a. Geometric mean (geometric %CV) for all parameters except: median (range) for T_{max}; arithmetic mean (±Std Dev) for $t_{½}$. Individual values were reported when n=2.

Interaction study with a PPI (Study 1008)

Please refer to Table 15 in section "Absorption, Influence of food" for PK results.

The effect of PPI use was evaluated in healthy subjects in Study 1008 and showed a 30% decrease in C_{max} with no effect on AUC. 20 mg QD rabeprazole was used for evaluation of gastric effect. The effect of PPI use on lorlatinib exposure was statistically significant in Pop PK analyses. Bootstrap analysis of 1000 simulated individuals showed some effect of PPI-use compared to without PPI-use.

Ongoing

In-vitro studies have indicated lorlatinib has potential for inhibition of CYP2C9, UGT1A1, P-gp and induction of CYP2B6. In-vivo studies with specific probe substrates are ongoing to investigate this further: a DDI study with the CYP2C9 substrate tolbutamide; a DDI study with the CYP2B6 substrate bupropion; a DDI study with a UGT substrate acetaminophen and a DDI study with the P-gp substrate fexofenadine. Lorlatinib may have the potential for DDI by inhibiting hepatic transporters OATP1B1, OATP1B3, OCT1, and renal transporters OAT3 and MATE1 at clinically relevant concentrations. No *in vivo* studies are planned to investigate this further.

Exposure relevant for safety evaluation

The PK for lorlatinib was comparable between patients and healthy subjects with no apparent gender differences. The exposure increased linearly with dose, however multiple dosing resulted in an accumulation ratio close to 1 due to a time-dependent auto-induction of metabolising enzymes. Pop PK analysis indicated clearance increased with increasing weight. Simulation of weight extremes impact on plasma exposure did not describe the range of weight extremes observed in the study population.

The majority of mean C_{trough} (pre-dose) values for lorlatinib ranged from 70-125 ng/ml (%CV high), throughout EXP-1 to EXP-6 in the PK concentration population up to Cycle 20, Day 1.

Peripheral neuropathy was observed in patients who received lorlatinib 100 mg QD.

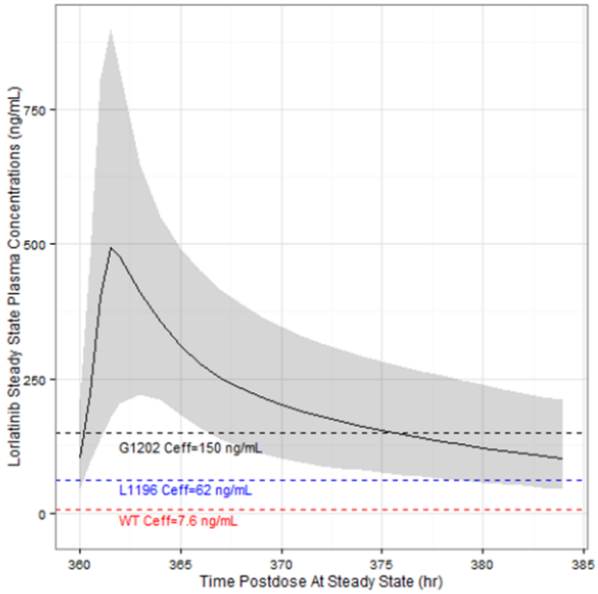
2.4.3. Pharmacodynamics

Mechanism of action

No dedicated mechanism of action studies have been submitted (see Section 2.3).

Primary and Secondary pharmacology

Primary pharmacology



Source: Appendix 3, Figure 3.1
C_{eff}=efficacious concentration of lorlatinib; hr=hour
The solid black line represents a typical median concentration vs time profile following administration of lorlatinib100 mg QD at steady state (Cycle 1 Day 15), based on the popPK model simulation. The shaded gray ribbon represents the 95% prediction interval, based on popPK model-estimated inter-patient variability. The dashed lines represent the C_{eff} values for each of the mutations based on the Shaw et al.

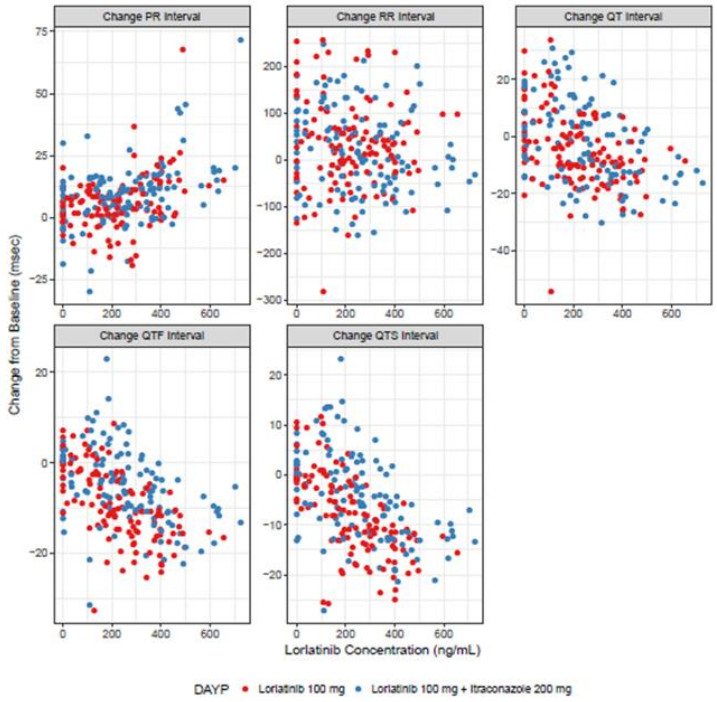
Figure 11: Predicted steady-state plasma lorlatinib concentration-time profile following oral administration of lorlatinib 100 mg QD

Dose rationale

In study 1001, a patient treated at 200 mg QD met the criteria for dose limiting toxicity and the majority of patients had treatment emergent adverse effects at the 150 and 200 mg QD cohorts. Simulations showed that 100 mg QD dose was the lowest dose that would exceed the effective concentration (C_{eff}) of 150 ng/ml to inhibit ALK G1202, for at least 8 hours, at steady-state.

Secondary pharmacology

The effect of lorlatinib on cardiac conduction was analysed in a non-clinical and in a clinical setting. A prolongation of PR interval was observed in the guinea pig heart model and in dog at a dose of 15 mg/kg/day. These data were confirmed in the analysis conducted by iCardiac on data from clinical Study 1012 (Holter monitoring) in which a prolongation of PR interval was observed in lorlatinib alone (12.7 msec at 1 hour post-dose) and in lorlatinib+itraconazole (16.6 msec at 1.5 hour post-dose). No subjects showed a PR interval >200 msec. A shortening in QTcF interval was observed 1 hour post lorlatinib dose and this effect was slightly more evident with itraconazole administration.



ePharmacology artifact ID RA13727264.
Scatterplots for the change from baseline (Period 1, Day -1) for PR, RR, QT, QTcF, and QTcS relative to the lorlatinib plasma concentrations are presented from Period 1, Day 1 and Period 2, Day 5. The red points correspond to the Period 1 Day 1 dose of lorlatinib 100 mg and the blue points correspond to the Period 2 Day 5 dose of lorlatinib 100 mg which followed 5 days of itraconazole 200 mg.
mL=milliliter; msec=millisecond; ng=nanogram; PR=time between the P wave and the R wave; QT=the distance between the T wave and the Q wave; QTcF=QTcF; QTcS=QTcS; RR=time between the successive R waves.

Figure 12: Change from baseline versus lorlatinib concentration

PKPD analysis showed no relationship of lorlatinib concentration on heart rate or QTc prolongation but confirmed the shortening of QTcS or QTcF due to lorlatinib concentration.

Increase in lorlatinib concentration was associated with PR prolongation and the baseline PR value was a predictor of PR prolongation. Simulations indicate the probability for PR intervals >200 msec is low.

Study 1001, Phase 2 further evaluated the effects of lorlatinib on the PR interval conducted via continuous Holter telemetry in a sub-group of patients. Of 292 patients in the 100-mg QD pooled group, 29 patients with baseline PR <200 ms had PR prolongation 200-<220 ms while 11 patients with baseline PR <200 ms had prolonged PR >220 ms after treatment. Seven (7) patients with PR 200-<220 ms at baseline had prolonged PR >220 ms after treatment and 1 patient with baseline PR >220 ms had PR prolongation ≥260 ms. There was treatment-related AV block (Grade 1) reported in 2 patients and 1 temporary treatment discontinuation. The sub-study confirmed lorlatinib 100 mg QD treatment could cause PR-prolongation.

Table 24: Estimated mean change from baseline in the study-specific QTc interval

Dosing	C_{max} Average	Change in QTc (msec)	95% CI
Single Dose Patients	695 ng/mL C_{max}	-26.68	(-31.32, -22.49)
Steady-State Patients	576 ng/mL C_{max}	-22.11	(-25.96, -18.64)

ePharmacology artifact ID RA13729974. Line 1 substituted.
The table provides the simulated mean QTcS change from baseline at the single dose C_{max} and the steady-state C_{max} along with respective 95% confidence intervals. The concentrations were taken from Phase 2 patient descriptive summaries from the source: Module 5, 3.5.1, B7461001 CSR, Table 14.4.4.1.2.1.
CI=confidence interval; mL=milliliter; msec=millisecond; ng=nanogram; QTc=corrected QT interval; QTcS=study-specific corrected QT interval.

Table 25: Estimated mean change from baseline in the Fridericia QTc interval

Dosing	C_{max} Average	Change in QTc (msec)	95% CI
Single Dose Patients	695 ng/mL C_{max}	-25.85	(-30.08, -21.32)
Steady-State Patients	576 ng/mL C_{max}	-21.42	(-24.93, -17.67)

ePharmacology artifact ID RA13729973. Line 1 substituted.
The table provides the simulated mean QTcF change from baseline at the single dose C_{max} and the steady-state C_{max} along with respective 95% confidence intervals. The concentrations were taken from Phase 2 patient descriptive summaries from the source: Module 5, 3.5.1, B7461001 CSR, Table 14.4.4.1.2.1.
CI=confidence interval; mL=milliliter; msec=millisecond; ng=nanogram; QTc=corrected QT interval; QTcF=Fridericia corrected QT interval.

Table 26: Simulated probability of a PR interval length over 200 milliseconds

C_{max}	Baseline PR Interval							
	151 (msec)	170 (msec)	175 (msec)	180 (msec)	185 (msec)	190 (msec)	195 (msec)	200 (msec)
576 ng/mL	<0.001	0.050	0.128	0.268	0.458	0.658	0.821	0.924
695 ng/mL	<0.001	0.078	0.187	0.360	0.569	0.760	0.892	0.962

ePharmacology artifact ID RA13733719. Line 1 substituted.
The simulated probabilities of experiencing a PR interval over 200 msec for a 48 year old subject (48 was the median age) at a given baseline PR interval value for both the single dose and steady-state concentrations observed in Patients are provided in the table.
mL=milliliter; msec=millisecond; ng=nanogram; PR=time between the P wave and the R wave.

PD interactions with other medicinal products or substances

Predicted effect of increasing plasma concentrations of lorlatinib on the development of the most frequently occurring AEs have been investigated appropriately (see below). From a PD perspective, clinical management in the event of lorlatinib-induced AEs belonging to the SOCs of metabolic disorders, CNS disorders, cardiac disorders and other AEs has been appropriately described in the SmPC. It is noteworthy that all-causality AEs of hypercholesterolemia and hypertriglyceridemia were reported at a frequency of 82.4% and 60.7%. The current SmPC proposal contains a warning with a recommendation to monitor plasma cholesterol and triglycerides. In the event that concomitant medication which independently increases plasma cholesterol and triglycerides is administered, synergistic increases may be expected. However, these are expected to be captured given that the current warnings and recommendations are followed.

Genetic differences in PD response

Analysis of ALK kinase domain mutation was performed in plasma and in tumour tissue in cancer patients from Phase 2 of Study 1001 to investigate the impact of genetic differences with regard to tyrosine kinase inhibition (data not shown). Results did not indicate any impact of the ALK kinase domain mutation or of the G1202R mutation on number of responders or duration of response compared to patients without detectable mutations in plasma and tumour tissue. Analysis for the ROS1 kinase domain mutation had not been performed at the time of data cut off.

Relationship between plasma concentration and effect

No exposure-response relationship of efficacy could be demonstrated by PK/PD modelling, using the efficacy endpoints: objective response rate (ORR) and intracranial objective response rate (IC-ORR) in patient data from Study 1001. The effective concentration C_{eff} was determined to be 150 ng/ml. The majority of patients included were probably exposed well-above this cutoff. 90% of the study population received 100 mg QD.

In Phase 1, maximum hypercholesterolemia adverse event Grade ≥2 (CHLGR) was found to be predictive of response. The Applicant suggested sensitivity to lorlatinib was a driver for response more than exposure. Asian race was somehow predictive of response correlated with higher baseline amylases (BAMY). Odds for achieving ORR or IC-ORR was found to be correlated with higher BAMY in

different patient groups. Odds of achieving ORR was lower for patients with 1 and 2+ prior systemic therapies. Odds of achieving IC-ORR were lower for patients with prior CNS radiation and higher baseline alkaline phosphatase (BAP).

Relationship between plasma concentration and safety endpoints

Baseline cholesterol, time on treatment and lorlatinib exposure were statistically significant predictors of hypercholesterolemia Grade ≥3. With each unit increase in log(C_{max} event), patients were 5.256 times more likely to experience Hypercholesterolemia Grade ≥3. Baseline bodyweight and time on treatment were significant predictors of Weight Gain Grade ≥2. Asian ethnicity, baseline triglycerides and time of treatment were significant predictors of Hypertriglyceridemia Grade ≥3. Age, concomitant use or narcotics and steroids, time on treatment and lorlatinib exposure were statistically significant predictors of TEAEs Grade ≥3.

The frequency of the CNS endpoints in the investigated population were too low to allow for a robust analysis, however it seemed lorlatinib exposure was not predictive of CNS effects when the majority of the studied population received 100 mg QD.

2.4.4. Discussion on clinical pharmacology

Overall, the bioanalytical method validations and PK analysis are considered thorough and acceptable according to guidelines. The Pop PK population included data from 425 subjects (healthy volunteers and patients). Although the model underestimates the exposure around C_{max} after a single dose, model performance at steady state in cancer patients is in general considered acceptable.

Peak lorlatinib concentrations in plasma are rapidly reached with the median T_{max} of 1.2 hours following a single 100 mg dose and 2.0 hours following multiple dosing of 100 mg once daily.

After oral administration of lorlatinib tablets, the mean absolute bioavailability is 80.8% (90% CI: 75.7, 86.2) compared to intravenous administration.

Administration of lorlatinib with a high fat, high calorie meal resulted in 5% higher exposure compared to fasted conditions. Lorlatinib may be administered with or without food.

At 100 mg once daily, the geometric mean (%CV) peak plasma concentration was 577 (42) ng/ml and the AUC_{24} was 5,650 (39) ng·h/ml in patients with cancer. The geometric mean (% CV) oral clearance was 17.7 (39) L/h.

In vitro binding of lorlatinib to human plasma proteins is 66% with moderate binding to albumin or to α_1-acid glycoprotein.

In humans, lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. *In vitro* data indicate that lorlatinib is metabolised primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5 and UGT1A3.

In plasma, a benzoic acid metabolite of lorlatinib resulting from the oxidative cleavage of the amide and aromatic ether bonds of lorlatinib was observed as a major metabolite, accounting for 21% of the circulating radioactivity. This oxidative cleavage metabolite is pharmacologically inactive.

The plasma half-life of lorlatinib after a single 100 mg dose was 23.6 hours. Following oral administration of a 100 mg radiolabelled dose of lorlatinib, a mean 47.7% of the radioactivity was recovered in urine and 40.9% of the radioactivity was recovered in faeces, with overall mean total recovery of 88.6%.

Unchanged lorlatinib was the major component of human plasma and faeces, accounting for 44% and 9.1% of total radioactivity, respectively. Less than 1% of unchanged lorlatinib was detected in urine.

At single dose, lorlatinib systemic exposure (AUC_{inf} and C_{max}) increased in a dose-related manner over the 10 to 200 mg dose range. Few data are available over the 10 to 200 mg dose range; however, no deviation from linearity was observed for AUC_{inf} and C_{max} after single dose.

At steady-state, the systemic exposure (AUC_{24}) increased less than proportionally over the 10 to 200 mg dose range.

Also, at steady-state lorlatinib plasma exposures are lower than those expected from single dose pharmacokinetics, indicative of a net time-dependent auto-induction effect.

As lorlatinib is metabolised in the liver, hepatic impairment is likely to increase lorlatinib plasma concentrations. Clinical studies that were conducted excluded patients with AST or ALT > 2.5 × ULN, or if due to underlying malignancy, > 5.0 × ULN or with total bilirubin > 1.5 × ULN. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n = 50). No dose adjustments are recommended for patients with mild hepatic impairment. No information is available for patients with moderate or severe hepatic impairment.

Less than 1% of the administered dose is detected as unchanged lorlatinib in urine. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild (n = 103) or moderate (n = 41) renal impairment (CL_{cr} > 30 ml/min). No starting dose adjustments are recommended for patients with mild or moderate renal impairment. Information for lorlatinib use in patients with severe renal impairment (CL_{cr} < 30 ml/min) is limited (n = 1).

The applicant will submit the results of studies investigating the use of lorlatinib in patients with hepatic (Study B7461009) and renal (Study B7461010) impairments (see RMP).

Population pharmacokinetic analyses in patients with advanced NSCLC and healthy volunteers indicate that there are no clinically relevant effects of age, gender, race, body weight, and phenotypes for CYP3A5 and CYP2C19.

The in-vitro interaction studies indicated that lorlatinib could induce CYP3A4, CYP2B6 mediated by hPXR and hCAR1. Until final results of DDI studies with CYP2C9, CYP2B6, UGT1A1, and P-gp are available, substrates of CYP2C9, CYP2B6, UGT1A1, and P-gp should be avoided. This information is mentioned in the SmPC Section 4.5 with an amended list of medicinal products with a narrow therapeutic index.

The in-vitro results also indicated that lorlatinib could inhibit CYP3A4/5, CYP2C9, UGT1A1, P-gp, BCRP (GI tract), OATP1B1, OATP1B3, OCT1, OAT3, and MATE1 at clinically relevant concentrations. In-vivo studies with specific probe substrates for CYP2C9, CYP2B6, UGT1A1 and P-gp are ongoing to investigate this further. No *in vivo* DDI studies with inhibition of OATP1B1-3, OCT1 or OAT3 are planned. Potential interactions with substrates of OATP1B1-3, OCT1 or OAT3 are not expected to be clinically relevant.

Itraconazole, a strong inhibitor of CYP3A4/5, administered at oral doses of 200 mg once daily for 5 days, increased the mean area under the curve (AUC) 42% and C_{max} 24% of a single 100 mg oral dose of lorlatinib in healthy volunteers. Concomitant administration of lorlatinib with strong CYP3A4/5 inhibitors (e.g. boceprevir, cobicistat, itraconazole, ketoconazole, posaconazole, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either elvitegravir, indinavir, lopinavir or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations and should be avoided. An alternative concomitant medicinal product with less potential to inhibit

CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor must be concomitantly administered, a dose reduction of lorlatinib is recommended (see Sections 4.2 and 4.5 of the SmPC).

Rifampin, a strong inducer of CYP3A4/5, administered at oral doses of 600 mg once daily for 12 days, reduced the mean lorlatinib AUC by 85% and C_{max} by 76% of a single 100 mg oral dose of lorlatinib in healthy volunteers; increases in AST and ALT were also observed. Concomitant administration of lorlatinib with strong CYP3A4/5 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) may decrease lorlatinib plasma concentrations. The use of a strong CYP3A4/5 inducer with lorlatinib is contraindicated. Concomitant use with moderate CYP3A4/5 inducers should be avoided, if possible, as they may also reduce lorlatinib plasma concentrations (see Sections 4.3, 4.4 and 4.5 of the SmPC).

In vitro studies indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5 and it activates the human pregnane-X-receptor (PXR), with the net effect *in vivo* being induction. Concurrent administration of lorlatinib in patients resulted in decreased oral midazolam AUC when midazolam was administered alone, suggesting that lorlatinib is an inducer of CYP3A4/5. Lorlatinib 150 mg orally once daily for 15 days decreased AUC_{inf} and C_{max} of a single oral 2 mg dose of midazolam (a sensitive CYP3A substrate) by 61% by 50%, respectively; hence, lorlatinib is a moderate CYP3A inducer. Thus, concurrent administration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by lorlatinib (see Sections 4.4 and 4.5 of the SmPC).

The ongoing DDI studies (sub-study of B7461001) with CYP2C9, P-gp, CYP2B6 and UGT1A1 substrates are performed following 15 days of lorlatinib 100 mg QD dosing, i.e. at steady-state, which is considered a sufficiently long period to cover the full induction potential. Results from the ongoing interactions studies will be included in the final CSR. The applicant is recommended to provide a summary of the PK data from the DDI sub-study in patients.

The rationale behind the daily dosing interval of 100 mg QD lorlatinib is adequately described.

In the clinical Study 1012 a prolongation of the PR interval was observed via Holter monitoring. PKPD simulations indicated the probability for PR intervals >200 msec is low. Study B7461001, Phase 2 evaluated the effects of lorlatinib on the PR interval conducted via continuous Holter telemetry in a sub-group of patients. The sub-study confirmed lorlatinib 100 mg QD treatment could cause PR-prolongation. The prolongation of PR interval occurred in a concentration dependent manner. There was treatment-related AV block (Grade 1) reported in 2 patients and 1 temporary treatment discontinuation. Adequate guidance is provided in Sections 4.2, 4.4 and 5.2 of the SmPC.

ALK kinase domain mutation analysis was performed in plasma and in tumour tissue in cancer patients from Phase 2 of Study 1001 to investigate the impact of genetic differences with regard to tyrosine kinase inhibition. Results indicated no impact of ALK kinase domain mutation or G1202R mutation on number of responders or duration of response compared to patients without detectable mutations in plasma and tumour tissue.

The exposure-response relationship was analysed for efficacy and safety endpoints. No exposure-response relationship was identified between any lorlatinib exposure metric ($C_{max,P1}$, $C_{trough,P1}$, $C_{avg,P1}$, as such or as its logarithmic value) and ORR or IC-ORR. Lorlatinib exposure was a statistically significant predictor of hypercholesterolemia Grade ≥3 and of TEAEs Grade ≥3. Age, concomitant use or narcotics and steroids, time on treatment and lorlatinib exposure were statistically significant predictors of TEAEs Grade ≥3. Adequate guidance for adverse reactions is provided in SmPC Section 4.2 and 4.4. The rate of CNS endpoints in the investigated population were too low to allow for a robust analysis.

No statistically significant exposure-safety relationship was found for any of the CNS-related safety endpoints.

2.4.5. Conclusions on clinical pharmacology

Overall, bioanalytical methods and the PK analysis were acceptable. The PK of lorlatinib is adequately described and the *in vitro* and *in vivo* interaction studies in healthy subjects and patients are considered acceptable.

The applicant will submit the following measures post authorisation to address remaining uncertainties in relation to pharmacology:

- In order to further investigate the effect of lorlatinib on patients with renal and hepatic impairment, the applicant should submit the results of studies B7461010 and B7461009 (see RMP)

- In order to further characterise the full induction potential of lorlatinib on CYP2C9, P-gp, CYP2B6 and UGT1A1 substrates, the applicant is recommended to provide a summary of the PK data from the DDI sub-study in patients

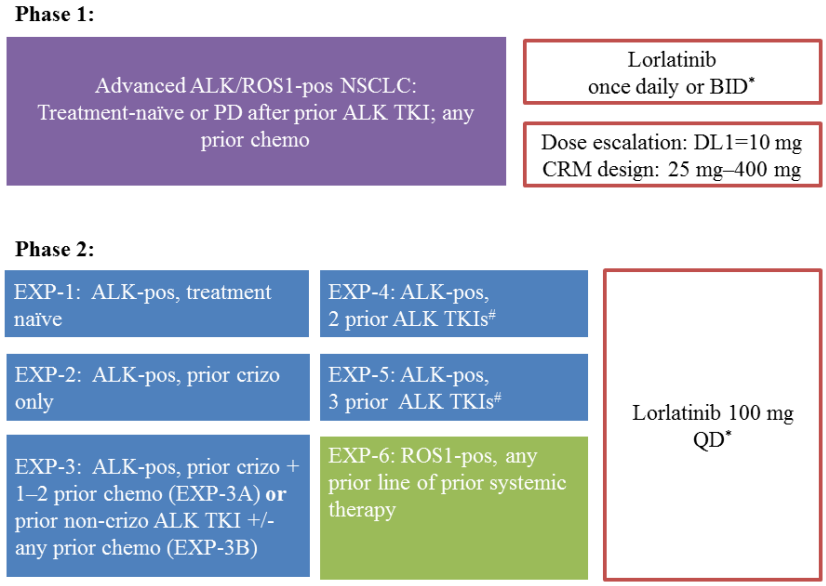
2.5. Clinical efficacy

The clinical study that provides the basis for the efficacy evaluations of lorlatinib consists of 2 portions, Phase 1 and Phase 2. Data from this study were initially based on the data cutoff date of 15 March 2017, at which time the study was ongoing, but enrollment in both Phases was complete. During the procedure, updated efficacy results were provided with data cutoff date of 02 February 2018, allowing for a median follow-up of 9.9 months of the pooled cohorts EXP-4 and 5. Efficacy results are presented for 41 patients with advanced ALK-positive NSCLC from the Phase 1 portion of Study 1001 and for 197 patients with advanced ALK-positive NSCLC from the Phase 2 portion of Study 1001, as well as 2 Japanese patients in the Japan LIC.

Table 27: Efficacy Cohorts of ALK-Positive NSCLC Patients Assessed by ICR (Phase 1 and Phase 2)

Study Portion	Cohort Name	Cohort Description	Total Number of Patients N	Patients with Brain Metastases at Baseline n
Phase 1	N/A	Treatment-naïve or pre-treated with 1 or more ALK-TKI[a]	41	34
Phase 2	EXP-3B	1 prior non-crizotinib ALK-TKI ± chemotherapy	27	12
	EXP-4:EXP-5	2 or more prior ALK-TKI ± chemotherapy	111	83
	EXP-2:3A	Prior crizotinib only ± prior chemotherapy	59	37

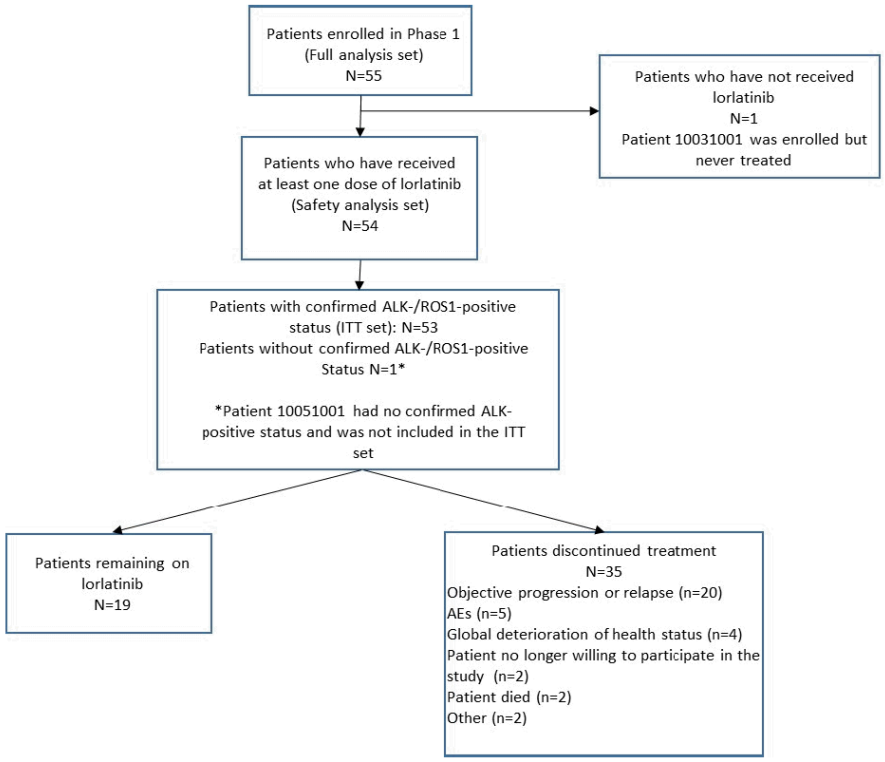
Source: SCE Tables 14.1.2.5.2.2.1 and 14.1.2.5.2.2.2, Study 1001 Phase 1 Table 14.1.1.1.1, and CO Table 14.1.1.1.2.co.
Abbreviations: ALK=anaplastic lymphoma kinase; EXP=expansion; ICR=independent central review; N/n=number of patients; N/A=not applicable; NSCLC=non-small cell lung cancer; QD=once daily; SCE=summary of clinical efficacy; TKI=tyrosine kinase inhibitor.
a. Patients in the dose-escalation part of Phase 1 were treated across all doses tested (10 to 200 mg QD).



* Treatment until PD or unacceptable toxicity
# Any number of lines of prior chemotherapy are allowed.
Asymptomatic brain metastases are allowed in all cohorts.
If the same TKI were given twice, that would be considered 2 prior lines of ALK TKIs
ALK=anaplastic lymphoma kinase; BID=twice a day; Chemo=Chemotherapy; CRM=continual reassessment method; crizo=crizotinib; DL1=dose level 1; EXP=expansion (cohort); NSCLC=non-small cell lung cancer; PD=progressive disease; pos=positive, QD=once daily; TKI=tyrosine kinase inhibitor.

Figure 13: Study 1001 Schema

2.5.1. Dose-response study(ies)



Source: Tables 14.1.1.1.1 and 14.1.1.3.1.
Abbreviations: AE=adverse event; ALK-positive=anaplastic lymphoma kinase-positive; ITT=intention to treat; N/n=number of patients.

Figure 14: Study flow chart (Phase 1)

In the dose-escalation Phase 1 portion of the 1001 study, the optimal dosing of lorlatinib was established. The MTD was not reached as only 1 patient met the dose-limiting criteria. This patient was treated with lorlatinib at 200 mg QD and did not receive 16 of the planned 21 doses of lorlatinib during Cycle 1 due to toxicities attributed to study drug, which met the protocol definition of a DLT. This patient experienced Grade 1 and Grade 2 CNS effects during Cycle 1, including Grade 2 aphasia and cognitive disorder, and Grade 1 visual impairment and abnormal dreams, so lorlatinib was temporarily discontinued for the remainder of the cycle. Additionally, in the 150 mg QD and 200 mg QD cohorts, the majority of patients experienced AEs resulting in temporary discontinuation and/or dose reduction. At 150 mg QD, these included temporary discontinuations for Hallucination (in 2 patients Grade 2), Confusional state (1 patient Grade 2), Mental status changes (1 patient Grade 3), and Seizure (1 patient Grade 2). At 200 mg QD, in addition to the patient with the DLT, temporary discontinuation included 1 additional patient who experienced Formication and Irritability (Grade 1 and Grade 2, respectively). As a result, it was agreed upon by the Sponsor and the Phase 1 Investigators to evaluate doses lower than 200 mg QD and consider an alternative dosing regimen. BID dosing was subsequently evaluated to assess whether reducing the C_{max} would lessen the CNS effects. Patients did not tolerate 75 mg or 100 mg BID dosing. Thus, while the MTD was not formally reached, lorlatinib was considered tolerable at the 100 mg QD dose level, which was declared the recommended Phase 2 dose (RP2D) in patients with ALK-positive or ROS1-positive NSCLC.

2.5.2. Main study

Study of PF-06463922 (an ALK Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harbouring Specific Molecular Alterations (study B7461001) – Phase 2 part

Methods

Study Participants

Inclusion criteria:

1. Evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, American Joint Committee on Cancer [AJCC] version 7.0) that carried an ALK rearrangement, as determined by the Food and Drug Administration (FDA)-approved fluorescence in situ hybridisation (FISH) assay (Abbott Molecular Inc) or by Immunohistochemistry (IHC) (Ventana Inc). All patients had to have archival tissue sample available and collected prior to enrollment.

2. Disease status requirements:

ALK-positive NSCLC patients were to either have or have had:

- Treatment naïve (i.e., no prior chemotherapy in the metastatic disease setting and no prior ALK inhibitor therapy allowed). [EXP-1];
- Disease progression after crizotinib only. No prior chemotherapy was allowed in the metastatic disease setting. [EXP-2];
- Disease progression after crizotinib and 1 or 2 prior regimens of chemotherapy in the metastatic disease setting. [EXP-3A];

- Disease progression after 1 prior ALK inhibitor therapy other than crizotinib. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP-3B];
- Disease progression after 2 prior ALK inhibitor therapies. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP-4];
- Disease progression after 3 prior ALK inhibitor therapies. Patients were allowed to have any number of prior chemotherapy regimens in any disease setting. [EXP-5].

3. Tumour Requirements:

All patients had at least 1 measurable target extracranial lesion according to RECIST version 1.1. In addition patients with asymptomatic CNS metastases (including patients controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry) were eligible. The brain metastases were either diagnosed or have been presented as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery (see Exclusion Criterion #3 for the lapsed time period required between the end of radiotherapy and study entry). Patients who had leptomeningeal disease (LM) or carcinomatous meningitis (CM) were eligible if the LM/CM was visualised on MRI or if documented baseline CSF positive cytology was available.

4. Age ≥18 years (or ≥20 years of age if required by local regulation).

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0, 1, or 2.

6. Adequate bone marrow function, including:

- ANC ≥1.5 × 109/L;
- Platelets ≥100 × 109/L;
- Haemoglobin ≥9 g/dL.

7. Adequate pancreatic function, including:

- Serum total amylase ≤1.5 upper limit of normal (ULN);
- Serum lipase ≤1.5 ULN.

8. Adequate renal function, including:

- Serum creatinine ≤1.5 × ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

9. Adequate liver function, including:

- Total serum bilirubin ≤1.5 × ULN;
- Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤2.5 × ULN; ≤5.0 × ULN if there were liver metastases involvement.

10. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator' judgment did not constitute a safety risk for the patient.

11. Serum pregnancy test (for females of childbearing potential) negative at Screening (before the patient was allowed to receive the investigational product [IP]). A patient was of childbearing potential if, in the opinion of the investigator, she was biologically capable of having children and was sexually active.

12. Evidence of a personally signed and dated informed consent document indicating that the patient had been informed of all pertinent aspects of the study.

13. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

14. Male and female patients of childbearing potential and at risk for pregnancy were required to agree to use 2 highly effective methods of contraception from the time of the first negative pregnancy test at Screening, throughout the study and for 90 days after the last dose of assigned treatment. A patient was of childbearing potential if, in the opinion of the investigator, he/she was biologically capable of having children and was sexually active.

Exclusion Criteria

Patients were ineligible to participate in this study if any of the following criteria were met:

1. Spinal cord compression was excluded unless the patient demonstrated good pain control attained through therapy and there was stabilisation or recovery of neurological function for the 4 weeks prior to study entry.

2. Major surgery within 4 weeks of study entry. Minor surgical procedures (e.g., port insertion) were not excluded, but sufficient time (e.g., up to 2 weeks) should have passed for wound healing.

3. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) had to be completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation had to be completed at least 2 weeks prior to study entry. Whole brain radiation had to be completed at least 4 weeks prior to study entry.

4. Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study entry (unless clinically meaningful tumour flare per discretion of the investigator, in which discussion with the Sponsor was warranted).

5. Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including, but not limited to, anti- programmed cell death receptor-1 (PD-1), anti-PD-ligand 1 (PD-L1), anti-PD ligand 2 (PD-L2), anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody.

6. Previous high-dose chemotherapy requiring stem cell rescue.

7. Prior irradiation to >25% of the bone marrow.

8. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

9. Clinically significant cardiovascular disease (that was, active or <3 months prior to enrollment): cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), second-degree or third-degree atrioventricular (AV) block (unless paced) or any AV block with pulse rate >220 msec. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient was otherwise healthy such as long-distance runners, etc.), machine-read ECG with QTc >470 msec, or congenital long QT syndrome.

10. Patients with predisposing characteristics for acute pancreatitis according to investigator judgment.

11. 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 (ILD), obliterative bronchiolitis and pulmonary fibrosis. Patients with history of prior radiation pneumonitis were not excluded.

12. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behaviour, or laboratory abnormality that could have increased the risk associated with study participation or IP administration or could have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.

13. Patients who were investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who were Pfizer employees directly involved in the conduct of the trial.

14. Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, ductal carcinoma in situ (DCIS) of the breast or localised and presumed cured prostate cancer) within the last 3 years.

15. Active inflammatory gastrointestinal disease, chronic diarrhoea, symptomatic diverticular disease or previous gastric resection or lap band.

16. Current use or anticipated need for food or drugs that were known strong or moderate CYP3A4 inhibitors, including their administration within 10 days prior to the first lorlatinib dose.

17. Current use or anticipated need for drugs that are known strong CYP3A4 inducers, including their administration within 12 days prior to the first lorlatinib dose.

18. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices.

19. Concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices.

20. Concurrent use of drugs that are sensitive CYP2B6 substrates.

21. Current use or anticipated need for drugs that are known strong CYP2C19 inhibitors, including their administration within 12 days prior to study entry.

22. Current use or anticipated need for drugs that are known strong CYP2C8 inhibitors, including their administration within 12 days prior to study entry.

23. Current use or anticipated need for drugs that are known P-gp substrates with a narrow therapeutic index, including their administration within 12 days prior to study entry.

24. Patients presenting with abnormal LVEF by echocardiogram or MUGA according to institutional lower limits.

25. Breastfeeding female patients (including patients who intended to interrupt breastfeeding).

Treatments

In all study parts, lorlatinib was administered orally QD continuously in 21-day cycles. Patients self-administered lorlatinib in the outpatient setting.

In the event of toxicities, dose reductions were contemplated by the protocol according to the following:

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

Objectives

Primary Objective:

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

Secondary Objectives:

- To confirm the safety and tolerability of single-agent lorlatinib at the RP2D.
- To confirm single- and multiple-dose PK profiles of single-agent lorlatinib at the RP2D.
- To assess secondary measures of clinical efficacy.
- To detect early signs of changes in mood, cognitive function, or suicidal ideation and behaviour (SIB).
- To evaluate PRO of global QoL, functioning and the impact of lorlatinib on disease/treatment-related symptoms of lung cancer at the RP2D.
- To further evaluate the effects of single-agent lorlatinib at the RP2D on the QTc interval.
- To further evaluate tumour and blood-based molecular markers of response and resistance to single-agent lorlatinib at the RP2D.
- To evaluate the safety and efficacy of single-agent crizotinib following lorlatinib in treatment-naïve patients with advanced ALK-positive NSCLC.
- To evaluate response to prior systemic therapies.

Exploratory Objective

The exploratory objective of the Phase 2 portion of the study was to explore the brain penetration of single-agent lorlatinib at the RP2D.

Outcomes/endpoints

Primary endpoints:

- ORR was defined as the percent of patients with Best Overall Response (BOR) of confirmed Complete Response (CR) or confirmed Partial Response (PR) according to RECIST version 1.1. Confirmed responses were those that persisted on repeat imaging at least 4 weeks after the initial documentation of response.
- Intracranial ORR (IC ORR) was defined as the percent of patients with CNS metastases at study entry with Best Overall Intracranial Response of confirmed CR or confirmed PR (considering only the lesions having brain as the disease site).

Secondary endpoints:

- TTR (IC TTR) was defined as the time from Cycle 1 Day 1 (C1D1) to first documentation of objective (intracranial) tumour response (CR or PR) that is subsequently confirmed.
- DOR (IC DOR) was defined as the time from the first documentation of objective (intracranial) tumour response, CR or PR, to the first documentation of disease progression or death associated with any cause, whichever occurs first.

- Progression-Free-Survival (PFS) was defined as the time from C1D1 to first documentation of objective disease progression or to death on study due to any cause, whichever came first. If tumour progression data include more than 1 date, the first date will be used.
- Overall Survival (OS) was defined as the time from C1D1 to the date of death due to any cause.
- Probabilities of survival at 1 year and 18 months were defined as the probabilities of survival at 1 year and 18 months, respectively, after the date of first dose.

Other analyses conducted in Phase 2 included Disagreement in Response assessment, PROs based on EORTC QLQ C30 (Version 3.0) and its lung cancer module, QLQ LC13, and Biomarker analyses.

Sample size

The Phase 2 study was initially designed to recruit 240 patients with 40 patients in each of the 6 cohorts. There was no sample size definition based on either expected desirable outcomes or a pre-specified precision of the estimates for the hypothesised ORR, as demonstrated by the large width of the 95% CI listed in the table below, showing possible estimated ORR and 95% CIs for different level of responses in populations of 30, 40 patients, 70 and 80 patients.

Responses/Cohort Sample Size	ORR (Estimated 95% CI)
21/30	70% (50.6-85.3)
23/30	77% (57.7-0.90)
25/30	83% (65.3-94.4)
16/40	40% (24.9-56.7)
20/40	50% (33.8-66.2)
24/40	60% (43.3-75.1)
24/70	34% (23.3-46.6)
28/70	40% (28.5-52.4)
32/70	45% (33.7-58.1)
32/80	40% (29.2-51.6)
40/80	50% (38.6-61.4)
48/80	60% (48.4-70.8)

Therefore, data only allow for descriptive statistics of results to be made.

Randomisation

The study was not randomised.

Blinding (masking)

The study was not blinded.

Statistical methods

Analysis Sets

The **intention-to-treat (ITT) analysis set** included all enrolled patients with documented ALK gene rearrangement who were treated with at least 1 dose of lorlatinib. The ITT Analysis Set is the primary efficacy analysis set and is the focus of the efficacy presentations in this SCE.

With the goal of increasing the precision of efficacy endpoints estimation, an additional analysis set (100mg QD pooled group), that was not pre-specified in the Statistical Analysis Plan (SAP), comprised all 215 previously treated patients with purported ALK-positive NSCLC who received the RP2D of lorlatinib 100 mg QD as a starting dose in the study (Phase 2, n=198).

The **safety analysis set** included all enrolled patients treated with at least 1 dose of lorlatinib (including the Day -7 lorlatinib dose).

PRO-evaluable analysis set is defined as all patients in the safety analysis set who completed a baseline and at least 1 post-baseline PRO assessment. The PRO-evaluable analysis set is the primary population for the analysis of change from baseline for PRO assessments (EORTC QLQ-C30 and QLQ-LC13).

The following **biomarker analysis sets** were defined:

a) CNA Peripheral Blood Analysis Set: defined as all patients of the ITT analysis set who had at least 1 molecular biomarker (analyte mutation) assayed,

b) Paired CNA Peripheral Blood Set: defined as all patients in the ITT analysis set who had valid paired results from at least 1 molecular biomarker (analyte mutation) assayed at Screening and post-treatment (i.e., EOT for Phase 2),

c) Tumour Tissue Analysis Set: defined as all patients in the ITT analysis set who had at least 1 molecular tumour biomarker assayed from either the screening archival or screening de novo tumour biopsy sample (or both),

d) Paired Tumour De Novo Analysis Set: defined as all patients in the ITT analysis set who had both 1) either archival tumour tissue or de novo biopsy at Screening, and 2) an EOT de novo biopsy with at least 1 molecular tumour biomarker assayed.

Statistical and Analytical Plans

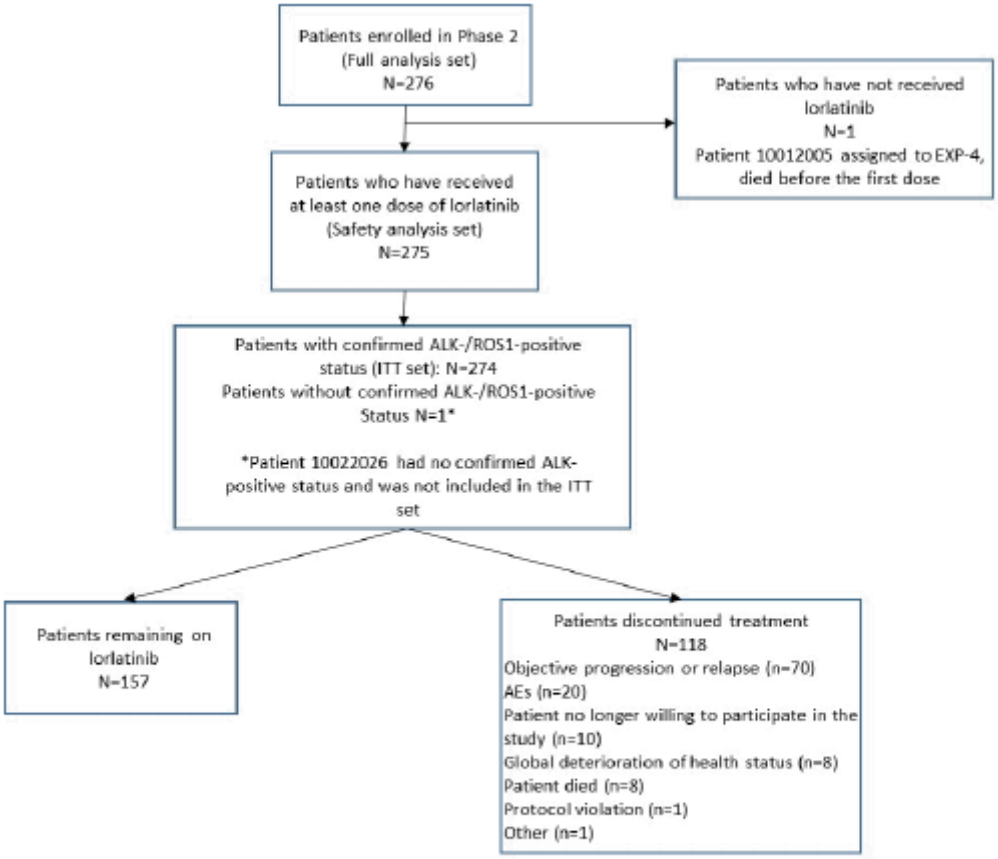
Table 28: Summary of Endpoints and Statistical Methodology – Study 1001

Endpoint	Statistical Method
ORR[a]	Percentage (2-sided 95% CI*)
IC ORR[a]	Percentage (2-sided 95% CI*)
TTR[a], IC TTR	Descriptive statistics; n (%)
DOR[a], IC DOR	K-M method (median and 2-sided 95% CI)*** Descriptive statistics; n (%)
PFS[a], OS	K-M method (median and 2-sided 95% CI)***
Probabilities of being event free/survival at 1 year and 18 months	K-M method (2-sided 95% CI**)
PROs	Descriptive statistics for absolute scores and change from baseline of the EORTC QLQ-C30 and QLQ-LC13 multiple-item and single-item scale scores
Biomarker related endpoints	Outlined in Study 1001 SAP Section 6.3.4

Source: Study 1001 Statistical Analysis Plan Version 5.
*Using exact method based on binomial distribution.
**Using the normal approximation to the log-transformed cumulative hazard function.
*** Confidence intervals for the median and quartiles using the method of Brookmeyer and Crowley.
a. Based on ICR and Investigator assessment.
Abbreviations: CI=confidence interval; CNS=central nervous system; DOR=duration of response; K-M=Kaplan-Meier; IC=intracranial; ICR=Independent Central Review; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QLQ-LC13=Quality of Life Questionnaire Lung Cancer 13; SAP=Statistical Analysis Plan; TTR=time to tumour response.

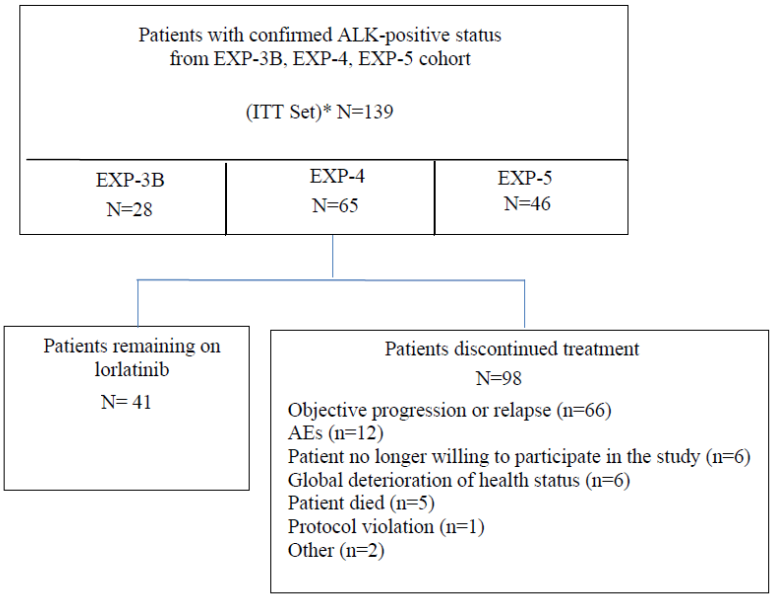
Results

Participant flow



Source: Tables 14.1.1.1.2, 14.1.1.2.2 and 14.1.1.3.2.
Abbreviations: AE=adverse event; ALK-positive=anaplastic lymphoma kinase-positive; ITT=intention to treat; N/n=number of patients.

Figure 15: Study Flow Chart (Phase 2)



* ITT set = Includes Patient 10022026 for whom confirmed ALK-positive status became available after 15 March 2017
Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; ITT=intention to treat; N/n=number of subjects.

Figure 16: Study Flow Chart for EXP3B:EXP5, data cutoff date 2 February 2018 (Phase 2)

Recruitment

The Phase 2 study was conducted at 47 centres in 14 countries, including Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Singapore, Spain, Switzerland, Taiwan, and United States (US).

Conduct of the study

The protocol of study 1001 was amended in consideration of safety aspects, selection of RP2D and for sample size adjustment in due course.

Protocol deviations

Table 29: Important protocol deviations in Phase 2 (Full analysis set)

Protocol Deviation Category	Protocol Deviation Subcategory	Total (N=276) n (%)
Inclusion criteria	No archival tissue available or no de novo biopsy performed	8 (2.9)
	ALK/ROS1 status not confirmed	1 (0.4)
	ALK/ROS1 testing method not per protocol	14 (5.1)
	Did not meet all other inclusion criteria	31 (11.2)
Concomitant treatment	Anti-cancer therapy administered prior to documented PD	1 (0.4)
Safety reporting	SAE delayed or not reported to sponsor	12 (4.3)
Informed consent	Required informed consent not obtained on time	6 (2.2)
Other	Special safety concern letter not relayed to patient in a timely manner	2 (0.7)

Source: Table 14.1.1.4.2.
Abbreviations: ALK =anaplastic lymphoma kinase; N/n=number of patients; SAE=serious adverse event

Baseline data

Table 30: Demographic characteristics (Phase 2) – safety analysis set

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=60)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=275)
Gender, n (%)							
Female	13	17	38	37	25	27	157
Male	17	10	22	28	21	20	118
Age (years), n (%)							
<18	0	0	0	0	0	0	0
18 - 44	4 (13.3)	5 (18.5)	14 (23.3)	19 (29.2)	13 (28.3)	12 (25.5)	67 (24.4)
45 - 64	18 (60.0)	13 (48.1)	34 (56.7)	37 (56.9)	26 (56.5)	27 (57.4)	155 (56.4)
≥65	8 (26.7)	9 (33.3)	12 (20.0)	9 (13.8)	7 (15.2)	8 (17.0)	53 (19.3)
Mean	57.4	57.1	54.0	52.2	51.5	52.8	53.6
SD	12.1	12.7	11.9	11.8	11.2	12.9	12.1
Range	27-75	35-85	30-77	29-83	32-78	19-77	19-85
Race, n (%)							
White	10 (33.3)	13 (48.1)	25 (41.7)	32 (49.2)	27 (58.7)	25 (53.2)	132 (48.0)
Black	1 (3.3)	0	1 (1.7)	0	0	1 (2.1)	3 (1.1)
Asian	17 (56.7)	10 (37.0)	23 (38.3)	23 (35.4)	14 (30.4)	16 (34.0)	103 (37.5)
Other	1 (3.3)	2 (7.4)	1 (1.7)	3 (4.6)	2 (4.3)	3 (6.4)	12 (4.4)
Unspecified	1 (3.3)	2 (7.4)	10 (16.7)	7 (10.8)	3 (6.5)	2 (4.3)	25 (9.1)
Weight (kg)							
Mean	68.1	69.7	66.3	66.4	69.0	68.8	67.7
SD	20.4	18.5	16.7	15.5	15.7	18.4	17.1
Range	41.6-102.6	43.7-121.6	43.3-116.0	32.6-106.1	44.9-126.7	38.0-133.0	32.6-133.0
BMI (kg/m^2)							
Mean	24.7	25.6	24.1	23.9	24.3	24.6	24.4
SD	5.6	5.0	5.0	4.5	4.0	4.4	4.7
Range	16.9-38.5	19.4-38.8	16.8-45.2	16.0-40.2	17.7-37.9	13.5-36.6	13.5-45.2

Source: Table 14.1.2.1.2

Abbreviation: BMI=body mass index; N/n=number of patients; SD=standard deviation.

Table 31: Baseline disease characteristics (Phase 2) – safety analysis set

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=60)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=275)
Involved disease site							
Bone	12 (40.0)	7 (25.9)	27 (45.0)	31 (47.7)	19 (41.3)	18 (38.3)	114 (41.5)
Brain	6 (20.0)	17 (63.0)	32 (53.3)	42 (64.6)	32 (69.6)	23 (48.9)	152 (55.3)
Liver	5 (16.7)	7 (25.9)	12 (20.0)	17 (26.2)	15 (32.6)	11 (23.4)	67 (24.4)
Lung	29 (96.7)	25 (92.6)	48 (80.0)	56 (86.2)	41 (89.1)	41 (87.2)	240 (87.3)
Lymph node	25 (83.3)	12 (44.4)	26 (43.3)	28 (43.1)	21 (45.7)	28 (59.6)	140 (50.9)
Other	7 (23.3)	9 (33.3)	22 (36.7)	22 (33.8)	16 (34.8)	14 (29.8)	90 (32.7)
Number of involved disease sitesa							
1	4 (13.3)	2 (7.4)	4 (6.7)	4 (6.2)	5 (10.9)	4 (8.5)	23 (8.4)
2	7 (23.3)	9 (33.3)	22 (36.7)	16 (24.6)	7 (15.2)	17 (36.2)	78 (28.4)
3	11 (36.7)	7 (25.9)	15 (25.0)	23 (35.4)	16 (34.8)	9 (19.1)	81 (29.5)
4	5 (16.7)	6 (22.2)	14 (23.3)	12 (18.5)	11 (23.9)	9 (19.1)	57 (20.7)
>4	3 (10.0)	3 (11.1)	5 (8.3)	10 (15.4)	7 (15.2)	8 (17.0)	36 (13.1)

Source: Table 14.1.2.5.1.2.2.

Abbreviations:EXP=expansion; N=number of patients.

Involved disease sites (per investigator assessment) included both target and non-target lesions. Disease sites with multiple lesions were counted once. Each 'Other' disease site was counted as separate disease site.

Numbers analysed

Table 32: Data Sets Analysed (Phase 2)

Number (%) of Patients	EXP-1	EXP-2	EXP-3	EXP-4	EXP-5	EXP-6	Total
Full analysis set	30	27	60	66	46	47	276
Analyzed for safety							
Safety analysis set	30 (100)	27 (100)	60 (100)	65 (100)	46 (100)	47 (100)	275 (100)
Analyzed for efficacy							
ITT	30 (100)	27 (100)	59 (98.3)	65 (100)	46 (100)	47 (100)	274 (99.6)
ITT (a)[a]	6 (20.0)	17 (63.0)	32 (53.3)	42 (64.6)	32 (69.6)	23 (48.9)	152 (55.3)
ITT (b)[b]	8 (26.7)	17 (63.0)	32 (53.3)	45 (69.2)	38 (82.6)	25 (53.2)	165 (60.0)

Source: Table 14.1.1.1.2.
Abbreviations: CNS=central nervous system; EXP=expansion; ITT=intention-to-treat.
a. ITT (a): Patients with CNS metastases in ITT by Investigator assessment.
b. ITT (b): Patients with CNS metastases in ITT by Independent Central Review.

Outcomes and estimation

Primary endpoint- ORR and Intra-cranial-ORR – UPDATED

- ORR

In Phase 2, the primary endpoint was ORR based on ICR assessment in the ITT population.

Table 33: Summary of Best Overall Response Based on Independent Central Review (Phase 2) – ITT Population, in EXP-1:EXP-6.

	EXP-1 (N=30) n (%)	EXP-2 (N=27) n (%)	EXP-3A (N=32) n (%)	EXP-3B (N=27) n (%)	EXP-4 (N=65) n (%)	EXP-5 (N=46) n (%)	EXP-6 (N=47) n (%)	Total (N=274) n (%)
Complete response [CR]	1 (3.3)	1 (3.7)	0	1 (3.7)	2 (3.1)	0	2 (4.3)	7 (2.6)
Partial response [PR]	26 (86.7)	19 (70.4)	21 (65.6)	8 (29.6)	25 (38.5)	16 (34.8)	15 (31.9)	130 (47.4)
Stable disease[a]	2 (6.7)	4 (14.8)	6 (18.8)	10 (37.0)	22 (33.8)	16 (34.8)	22 (46.8)	82 (29.9)
Objective progression	1 (3.3)	3 (11.1)	3 (9.4)	6 (22.2)	10 (15.4)	10 (21.7)	2 (4.3)	35 (12.8)
Indeterminate	0	0	2 (6.3)	2 (7.4)	6 (9.2)	4 (8.7)	6 (12.8)	20 (7.3)
Objective response rate: [CR + PR]	27 (90.0)	20 (74.1)	21 (65.6)	9 (33.3)	27 (41.5)	16 (34.8)	17 (36.2)	137 (50.0)
95% exact CI[b]	73.5, 97.9	53.7, 88.9	46.8, 81.4	16.5, 54.0	29.4, 54.4	21.4, 50.2	22.7, 51.5	43.9, 56.1

Source: Tables 14.2.2.1.1.1.1.2.1 and 14.2.2.1.2.1.1.2.1.
Stable disease at day <42 were rated as indeterminate.
Abbreviations: BOR=best overall response; CI = confidence interval; CR=complete response; EXP=expansion; ITT = intention-to-treat; N/n = number of patients; PD=progressive disease; PR=partial response.
a. For a patient to be called having a BOR of SD, he/she must have maintained the status of SD for at least 6 weeks after treatment start. Patients with only non-measurable disease at baseline and a BOR of non-CR/non-PD were counted as patients with SD.
b. Using exact method based on binomial distribution.

Table 34: Best overall response based on ICR in patients with ALK-positive NSCLC – ITT population in EXP cohorts (Phase 2) Data cutoff date: 15 March 2017

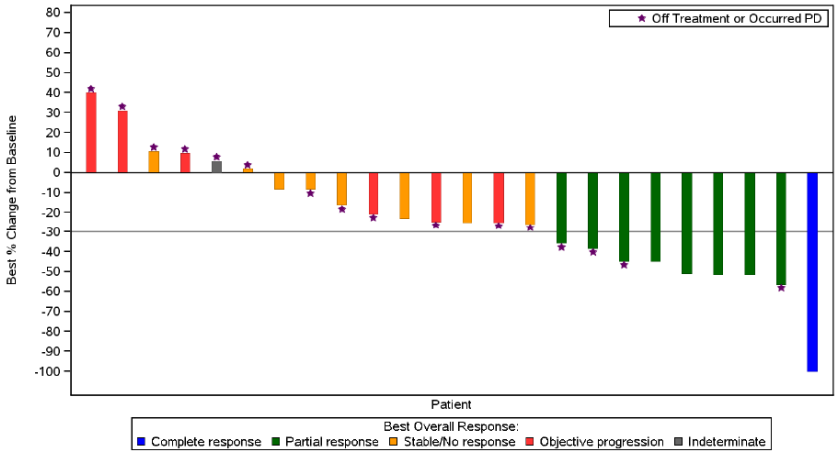
Variable	EXP-3B (N=27)	EXP-4:EXP-5 (N=111)	EXP-2:EXP-3A (N=59)
Objective response rate [CR + PR], n (%)	9 (33.3)	43 (38.7)	41 (69.5)
95% exact CIa	(16.5, 54.0)	(29.6, 48.5)	(56.1, 80.8)
Best overall response, n (%)			
Complete response (CR)	1 (3.7)	2 (1.8)	1 (1.7)
Partial response (PR)	8 (29.6)	41 (36.9)	40 (67.8)
Stable/no response	10 (37.0)	38 (34.2)	10 (16.9)
Objective progression	6 (22.2)	20 (18.0)	6 (10.2)

Indeterminate	2 (7.4)	10 (9.0)	2 (3.4)

Source: Study 1001 CSR Table 14.2.2.1.2.1.1.2.1.
Stable disease at Day <42 were rated as indeterminate EXP 2: patients relapsing after only crizotinib therapy.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; EXP=expansion; ICR=independent central review; ITT=intention-to-treat; N/n=number of patients; NSCLC=non-small cell lung cancer; PR=partial response.
a. Using exact method based on binomial distribution.

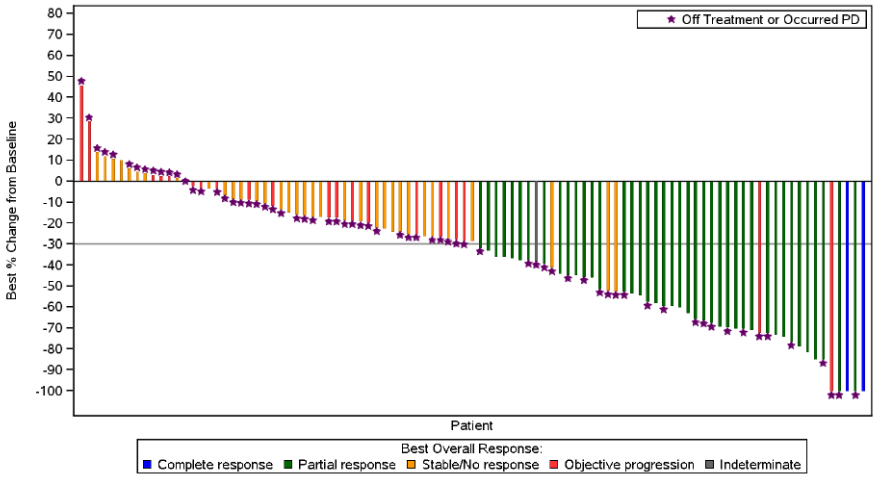
Table 35: Best overall response based on ICR assessment in patients with ALK-positive NSCLC-ITT population in EXP cohorts (Phase 2) – Data cutoff date: 02 February 2018

Data cutoff: 02 Feb 2018	EXP-3B (N=28)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-4:EXP-5 (N=111)	EXP-3B:EXP-5 (N=139)
ORR [CR+PR]	**12 (42.9)**	**27 (41.5)**	**17 (37.0)**	**44 (39.6)**	**56 (40.3)**
95% exact CI[a]	(24.5, 62.8)	(29.4, 54.4)	(23.2, 52.5)	(30.5, 49.4)	(32.1, 48.9)
Best overall response					
CR	1 (3.6)	2 (3.1)	0	2 (1.8)	3 (2.2)
PR	11 (39.3)	25 (38.5)	17 (37.0)	42 (37.8)	53 (38.1)
Stable/no response	8 (28.6)	22 (33.8)	15 (32.6)	37 (33.3)	45 (32.4)
Objective progression	6 (21.4)	10 (15.4)	10 (21.7)	20 (18.0)	26 (18.7)
Indeterminate	2 (7.1)	6 (9.2)	4 (8.7)	10 (9.0)	12 (8.6)



Source: Study 1001 CSR Figure 14.2.2.1.2.1.2.2.2.

Figure 17: Waterfall plot of best percentage change in tumour size based on ICR in patients with ALK-positive NSCLC – ITT population in Cohort EXP-3B (Phase 2)



Source: Study 1001 CSR Figure 14.2.2.1.2.1.2.2.2.

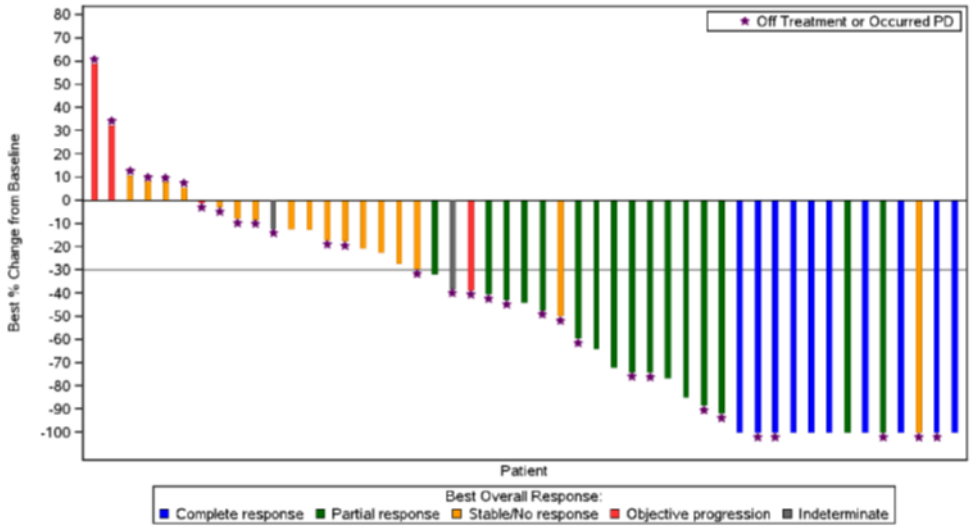
Figure 18: Waterfall plot of best percentage change in tumour size based on ICR in patients with ALK-positive NSCLC – ITT population in pooled Cohort EXP-4:EXP-5 (Phase 2)

- IC-ORR

Table 36: Best overall intracranial response based on ICR by ALK-positive NSCLC and brain metastases – ITT population in EXP cohorts (Phase 2)

Variable	EXP-3B (N=12)	EXP-4:EXP-5 (N=83)	EXP-2:EXP-3A (N=37)
Objective response rate (CR + PR)	5 (41.7)	40 (48.2)	25 (67.6)
95% exact CIa	(15.2, 72.3)	(37.1, 59.4)	(50.2, 82.0)
Best Overall Response			
Complete response (CR)	1 (8.3)	24 (28.9)	10 (27.0)
Partial response (PR)	4 (33.3)	16 (19.3)	15 (40.5)
Stable/no response	3 (25.0)	28 (33.7)	9 (24.3)
Objective progression	3 (25.0)	6 (7.2)	2 (5.4)
Indeterminate	1 (8.3)	9 (10.8)	1 (2.7)

Source: Study 1001 CSR Table 14.2.2.1.2.2.1.2.1.
Stable disease at Day <42 were rated as indeterminate.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; CSR=clinical study report; EXP=Expansion; ITT=intention-to-treat; N=number of patients; NSCLC=non-small cell lung cancer; PR=partial response.
a. Using exact method based on binomial distribution.



Source: Study 1001 CSR Figure 14.2.2.1.2.2.2.2.2.

Figure 19: Waterfall plot of best percentage change from baseline in intracranial tumour size based on ICR assessment – ITT population in patients with brain metastases in pooled Cohort EXP-4:EXP-5 (Phase 2)

Table 37: Best overall intracranial response based on ICR assessment in patients with ALK-positive NSCLC and brain metastases with at least 1 measurable lesion – ITT population in EXP cohorts (Phase 2)

Data cutoff: 02 Feb 2018	EXP-3B (N=9)	EXP-4 (N=24)	EXP-5 (N=24)	EXP-4:EXP-5 (N=48)	EXP-3B:EXP-5 (N=57)
ORR (CR + PR) n (%)	6 (66.7)	14 (58.3)	11 (45.8)	25 (52.1)	31 (54.4)
95% exact CI[a]	(29.9, 92.5)	(36.6, 77.9)	(25.6, 67.2)	(37.2, 66.7)	(40.7, 67.6)
Best Overall Response n (%)					
CR	2 (22.2)	6 (25.0)	4 (16.7)	10 (20.8)	12 (21.1)
PR	4 (44.4)	8 (33.3)	7 (29.2)	15 (31.3)	19 (33.3)
Stable/no response	0	8 (33.3)	9 (37.5)	17 (35.4)	17 (29.8)
Objective progression	2 (22.2)	2 (8.3)	2 (8.3)	4 (8.3)	6 (10.5)
Indeterminate	1 (11.1)	0	2 (8.3)	2 (4.2)	3 (5.3)
Data cutoff: 15 Mar 2017	**EXP-3B (N=9)**	**EXP-4 (N=25)**	**EXP-5 (N=24)**	**EXP-4:EXP-5 (N=49)**	**EXP-3B:EXP-5[b]**
ORR (CR + PR) n (%)	5 (55.6)	16 (64.0)	10 (41.7)	26 (53.1)	-
95% exact CI[a]	(21.2, 86.3)	(42.5, 82.0)	(22.1, 63.4)	(38.3, 67.5)	-
Best Overall Response n (%)					
CR	1 (11.1)	6 (24.0)	4 (16.7)	10 (20.4)	-
PR	4 (44.4)	10 (40.0)	6 (25.0)	16 (32.7)	-
Stable/no response	0	7 (28.0)	10 (41.7)	17 (34.7)	-
Objective progression	3 (33.3)	2 (8.0)	2 (8.3)	4 (8.2)	-
Indeterminate	1 (11.1)	0	2 (8.3)	2 (4.1)	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.1.2.3.1.2.1.ema
15 Mar 2017: Module 5.3.5.3 D120 Supporting Table 14.2.2.1.1.2.1.2.1.t; Table 14.2.2.1.2.2.1.2.1.t.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; EXP=expansion; ICR=Independent Central Review; ITT=intention-to-treat; N/n=number of patients; NSCLC=non-small cell lung cancer; ORR=objective response rate; PR=partial response; SCE=Summary of Clinical Efficacy.

a. Using exact method based on binomial distribution.
b. Data (15 March 2017 data cutoff) were not provided before.

ORR by investigator

Table 38: Summary of best overall response based on derived investigator assessment (Phase 2) – ITT population by EXP-1:EXP-6 – Data cutoff date: 15 March 2017

	EXP-1 (N=30)		EXP-2 (N=27)		EXP-3 (N=59)		EXP-4 (N=65)		EXP-5 (N=46)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Complete response	1	(3.3)	0		0		1	(1.5)	0	
Partial response	23	(76.7)	19	(70.4)	29	(49.2)	19	(29.2)	16	(34.8)
Stable/No response	5	(16.7)	8	(29.6)	21	(35.6)	32	(49.2)	16	(34.8)
Objective progression	0		0		6	(10.2)	7	(10.8)	9	(19.6)
Indeterminate	1	(3.3)	0		3	(5.1)	6	(9.2)	5	(10.9)
Objective Response Rate (CR+PR)	24	(80.0)	19	(70.4)	29	(49.2)	20	(30.8)	16	(34.8)
95% Exact CI [1]	[61.4, 92.3]		[49.8, 86.2]		[35.9, 62.5]		[19.9, 43.4]		[21.4, 50.2]	

[1] Using exact method based on binomial distribution
Unconfirmed CR/PR are downgraded to SD, SD at day < 42 are rated as Indeterminate.
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.4.2.1.1 Date of Reporting Dataset Creation: 10MAY2017 Date of Table Generation: 29JUN2017 (03:53)

Concordance rates

The summary of response disagreement in ORR and in the different cohorts is reported below:

Table 39: Summary of Response Disagreement Rate (Phase 2) – ITT Population based on either Derived Investigator Assessment or Independent Central Review, by EXP-1:EXP-6

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=59)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=274)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Response Disagreement Rate (c+d)/N	3 (10.0)	3 (11.1)	11 (18.6)	15 (23.1)	6 (13.0)	7 (14.9)	45 (16.4)

n = c+d is the number of disagreement cases.
c: Derived Investigator Assessment indicates response; Independent Central Review assessment indicates no response or no scan available.
d: Independent Central Review assessment indicates response; Derived Investigator Assessment indicates no response or no scan available.
Unconfirmed CR/PR are downgraded to SD, SD at day < 42 are rated as Indeterminate.
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.6.3.1.2 Date of Reporting Dataset Creation: 10MAY2017 Date of Table Generation: 29JUN2017 (04:27)

Table 40: Summary of Intra-Cranial Response Disagreement Rate (Phase 2) – ITT Population in Patients with CNS Metastases based on either Derived Investigator Assessment or Independent Central Review, by EXP-1:EXP-6

	EXP-1 (N=8)	EXP-2 (N=17)	EXP-3 (N=33)	EXP-4 (N=45)	EXP-5 (N=40)	EXP-6 (N=26)	Total (N=169)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Response Disagreement Rate (c+d)/N	3 (37.5)	3 (17.6)	9 (27.3)	13 (28.9)	10 (25.0)	12 (46.2)	50 (29.6)

n = c+d is the number of disagreement cases.
c: Derived Investigator Assessment indicates response; Independent Central Review assessment indicates no response or no scan available.
d: Independent Central Review assessment indicates response; Derived Investigator Assessment indicates no response or no scan available.
Unconfirmed CR/PR are downgraded to SD, SD at day < 42 are rated as Indeterminate.
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.6.3.2.2 Date of Reporting Dataset Creation: 23MAY2017 Date of Table Generation: 29JUN2017 (10:26)

The ORR by IRC in the Phase 2 part was 42.9% (95%CI: 24.5-62.8) in EXP-3B and 39.6% (95%CI: 30.5-49.4) in EXP-4:EXP-5, although the CI's are wide. In addition, approximately a third of the patients in both cohorts had stable disease.

A summary of the best IC-ORR across the different cohorts are reported below:

Table 41: Summary of Best Intra-Cranial Overall Response Based on ICR (Phase 2) – ITT Population in Patients with CNS Metastases, in EXP-1: EXP-6

	EXP-1 (N=8)	EXP-2 (N=17)	EXP-3A (N=20)	EXP-3B (N=12)	EXP-4 (N=45)	EXP-5 (N=38)	EXP-6 (N=25)	Total (N=165)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Complete response [CR]	4 (50.0)	6 (35.3)	4 (20.0)	1 (8.3)	15 (33.3)	9 (23.7)	9 (36.0)	48 (29.1)
Partial response [PR]	2 (25.0)	4 (23.5)	11 (55.0)	4 (33.3)	10 (22.2)	6 (15.8)	5 (20.0)	42 (25.5)
Stable disease[a]	2 (25.0)	6 (35.3)	3 (15.0)	3 (25.0)	13 (28.9)	15 (39.5)	7 (28.0)	49 (29.7)
Objective progression	0	1 (5.9)	1 (5.0)	3 (25.0)	4 (8.9)	2 (5.3)	0	11 (6.7)
Indeterminate	0	0	1 (5.0)	1 (8.3)	3 (6.7)	6 (15.8)	4 (16.0)	15 (9.1)
Objective response rate: [CR + PR]	6 (75.0)	10 (58.8)	15 (75.0)	5 (41.7)	25 (55.6)	15 (39.5)	14 (56.0)	90 (54.5)
95% exact CI[b]	34.9, 96.8	32.9, 81.6	50.9, 91.3	15.2, 72.3	40.0, 70.4	24.0, 56.6	34.9, 75.6	46.6, 62.3

Source: Tables 14.2.2.1.1.2.1.2.1 and 14.2.2.1.2.2.1.2.1.
Stable disease at day <42 were rated as indeterminate.
Abbreviations:BOR=best overall response; CI = confidence interval; CNS=cerebrospinal;CR=complete response; EXP=expansion; ITT = intention-to-treat; N/n= number of patients; PD=progressive disease; SD=stable disease.
a. Patients with only non-measurable CNS metastasis at baseline and an intracranial BOR of non-CR/non-PD were counted as patients with SD.
b. Using exact method based on binomial distribution.

Secondary endpoints

Time to tumour response (TTR):

Table 42: Time to tumour response in EXP cohorts – ITT population (Phase 2)

Data cutoff: 02 Feb 2018	**EXP-3B**	**EXP-4**	**EXP-5**	**EXP-4:EXP-5**	**EXP-3B:EXP-5**
Overall Response, N	12	27	17	44	56
Median TTR, months (range)	1.4 (1.2-16.6)	2.6 (1.2-16.4)	1.4 (1.2-9.3)	1.4 (1.2-16.4)	1.4 (1.2-16.6)
IC response,[a] N	6	14	11	25	31
Median IC TTR[a], months (range)	1.4 (1.2-3.0)	1.5 (1.2-16.2)	1.4 (1.2-10.6)	1.4 (1.2-16.2)	1.4 (1.2-16.2)
Data cutoff: 15 Mar 2017	**EXP-3B**	**EXP-4**	**EXP-5**	**EXP-4:EXP-5**	**EXP-3B:EXP-5[b]**
Overall Response, N	9	27	16	43	
Median TTR, months (range)	1.4 (1.3-3.0)	2.6 (1.2-9.9)	1.4 (1.2-4.0)	1.4 (1.2-9.9)	-
IC response, [a] N	5	16	10	26	-
Median IC TTR[a], months (range)	1.4 (1.3-3.0)	1.5 (1.2-6.2)	1.4 (1.2-3.3)	1.4 (1.2-6.2)	-

Source: **02 Feb 2018**: Module 5.3.5.3 D120 Supporting Table mo.171.2; Module 5.3.5.3 D120 Supporting Tables ema.233.feb.7; ema.233.feb.7.1.
15 Mar 2017: Module 5.3.5.2 Study 1001 CSR Supporting Tables 14.2.2.3.1.1.3.2.1; 14.2.2.3.2.1.3.2.1; Module 5.3.5.3 D120 Supporting Tables 14.2.2.3.2.2.3.2.1.t; 14.2.2.3.1.2.3.2.1.t.
Abbreviations: CSR=clinical study report; EXP=expansion; IC=intracranial; ITT=intention-to-treat; N=number of patients; TTR=time to tumor response.
a. In patients with at least 1 measurable CNS lesion.
b. Data (15 March data cutoff) were not provided before.

Disease Control Rate:

The overall DCRs at 12 and 24 weeks in cohorts EXP-1:EXP-6 based on ICR assessment in the ITT population are summarised in the table below:

Table 43: Summary of Disease Control Rate Based on ICR (Phase 2) - ITT Population, by EXP-1:EXP-6

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=59)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=274)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Disease Control Rate at 12 Weeks	28 (93.3)	23 (85.2)	40 (67.8)	41 (63.1)	24 (52.2)	30 (63.8)	186 (67.9)
95% Exact CI [1]	[77.9, 99.2]	[66.3, 95.8]	[54.4, 79.4]	[50.2, 74.7]	[36.9, 67.1]	[48.5, 77.3]	[62.0, 73.4]
Disease Control Rate at 24 Weeks	23 (76.7)	17 (63.0)	30 (50.8)	27 (41.5)	16 (34.8)	21 (44.7)	134 (48.9)
95% Exact CI [1]	[57.7, 90.1]	[42.4, 80.6]	[37.5, 64.1]	[29.4, 54.4]	[21.4, 50.2]	[30.2, 59.9]	[42.8, 55.0]

[1] Using exact method based on binomial distribution
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.4.2.1.2 Date of Reporting Dataset Creation: 23MAY2017 Date of Table Generation: 29JUN2017 (02:40)

The intracranial DCRs at 12 and 24 weeks in cohorts EXP-1:EXP-6 based on ICR assessment in the ITT population are summarised in the table below:

Table 44: Summary of Intra-Cranial Disease Control Rate Based on ICR (Phase 2) - ITT Population in Patients with CNS Metastases, by EXP-1:EXP-6

	EXP-1 (N=8)	EXP-2 (N=17)	EXP-3 (N=32)	EXP-4 (N=45)	EXP-5 (N=38)	EXP-6 (N=25)	Total (N=165)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Disease Control Rate at 12 Weeks	7 (87.5)	16 (94.1)	24 (75.0)	35 (77.8)	26 (68.4)	18 (72.0)	126 (76.4)
95% Exact CI [1]	[47.3, 99.7]	[71.3, 99.9]	[56.6, 88.5]	[62.9, 88.8]	[51.3, 82.5]	[50.6, 87.9]	[69.1, 82.6]
Disease Control Rate at 24 Weeks	6 (75.0)	12 (70.6)	19 (59.4)	28 (62.2)	19 (50.0)	13 (52.0)	97 (58.8)
95% Exact CI [1]	[34.9, 96.8]	[44.0, 89.7]	[40.6, 76.3]	[46.5, 76.2]	[33.4, 66.6]	[31.3, 72.2]	[50.9, 66.4]

[1] Using exact method based on binomial distribution
PFIZER CONFIDENTIAL Source Data: Table 16.2.6.4.2.2.2 Date of Reporting Dataset Creation: 23MAY2017 Date of Table Generation: 29JUN2017 (03:32)

Duration of response

Table 45: ICR-assessed duration of response (objective responders only) – ITT population in EXP cohorts (Phase 2)

Data cutoff: 15 Mar 2017	EXP-3B (N=27)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-4:EXP-5 (N=111)	EXP-3B:EXP-5[b]
Patients with confirmed objective response (CR or PR), n	9	27	16	43	-
Median DOR (in months)	NR	6.9	NR	NR	-
95% CI[a]	(4.1, NR)	(5.2, NR)	(4.2, NR)	(5.5, NR)	-
N (%) of patients with events (PD or death) among the responders, n (%)	4 (44.4)	11 (40.7)	6 (37.5)	17 (39.5)	-
<3 months	0	4 (14.8)	4 (25.0)	8 (18.6)	-
3 to <6 months	4 (44.4)	5 (18.5)	1 (6.3)	6 (14.0)	-
6 to <9 months	0	2 (7.4)	1 (6.3)	3 (7.0)	-
9 to <12 months	0	0	0	0	-
12 <15 months	0	0	0	0	-
18 <21 months	0	0	0	0	-
21 <24 months	0	0	0	0	-
≥24 months	0	0	0	0	-
Number (%) of patients censored among the responders	5 (55.6)	16 (59.3)	10 (62.5)	26 (60.5)	-
<3 months	0	5 (18.5)	0	5 (11.6)	-
3 to <6 months	2 (22.2)	0	4 (25.0)	4 (9.3)	-
6 to <9 months	2 (22.2)	5 (18.5)	5 (31.3)	10 (23.3)	-
9 to <12 months	0	5 (18.5)	0	5 (11.6)	-
12 to <15 months	1 (11.1)	1 (3.7)	1 (6.3)	2 (4.7)	-
15 to <18 months	0	0	0	0	-
18 <21 months	0	0	0	0	-
21 <24 months	0	0	0	0	-
≥24 months	0	0	0	0	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.8.2.1.3.2.1.ema; Table 14.2.2.7.2.1.3.2.1.ema
15 Mar 2017: Module 2.7.3 SCE Table 12; Module 5.3.5.2 Study 1001 CSR Table 35; Study 1001 CSR Supporting Table 14.2.2.7.1.1.3.2.1; Supporting Table 14.2.2.7.2.1.3.2.1.
Abbreviations: CSR=clinical study report; CI=confidence interval; CR=complete response; DOR=duration of response; EXP=expansion cohort; ICR=Independent Central Review; ITT=intention-to-treat; N/n=number of patients; NR=not reached, PR=partial response; PD=progressive disease; SCE=Summary of Clinical Efficacy.
a. Using Brookmeyer Crowley method.
b. Data (15 March 2017 data cutoff) were not provided before.

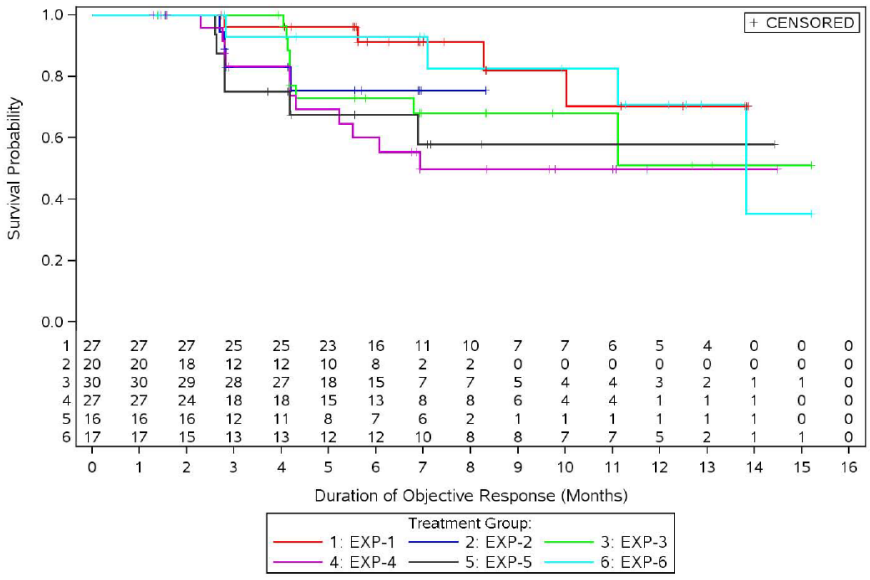


Figure 20: Kaplan-Meier Plot of Duration of Objective Response Based on ICR (Phase 2) - in Patients with a Confirmed Response, by EXP-1:EXP-6

Table 46: Duration of Intracranial response (objective responders with a confirmed response only) based on ICR assessment in patients with at least 1 measurable CNS lesion – ITT population in EXP cohorts (Phase 2)

Data cutoff: 02 Feb 2018	EXP-3B (N=9)	EXP-4 (N=24)	EXP-5 (N=24)	EXP-4:EXP-5 (N=48)	EXP-3B:EXP-5 (N=57)
Patients with confirmed objective response (CR or PR), n	6	14	11	25	31
Median DOR (in months)	NR	11.1	12.4	12.4	12.4
95% CI[a]	(4.1, NR)	(5.8, NR)	(5.6, NR)	(6.0, NR)	(5.8, NR)
N (%) of patients with events (PD or death) among the responders	3 (50.0)	7 (50.0)	7 (63.6)	14 (56.0)	17 (54.8)
<3 months	0	2 (14.3)	1 (9.1)	3 (12.0)	3 (9.7)
3 to <6 months	3 (50.0)	2 (14.3)	2 (18.2)	4 (16.0)	7 (22.6)
6 to <9 months	0	1 (7.1)	2 (18.2)	3 (12.0)	3 (9.7)
9 to <12 months	0	1 (7.1)	0	1 (4.0)	1 (3.2)
12 to <15 months	0	1 (7.1)	2 (18.2)	3 (12.0)	3 (9.7)
N (%) of patients censored among the responders	3 (50.0)	7 (50.0)	4 (36.4)	11 (44.0)	14 (45.2)
<3 months	0	1 (7.1)	0	1 (4.0)	1 (3.2)
3 to <6 months	0	0	0	0	0
6 to <9 months	0	1 (7.1)	1 (9.1)	2 (8.0)	2 (6.5)
9 to <12 months	1 (16.7)	2 (14.3)	1 (9.1)	3 (12.0)	4 (12.9)
12 to <15 months	1 (16.7)	1 (7.1)	0	1 (4.0)	2 (6.5)
15 to <18 months	0	2 (14.3)	0	2 (8.0)	2 (6.5)
18 to <21 months	0	0	1 (9.1)	1 (4.0)	1 (3.2)
21 to <24 months	1 (16.7)	0	0	0	1 (3.2)
≥24 months	0	0	1 (9.1)	1 (4.0)	1 (3.2)
Data cutoff: 15 Mar 2017	**EXP-3B (N=9)**	**EXP-4 (N=25)**	**EXP-5 (N=24)**	**EXP-4:EXP-5 (N=49)**	**EXP-3B:EXP-5[b]**
Patients with confirmed objective response (CR or PR), n	5	16	10	26	-
Median DOR (in months)	NR (4.1, NR)	14.5	NR	14.5 (6.9, 14.5)	-
95% CI[a]	-	(6.0, 14.5)	(6.9, NR)	-	-
N (%) of patients with events (PD or death) among the responders	2 (40.0)	5 (31.3)	4 (40.0)	9 (34.6)	-
<3 months	0	2 (12.5)	1 (10.0)	3 (11.5)	-
3 to <6 months	2 (40.0)	1 (6.3)	1 (10.0)	2 (7.7)	-
6 to <9 months	0	1 (6.3)	2 (20.0)	3 (11.5)	-
9 to <12 months	0	0	0	0	-
12 to <15 months	0	1 (6.3)	0	1 (3.8)	-
N (%) of patients censored among the responders	3 (60.0)	11 (68.8)	6 (60.0)	17 (65.4)	
<3 months	0	2 (12.5)	0	2 (7.7)	-
3 to <6 months	2 (40.0)	2 (12.5)	1 (10.0)	3 (11.5)	-
6 to <9 months	0	4 (25.0)	4 (40.0)	8 (30.8)	-
9 to <12 months	0	2 (12.5)	0	2 (7.7)	-
12 to <15 months	1 (20.0)	1 (6.3)	1 (10.0)	2 (7.7)	-
15 to <18 months	0	0	0	0	-

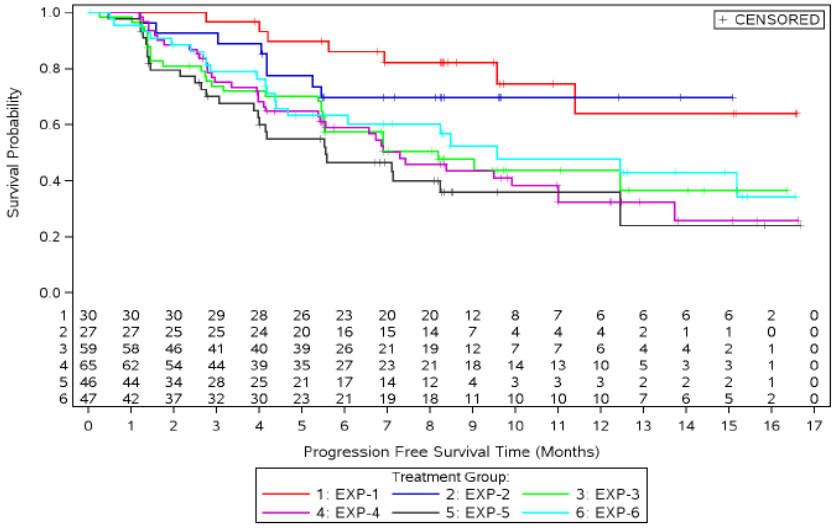
Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.8.3.2.4.2.1.ema; Table 14.2.2.7.3.2.4.2.1.ema.
15 Mar 2017: Module 5.3.5.3 D120 Supporting Tables 14.2.2.8.1.2.3.2.1.t; 14.2.2.8.2.2.3.2.1.t; 14.2.2.7.1.2.3.2.1.t; 14.2.2.7.2.2.3.2.1.t
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; DOR=duration of response; EXP=expansion; ICR=Independent Central Review; ITT=intention-to-treat; N/n=number of patients; NSCLC=non-small cell lung cancer; PD=progressive disease. PR=partial response.
a. Using Brookmeyer Crowley method.
b. Data (15 March 2017 data cutoff) were not provided before.

Progression Free Survival (PFS)

Table 47: PFS based on ICR (Phase 2) – ITT population, by EXP-1:EXP-6

	EXP-1 N=30	EXP-2 N=27	EXP-3A N=32	EXP-3B N=27	EXP-4 N=65	EXP-5 N=46	EXP-6 N=47	Total N=274
% Censored	**76.7**	**70.4**	**59.4**	**37.0**	**44.6**	**43.5**	**55.3**	**53.3**
Median (months) (95% CI)a	NR (11.4, NR)	NR (NR, NR)	12.5 (6.9, NR)	5.5 (2.9, 9.0)	7.3 (5.4, 11.0)	5.6 (4.0, 12.5)	9.6 (4.7, NR)	9.6 (7.1, 12.5)

Source: Table 14.2.2.5.1.1.1.2.1 and 14.2.2.5.2.1.1.2.1.
Abbreviations: CI=confidence interval; EXP=expansion; ITT=intention to treat; N/n=number of patients; NR=not reached.
a. Using Brookmeyer Crowley method



Source: Figure 14.2.2.5.1.1.1.2.2.
Abbreviations: EXP=expansion; ITT = intention-to-treat.

Figure 21: Kaplan-Meier plot of PFS based on ICR (Phase 2) – ITT population, in EXP1:EXP-6

Table 48: PFS in patients with ALK-positive NSCLC – ITT population in EXP cohorts (Phase 2)

Data cutoff: 02 Feb 2018	EXP-3B (N=28)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-4:EXP-5 (N=111)	EXP-3B:EXP-5 (N=139)
Median Time to Event (months)	5.5	7.4	5.6	6.9	6.9
95% CI[a]	(2.9, 8.2)	(5.4, 11.1)	(4.0, 8.3)	(5.4, 9.5)	(5.4, 8.2)
Number with event, n (%)	20 (71.4)	44 (67.7)	33 (71.7)	77 (69.4)	97 (69.8)
Number censored, n (%)	8 (28.6)	21 (32.3)	13 (28.3)	34 (30.6)	42 (30.2)
% Probability of being event free at Month 12[b] (95% CI)[c]	27.3 (12.2, 45.0)	36.7 (24.6, 48.7)	28.3 (15.2, 42.9]	33.3 (24.2, 42.6)	32.1 (24.0, 40.3)
% Probability of being event free at Month 18[b] (95% CI)[c]	21.9 (8.1, 39.9)	27.1 (16.3, 39.0)	17.0 (7.1, 30.6)	23.1 (15.2, 32.0)	22.6 (15.5, 30.6)
Data cutoff: 15 Mar 2017	**EXP-3B (N=27)**	**EXP-4 (N=65)**	**EXP-5 (N=46)**	**EXP-4:EXP-5 (N=111)**	**EXP-3B:EXP-5[b]**
Median Time to Event (months)	5.5	7.3	5.6	6.9	-
95% CI[a]	(2.9, 9.0)	(5.4, 11.0)	(4.0, 12.5)	(5.4, 9.5)	-
Number with event, n (%)	17 (63.0)	36 (55.4)	26 (56.5)	62 (55.9)	-
Number censored, n (%)	10 (37.0)	29 (44.6)	20 (43.5)	49 (44.1)	- -
% Probability of being event free at Month 12[c] (95% CI)[d]	29.3 (11.9, 49.3)	32.4 (19.3, 46.3)	36.0 (20.6, 51.6)	31.9 (21.2, 43.1)	-
% Probability of being event free at Month 18[c] (95% CI)[d]	-	-	-	-	-

Source: **02 Feb 2018:** Module 5.3.5.3 D120 Supporting Table 14.2.2.5.2.1.1.2.1.ema.
15 Mar 2017: Module 5.3.5.2 Study 1001 CSR Supporting Tables 14.2.2.5.2.1.1.2.1; 14.2.2.5.1.1.1.2.1.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CSR=clinical study report; EXP=expansion; ITT=intention to treat; N/n=number of patients; NSCLC=non-small-cell lung cancer.
Note: The difference in number of patients in EXP-3B across the 2 data cutoffs was due to the positive ALK status confirmation for Patient 10022026 as of the 02 February 2018 data cutoff.

a. Based on the Brookmeyer Crowley Method.
b. Data (15 March 2017 data cutoff) were not provided before.
c. Estimated from the Kaplan-Meier curve.
d. Calculated using the normal approximation to the log transformed cumulative hazard rate.

Overall Survival

In Phase 2, the updated median duration of follow-up for OS was approximately 20 months for the cohorts EXP-3B:EXP-5.

In cohort **EXP-3B**, the median OS was 21.1 months (95% CI: 12.3, NR) and 60.7% patients were still censored for OS. Most patients 14 (50.0%) were alive and in follow up at the data cutoff date. The survival probability for EXP-3B at 12 months was 69.8% (95% CI: 48.5, 83.6) and at 18 months was 61.6% (95% CI: 40.2, 77.2).

In pooled cohort **EXP-4:EXP-5**, the median OS for the 111 ALK-positive NSCLC patients was 19.2 months (95% CI: 15.4, NR). A total of 55 (49.5%) patients were censored for OS. Most patients were censored 47 (42.3%) because they were alive at the data cutoff date. The survival probability for EXP-4:EXP-5 at 12 months was 67.3% (95% CI: 57.6, 75.4) and at 18 months was 54.2% (95% CI: 44.0, 63.2).

Time to Tumour Progression

The median TTP based on independent assessment was 11 months (95%CI: 8.2, 13.7) overall, 9.0 months for cohort EXP-3 (95%CI: 5.5, NR), 8.4 months for cohort EXP-4 (95%CI: 5.6, 13.7), and 7.1 months (95%CI: 4.1, 12.5) for cohort EXP-5.

Comparison between TTP on lorlatinib and the TTP on last treatment prior to lorlatinib

For patients who had received ALK-inhibitor treatment prior to lorlatinib, the median TTP was 12.9 months (95%CI: 11.2, 18.1) for cohort EXP-3, 12.1 months (95%CI: 7.9, 16.4) for cohort EXP-4, and 3.7 months (95%CI: 2.1, 6.6) for cohort EXP-5. The corresponding hazard ratios (lorlatinib versus prior therapy) were 0.572 (95%CI: 0.324, 1.010) for EXP-3, 0.757 (95%CI: 0.489, 1.173) for EXP-4, and 0.628 (95%CI: 0.382, 1.034) for EXP-5.

For patients who had received systemic therapy other than ALK-TKI treatment prior to lorlatinib, the median TTP was 8.5 months (95%CI: 5.0, 12.6) for EXP-3, 5.0 months (95%CI: 3.1, 10.8) for cohort EXP-4, and 5.6 months (95%CI: 4.7, 11.2) for cohort EXP-5. The corresponding hazard ratios (lorlatinib versus prior therapy) were 0.314 (95%CI: 0.086, 1.148) for EXP-3, 0.745 (95%CI: 0.357, 1.552) for EXP-4, and 0.886 (95%CI: 0.398, 1.972) for EXP-5.

Data were not provided specifically for cohort EXP-3B.

During the procedure, the applicant was requested to provide information on TTP on last treatment prior to lorlatinib as grouped by first and second-generation ALK inhibitors in cohorts EXP-3:EXP-5, with data provided by both individual cohorts (including EXP-3B) and pooled analysis (data not shown). No significant differences were observed in terms of TTP between lorlatinib and prior ALK-TKI.

Intracranial Time to Tumour Progression

The median IC-TTP based on independent assessment was not reached (95% CI: 6.9, NR) for cohort EXP-3, 15.7 months (95%CI: 11.0, 15.7) for cohort EXP-4, and NR (95% CI: 8.3, NR) for cohort EXP-5.

Probability of First Event Being a CNS Progression, non-CNS Progression, or Death

- Overall efficacy population

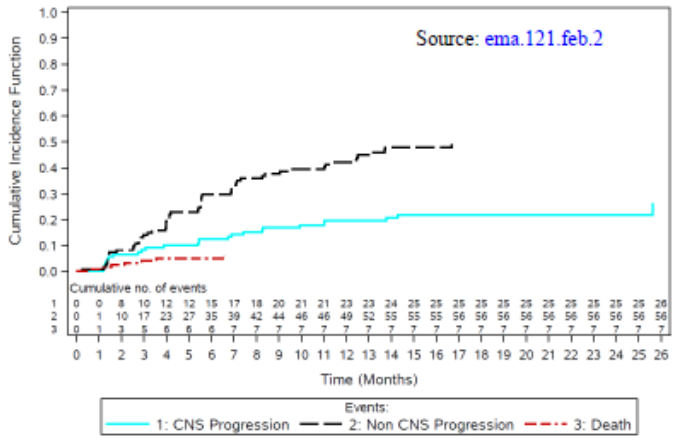


Figure 22: Plot of cumulative incidence function based on ICR (pooled EXP-3B: EXP-5) – ITT population excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018

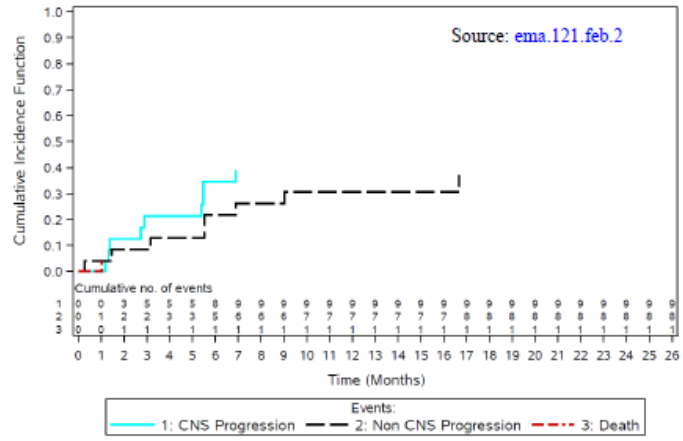


Figure 23: Plot of cumulative incidence function based on ICR (EXP-3B) – ITT population excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018

- Patients with brain metastases at baseline

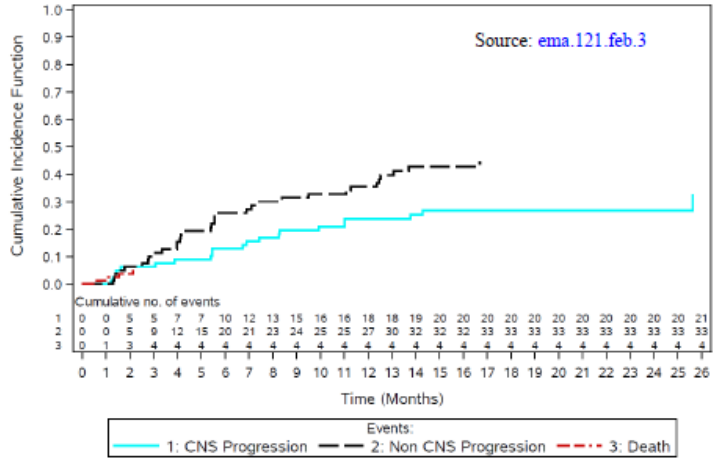


Figure 24: Plot of cumulative incidence function based on ICR (pooled EXP-3B: EXP-5) – ITT population in patients with CNS metastases at baseline, excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018

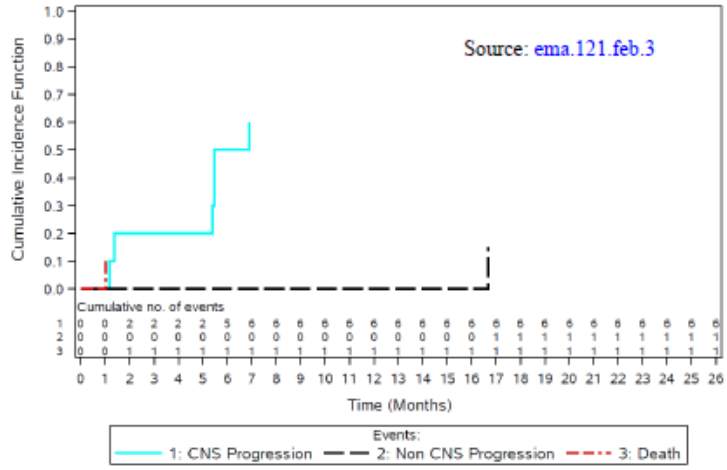


Figure 25: Plot of cumulative incidence function based on ICR (EXP-3B) – ITT population in patients with CNS metastases at baseline, excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018- Patients without brain metastases at baseline

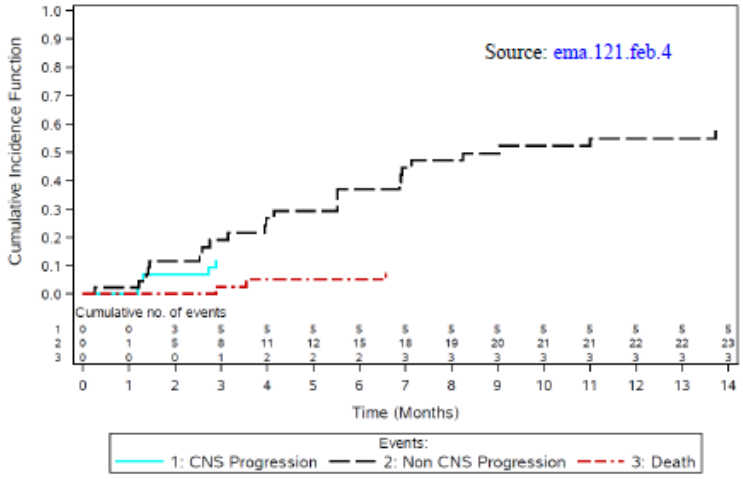


Figure 26: Plot of cumulative incidence function based on ICR (pooled EXP-3B: EXP-5) – ITT population in patients without CNS metastases at baseline, excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018

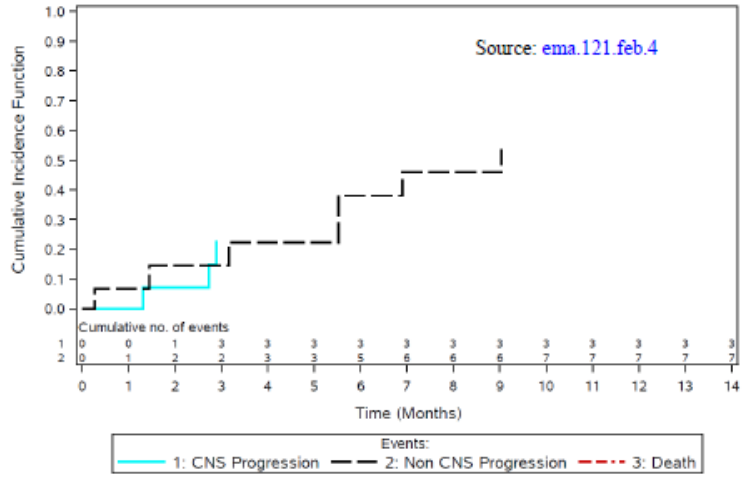


Figure 27: Plot of cumulative incidence function based on ICR (EXP-3B) – ITT population in patients without CNS metastases at baseline, excluding patients receiving radiotherapy for brain metastases up to 8 weeks before starting lorlatinib - Data cutoff date: 02 February 2018

Efficacy by ALK mutation status

The BOR based on independent central review and median duration of treatment by expansion cohort and according to either presence or absence of ALK mutations measured in blood or tumour samples are summarised in the following tables:

Table 49: Summary of Subjects with None vs. ≥1 Plasma CNA Mutation at Baseline (Phase 2) - CNA Peripheral Blood Analysis Set, by EXP-1:EXP-5

		EXP-1 (N=30)	EXP-2 (N=26)	EXP-3 (N=58)	EXP-4 (N=61)	EXP-5 (N=45)
No ALK Mutation Detected	n (%)	28 (93.3)	19 (73.1)	48 (82.8)	42 (68.9)	30 (66.7)
	Responders n (%)	25 (83.3)	14 (53.8)	23 (39.7)	14 (23.0)	7 (15.6)
	Best Overall Response (%)					
	Complete response	1 (3.3)	1 (3.8)	1 (1.7)	2 (3.3)	0
	Partial response	24 (80.0)	13 (50.0)	22 (37.9)	12 (19.7)	7 (15.6)
	Stable/No response	2 (6.7)	4 (15.4)	16 (27.6)	18 (29.5)	12 (26.7)
	Objective progression	1 (3.3)	1 (3.8)	7 (12.1)	7 (11.5)	8 (17.8)
	Indeterminate	0	0	2 (3.4)	3 (4.9)	3 (6.7)
	Median Treatment Duration (Months)	9.1	8.8	7.8	8.0	7.7
	Treatment Duration Range (Months)	(1.68, 17.08)	(0.36, 15.83)	(0.26, 17.77)	(0.23, 17.48)	(0.39, 17.28)
>=1 CNA ALK Mutation	n (%)	1 (3.3)	6 (23.1)	8 (13.8)	17 (27.9)	14 (31.1)
	Responders n (%)	1 (3.3)	5 (19.2)	4 (6.9)	12 (19.7)	8 (17.8)
	Best Overall Response (%)					
	Complete response	0	0	0	0	0
	Partial response	1 (3.3)	5 (19.2)	4 (6.9)	12 (19.7)	8 (17.8)
	Stable/No response	0	0	0	2 (3.3)	3 (6.7)
	Objective progression	0	1 (3.8)	2 (3.4)	1 (1.6)	2 (4.4)
	Indeterminate	0	0	2 (3.4)	2 (3.3)	1 (2.2)
	Median Treatment Duration (Months)	9.9	7.8	8.0	7.6	7.7
	Treatment Duration Range (Months)	(9.86, 9.86)	(4.11, 13.63)	(1.38, 15.11)	(0.46, 15.70)	(1.22, 11.96)
Other	n (%)	1 (3.3)	1 (3.8)	2 (3.4)	2 (3.3)	1 (2.2)
	Responders n (%)	1 (3.3)	1 (3.8)	2 (3.4)	1 (1.6)	1 (2.2)
	Best Overall Response (%)					
	Complete response	0	0	0	0	0
	Partial response	1 (3.3)	1 (3.8)	2 (3.4)	1 (1.6)	1 (2.2)
	Stable/No response	0	0	0	1 (1.6)	0
	Objective progression	0	0	0	0	0
	Indeterminate	0	0	0	0	0
	Median Treatment Duration (Months)	16.3	10.6	8.7	10.2	6.1
	Treatment Duration Range (Months)	(16.33, 16.33)	(10.58, 10.58)	(8.25, 9.17)	(8.51, 11.83)	(6.08, 6.08)

Source Data: Table 16.2.8.5.1.1.1.2, Table 16.2.8.5.1.1.2.2 and Table 16.2.6.4.2.1.2
Other: Sample failed analysis; Uninformative; Or not analyzed.
Responder is based on Independent Central Review.
The duration of treatment is defined as the total number of months =(Last Dose Date - Cycle 1 Day 1 + 1)/30.44.
Only ALK results for ALK+ patients are included.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 19MAY2017 Date of Table Generation: 02JUL2017 (06:17)

Table 50: Summary of Subjects with None vs. ≥1 DNA Mutation at Baseline (Phase 2) - Tumour Tissue Analysis Set, by EXP-1:EXP-5

		EXP-1 (N=28)	EXP-2 (N=26)	EXP-3 (N=57)	EXP-4 (N=62)	EXP-5 (N=43)
No ALK Mutation Detected	n (%)	26 (92.9)	19 (73.1)	44 (77.2)	37 (59.7)	20 (46.5)
	Responders n (%)	23 (82.1)	13 (50.0)	23 (40.4)	12 (19.4)	4 (9.3)
	Best Overall Response (%)					
	Complete response	1 (3.6)	1 (3.8)	0	1 (1.6)	0
	Partial response	22 (78.6)	12 (46.2)	23 (40.4)	11 (17.7)	4 (9.3)
	Stable/No response	2 (7.1)	4 (15.4)	12 (21.1)	12 (19.4)	7 (16.3)
	Objective progression	1 (3.6)	2 (7.7)	6 (10.5)	9 (14.5)	5 (11.6)
	Indeterminate	0	0	3 (5.3)	4 (6.5)	4 (9.3)
	Median Treatment Duration (Months)	9.7	9.2	7.9	6.4	3.0
	Treatment Duration Range (Months)	(1.68, 17.08)	(0.36, 15.83)	(0.26, 17.77)	(0.23, 17.48)	(0.39, 10.78)
>=1 DNA ALK Mutation	n (%)	0	7 (26.9)	8 (14.0)	11 (17.7)	13 (30.2)
	Responders n (%)	0	6 (23.1)	5 (8.8)	7 (11.3)	7 (16.3)
	Best Overall Response (%)					
	Complete response	0	0	1 (1.8)	0	0
	Partial response	0	6 (23.1)	4 (7.0)	7 (11.3)	7 (16.3)
	Stable/No response	0	0	0	3 (4.8)	5 (11.6)
	Objective progression	0	1 (3.8)	2 (3.5)	1 (1.6)	1 (2.3)
	Indeterminate	0	0	1 (1.8)	0	0
	Median Treatment Duration (Months)		7.6	8.0	9.0	8.8
	Treatment Duration Range (Months)		(4.11, 13.63)	(2.56, 9.66)	(3.71, 15.70)	(1.41, 17.28)
Not Analyzable	n (%)	2 (7.1)	0	5 (8.8)	14 (22.6)	10 (23.3)
	Responders n (%)	2 (7.1)	0	1 (1.8)	5 (8.1)	4 (9.3)
	Best Overall Response (%)					
	Complete response	0	0	0	0	0
	Partial response	2 (7.1)	0	1 (1.8)	5 (8.1)	4 (9.3)
	Stable/No response	0	0	3 (5.3)	7 (11.3)	3 (7.0)
	Objective progression	0	0	1 (1.8)	0	3 (7.0)
	Indeterminate	0	0	0	2 (3.2)	0
	Median Treatment Duration (Months)	6.5		8.3	8.5	8.9
	Treatment Duration Range (Months)	(6.24, 6.77)		(2.27, 10.22)	(1.68, 16.16)	(4.40, 16.82)

Source Data: Table 16.2.8.5.2.1.2 and Table 16.2.6.4.2.1.2
Responder is based on Independent Central Review.
The duration of treatment is defined as the total number of months =(Last Dose Date - Cycle 1 Day 1 + 1)/30.44.
Only ALK results for ALK+ patients are included.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 19MAY2017 Date of Table Generation: 02JUL2017 (07:29)

In order to investigate the impact of the last therapy used prior to lorlatinib (either ALK-targeted or untargeted systemic therapy) the MAH submitted results of clinical outcomes based on last therapy prior to lorlatinib.

Table 51: Summary of clinical outcomes based on ICR (pooled EXP-3B: EXP-5) by last prior therapy immediately prior to lorlatinib – CAN peripheral analysis set

Last Prior Therapy	N	Mutational Status	N1 (%)	Clinical Outcomes							
				CR	PR	SD	PD	IND	ORR (95% CI)	mDOR[a] (95% CI)	mPFS[a] (95% CI)
Alectinib	49	None	33 (67.3)	2 (6.1)	6 (18.2)	14 (42.4)	9 (27.3)	2 (6.1)	24.2 (11.1, 42.3)	8.3 (4.2)	4.2 (2.9, 5.6)
		≥1 Mutation	15 (30.6)		11 (73.3)	3 (20.0)	1 (6.7)		73.3 (44.9, 92.2)	5.2 (2.8, 24.4)	8.2 (4.1, 25.6)
		Other[b]	1 (2.0)			1 (100.0)					
Brigatinib	7	None	3 (42.9)		1 (33.3)		1 (33.3)	1 (33.3)			
		≥1 Mutation	4 (57.1)		2 (50.0)	1 (25.0)	1 (25.0)		50.0 (6.8, 93.2)	NE	4.8 (1.4)
		Other[b]									
Ceritinib	39	None	32 (82.1)		13 (40.6)	13 (40.6)	4 (12.5)	2 (6.3)	40.6 (23.7, 59.4)	6.1 (4.2, 12.5)	6.9 (4.0, 11.1)
		≥1 Mutation	4 (10.3)		2 (50.0)	1 (25.0)	1 (25.0)		50.0 (6.8, 93.2)	NE	8.4 (1.4)
		Other[b]	3 (7.7)		3 (100.0)						
Crizotinib	17	None	13 (76.5)		4 (30.8)	4 (30.8)	4 (30.8)	1 (7.7)	30.8 (9.1, 61.4)	12.6 (5.2)	8.3 (2.6)
		≥1 Mutation	4 (23.5)		3 (75.0)		1 (25.0)		75.0 (19.4, 99.4)	9.9 (7.0)	11.1 (1.2)
		Other[b]									
Other TKI[c]	3	None	1 (33.3)			1 (100.0)					
		≥1 Mutation	2 (66.7)					2 (100.0)			
		Other[b]									
Chemotherapy	17	None	12 (70.6)	1 (8.3)	3 (25.0)	5 (41.7)	2 (16.7)	1 (8.3)	33.3 (9.9, 65.1)	NE	9.9 (2.7)
		≥1 Mutation	5 (29.4)		3 (60.0)			2 (40.0)	60.0 (14.7, 94.7)	NE	4.1 (1.5)
		Other[b]									

Source: Module 5.3.5.3 D120 Supporting Table ema.225.2.1; ema.225.2.2; ema.225.2.3
Response based on Independent Central Review.
N=CNA Peripheral Blood Analysis Set population for the associated last prior therapy; Percentages in the N1column (by mutational status) are calculated using N as the denominator. Percentages in subsequent columns are calculated using N1 as the denominator.
CI=confidence interval; CR=complete response; DOR=duration of response; IND=indeterminate; KM=Kaplan-Meier; mDR=median duration of response; mPFS=median progression free survival; NE=not estimated; PR=partial response; PD=progressive disease.
When N1≥4, ORR (95% CI) and KM estimate of DOR/PFS median (95% CI) in months are presented in the table.
a. Using Brookmeyer Crowley method.
b. Sample failed analysis; Sample not analyzed; Or result uninformative.
c. Other ALK TKIs included Ensartinib and Entrectinib.

The incidence of ALK-mutations varied across the different groups according to the previously used ALK-inhibitor. The efficacy of lorlatinib was overall reduced in the absence of ALK-mutations.

Patient-reported outcome

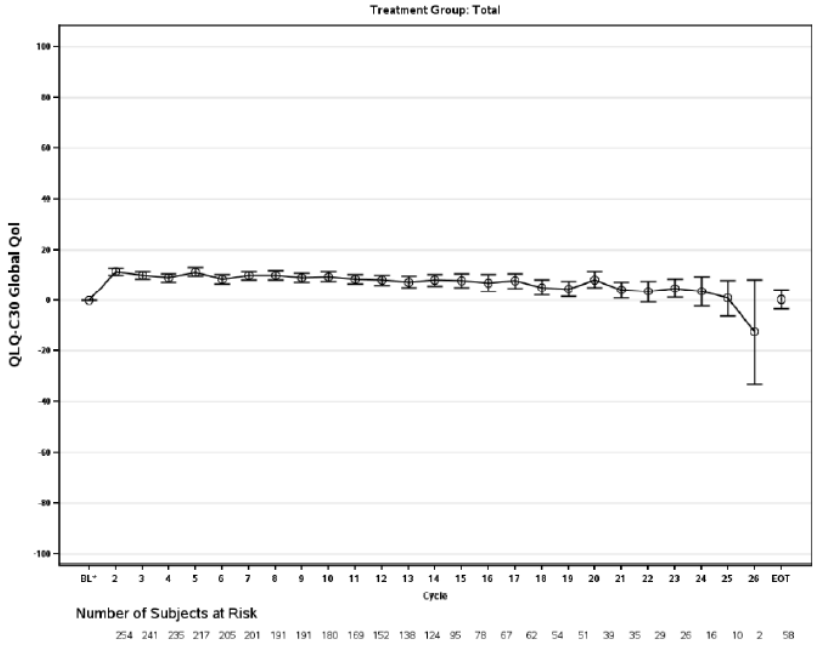


Figure 28: Mean change from baseline in patient-reported global QoL (PRO-evaluable population)

The majority of patients had either improved (42.7%) or stable (39.6%) scores in global QoL during treatment (including all cycles).

Table 52: Change in EORTC (QLQ-C30 and QLQ-LC13) scales (PRO-evaluable population)

EORTC (QLQ-C30 and QLQ-LC13) Scales		No. (%) of Patients N=255		
		Improved	Stable	Worsening
Global QoL (QLQ-C30)	Global QoL	109 (42.7)	101 (39.6)	44 (17.3)
Functional Scales QLQ-C30	Physical functioning	73 (28.6)	146 (57.3)	35 (13.7)
	Role functioning	96 (37.6)	111 (43.5)	46 (18.0)
	Emotional functioning	98 (38.4)	129 (50.6)	27 (10.6)
	Cognitive functioning	62 (24.3)	131 (51.4)	61 (23.9)
	Social functioning	86 (33.7)	135 (52.9)	33 (12.9)
Symptom Scales/Items QLQ-C30	Fatigue	125 (49.0)	97 (38.0)	32 (12.5)
	Nausea and vomiting	63 (24.7)	181 (71.0)	10 (3.9)
	Pain	104 (40.8)	111 (43.5)	39 (15.3)
	Dyspnoea	82 (32.2)	121 (47.5)	51 (20.0)
	Insomnia	115 (45.1)	107 (42.0)	32 (12.5)
	Appetite loss	106 (41.6)	142 (55.7)	6 (2.4)
	Constipation	64 (25.1)	151 (59.2)	39 (15.3)
	Diarrhoea	44 (17.3)	177 (69.4)	33 (12.9)
	Financial difficulties	61 (23.9)	155 (60.8)	38 (14.9)
Symptom Scales/Items QLQ-LC13	Dyspnoea	72 (28.2)	141 (55.3)	41 (16.1)
	Coughing	111 (43.5)	108 (42.4)	35 (13.7)
	Haemoptysis	25 (9.8)	220 (86.3)	9 (3.5)
	Sore mouth	23 (9.0)	189 (74.1)	42 (16.5)
	Dysphagia	25 (9.8)	203 (79.6)	26 (10.2)
	Peripheral neuropathy	34 (13.3)	122 (47.8)	98 (38.4)
	Alopecia	31 (12.2)	173 (67.8)	50 (19.6)
	Pain in chest	76 (29.8)	150 (58.8)	27 (10.6)
	Pain in arm or shoulder	64 (25.1)	146 (57.3)	44 (17.3)
	Pain in other parts	83 (32.5)	102 (40.0)	68 (26.7)

Source: Tables 14.5.1.8.1.2 and 14.5.1.9.1.2.
For functioning and Global QoL, "improved" was defined as ≥10-point increase from Baseline and "worsening" was defined as ≥10-point decrease from Baseline. "Stable" was defined as a patient who was neither improved nor worsened.
For symptoms, "improved" was defined as ≥10-point decrease from Baseline and "worsening" was defined as ≥10-point increase from Baseline. "Stable" was defined as a patient who was neither improved nor worsened.
Abbreviations: EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Questionnaire; N = number of patients; No. = number; PRO = patient-reported outcome; QoL = quality of life; QLQ-LC13=modular supplement to QLQ-C30.

Ancillary analyses

Prior treatment

- The sixty-five (65) patients treated with lorlatinib in the subgroup of patients with 2 prior ALK-inhibitor (ALKi) therapy (EXP-4) received the following prior treatments:

First-Line	Second-Line	N
Crizotinib	second-generation ALKi	61
Second-generation ALKi	second-generation ALKi	3
Second-generation ALKi	crizotinib	1

In the group of patients receiving crizotinib in first-line and a second-generation ALK-inhibitor in second-line, the ORR and IC-ORR in patients with Intra Cranial lesion at baseline were as follows:

ORR = 27/61=44.3% (95% CI 31.5%-57.6%)

IC-ORR= 23/42=54.8% (95% CI 38.7%-70.2%)

- The 46 patients treated with lorlatinib in cohort EXP-5 received the following prior treatments:

First-Line	Second-Line	Third Line	N
crizotinib	crizotinib	second-generation ALKi	4
crizotinib	second-generation ALKi	second-generation ALKi	23
crizotinib	second-generation ALKi	crizotinib	16
second-generation ALKi	crizotinib	second-generation ALKi	2
second-generation ALKi	second-generation ALKi	crizotinib	1

Five (5) patients, who received also a fourth line ALK inhibitor have been categorised to the corresponding line of therapy group based on the first 3 lines received.

Prior Lines of ALKi in EXP-5	ORR	IC-ORR
crizotinib (1L and 2L) and second generation ALKi (3L)	2/4=50.0% (95% CI 6.8%-93.2%)	1/2=50.0% (95% CI 1.3%-98.7%)
crizotinib (1L) and second generation ALKi (2L and 3L)	7/23=30.4% (95% CI 13.2%-52.9%)	6/20=30.0% (95% CI 11.9%-54.3%)
crizotinib (1L), second generation ALKi (2L) and crizotinib (3L)	7/16=43.8% (95% CI 19.8%-70.1%)	8/13=61.5% (95% CI 31.6%-86.1%)
second generation ALKi (1L), crizotinib (2L) and second generation ALKi (3L)	1/2=50.0% (95% CI 1.3%-98.7%)	1/2=50.0% (95% CI 1.3%-98.7%)
second generation ALKi (1L and 2L) and crizotinib (3L)	0/1= 0.0% (95% CI 0.0%-97.5%)	NA
TOTAL	17/46=37.0% (95% CI 23.2%-52.5%)	16/37=43.2% (95% CI 27.1%-60.5%)

NA: the patient receiving second generation ALKi in 1L and 2L and crizotinib in 3L had No Intra-cranial lesions at baseline

Moreover, information was provided regarding the time lapse between last tumour irradiation and first dose of lorlatinib, particularly in the population of patients with CNS involvement.

Table 53: Summary of prior radiation therapy (pooled EXP-3B:EXP-5)

	Pooled EXP-3B: EXP-5 (N =139)
	n (%)
Prior RT Site(s) of Prior RT*	95 (68.3)
Abdominal	1 (1.1)
Adrenal Gland	1 (1.1)
Bone	7 (7.4)
Brain	67 (70.5)

Eye	1 (1.1)
Face	1 (1.1)
Liver	1 (1.1)
Lung	20 (21.1)
Mediastinum	9 (9.5)
Neck	1 (1.1)
Pelvis	3 (3.2)
Spine	14 (14.7)
Thorax	6 (6.3)
Unknown	1 (1.1)

Source: Module 5.3.5.3 D120 Supporting Table ema.114.2
Date of Data Cutoff: 02 Feb 2018 and Date of Data Snapshot: 17 Apr 2018
The denominator of Prior RT is N. The denominator of site(s) of prior RT is the number of subjects with prior RT. One prior RT may be classified into multiple sites of RT. The patient with this RT is counted in each corresponding site.
* Patients could have more than one prior RT.
RT=radiation therapy

Table 54: Summary of time from prior brain radiation therapies to the start of lorlatinib in patients with CNS metastases at baseline based on ICR (pooled EXP-3B: EXP-5)

	Pooled EXP-3B: EXP-5 (N=139)
Time from Radiation Therapy to the Start of Lorlatinib (Weeks)	
n	59
Mean	71.6
STD	61.49
Median	52.3
Min	2.1
Max	199.0

Source: Module 5.3.5.3 D120 Supporting Table ema.114.4
Date of Data Cutoff: 02 Feb 2018 and Date of Data Snapshot: 17 Apr 2018
N is the number of patients of EXP-3B: EXP-5.
n is the number of patients with CNS Metastases at baseline according to ICR and who received prior brain radiation therapy.
For a subject with multiple prior radiation therapy, the one closest to the start of lorlatinib (but still prior) is used in the analysis.
Time from Radiation Therapy to the Start of Lorlatinib = Start of Lorlatinib - Start of Radiation Therapy

Biomarker assessments

Plasma biospecimens were available from at least 93% of the patients in each of the ALK-positive expansion cohorts (EXP-2:EXP-5), for a total of 190 (96.4%).

Plasma CNA samples were analysed for ALK gene rearrangements and kinase domain mutations by NGS. Patients in EXP-3B were not analysed separately. The ALK gene rearrangement and ALK kinase domain mutation data and sample disposition are summarised in Table 55.

Of note, lorlatinib exhibited antitumor activity across a variety of ALK kinase domain resistance mutations, including the well characterised L1196M and G1269A crizotinib resistance mutations as well as the difficult-to-treat G1202R/G1202del mutations, but also in rarer, newly identified mutations such as P1329S.

Table 55: Sample Disposition and Summary Results for Patients with ALK-Positive NSCLC - CNA Peripheral Blood Analysis Set by EXP Cohort (Phase 2)

	Total (N=190) n (%)	EXP-2 (N=26) n (%)	EXP-3 (N=58) n (%)	EXP-4 (N=61) n (%)	EXP-5 (N=45) n (%)
No ALK Alteration Detected	49 (25.8)	8 (30.8)	16 (27.6)	16 (26.2)	9 (20.0)
ALK Gene Rearrangement	79 (41.6)	13 (50.0)	24 (41.4)	17 (27.9)	25 (55.6)
ALK Mutation (w/o Rearrangement)	13 (6.8)	1 (3.8)	1 (1.7)	7 (11.5)	4 (8.9)
ALK Mutation (w/ Rearrangement)	31 (16.3)	5 (19.2)	7 (12.1)	9 (14.8)	10 (22.2)
No cfDNA detected	38 (20.0)	3 (11.5)	13 (22.4)	17 (27.9)	5 (11.1)
Not analyzable	6 (3.2)	1 (3.8)	2 (3.4)	2 (3.3)	1 (2.2)
Missing	5 (2.6)	0 (0)	2 (3.4)	2 (3.3)	1 (2.2)

Source: Study 1001 CSR Table 14.3.4.5.1.6.1.2
Abbreviations: ALK=anaplastic lymphoma kinase; CNA=circulating nucleic acid; cfDNA=circulating free deoxyribonucleic acid; EXP=expansion; N=number of patients; NSCLC=non-small cell lung cancer; w/=with; w/o=without. Missing: result missing at the time of the data cutoff.

Tumour tissue biospecimens (archival tumour and/or de novo tumour biopsy) were available in total for 188 patients with ALK-positive NSCLC.

Table 56: Tumour Tissue Disposition and Summary Results for Patient with ALK-Positive NSCLC – Tumour Tissue Analysis Set by EXP Cohort (Phase 2)

	Total (N= 188)	EXP-2 (N=26)	EXP-3 (N=57)	EXP-4 (N=62)	EXP-5 (N=43)
No ALK mutation detected	120	19	44	37	20
ALK mutation detected	39	7	8	11	13
Not analyzable	29	0	5	14	10

Source: Study 1001 CSR Table 14.3.4.5.2.9.1.2
Abbreviations: ALK=anaplastic lymphoma kinase; EXP=expansion; N=number of patients; NSCLC=non-small cell lung cancer.

Summary of main study

The following table summarises 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 57: Summary of Efficacy for study B7461001 (study 1001)

Title: Phase 1/2 study on patient safety and efficacy					
Study identifier	B7461001 (1001)				
Design	Multicenter, multiple-dose, dose-escalation, safety, PK, Pharmacodynamics, and antitumor activity study.				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Phase 2 not applicable not applicable		
Hypothesis	Exploratory: Non-comparative study				
Treatments groups	Phase 1		Lorlatinib 100 mg QD. Until PD or unacceptable toxicity, 41 patients in Phase 1		
	EXP-3B		Lorlatinib 100 mg QD. Until PD or unacceptable toxicity, 27 patients		
	EXP-4-5		Lorlatinib 100 mg QD. Until PD or unacceptable toxicity, 111 patients		
	EXP-2-3A		Lorlatinib 100 mg QD. Until PD or unacceptable toxicity, 59 patients		
Endpoints and definitions	Primary endpoint (Phase 2)	ORR	IRC according to RECIST 1.1		
	Secondary endpoints	Efficacy	IC ORR, TTR, IC TTR, PFS, 1 year survival		
	Secondary endpoints	Other analyses	PROs and biomarker-related endpoint		
Database lock	02 February 2018				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat population at primary analysis				
Descriptive statistics and estimate variability	Treatment group	EXP-3B	EXP-4:EXP-5	EXP-2:EXP-3A	
	Number of subject	N=28	N=111	N=59	
	ORR (%) 95%CI	42.9 % [24.5; 62.8]	38.7 % [29.6; 48.5]	69.5% [56.1;80.8]	
	CR (%)	3.6	1.8	1.7	
	PR (%)	39.3	36.9	67.8	
	IC-ORR (%) 95%CI	66.7 % [29.9; 92.5]	52.1 % [37.2; 66.7]	N/A N/A	
Effect estimate per comparison	Disease control rate DCR (%)	71.4	73.0	86.0	
	Time to response (TTR) (months) Range	1.4 1.2-16.6	1.4 1.2-16.4	1.4 1.1-11.0	
	Duration of response (DOR) (months) Range	5.6 4.17-NR	9.9 5.65-24.44	NR 11.1-NR	
	PFS (months) 95%CI	5.5 months 2.9, 8.2	6.9 5.4, 9.5	NR 12.5, NR	
	OS (months) 95%CI	21.9 19.2, 23.5	20.2 19.4, 21.4	NR NA	
Notes	IC= Intracranial				
Analysis description	**Secondary analysis:**				
	N/A				

Clinical studies in special populations

Table 58: Number of elderly patients (by age group) included in efficacy and safety analyses

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Study B7461001	45/334	16/334	1/334

Subgroup analyses of the ORR according to sex, age, race group, and performance status did not show any significant differences.

Table 59: ORR and IC-ORR outcomes by age group, gender, race and baseline ECOG performance status

Baseline Characteristic	N 215	ORR 100-mg QD Pooled Group n (%) [CI]	N 149	IC ORR 100-mg QD Pooled Group n (%) [CI]
Sex				
Male	88	39 (44.3) [33.7, 55.3]	60	29 (48.3) [35.2, 61.6]
Female	127	60 (47.2) [38.3, 56.3]	89	50 (56.2) [45.3, 66.7]
Age				
<65 years	177	83 (46.9) [39.4, 54.5]	130	68 (52.3) [43.4, 61.1]
≥65 years	38	16 (42.1) [26.3, 59.2]	19	11 (57.9) [33.5, 79.7]
Race group				
Asian	74	39 (52.7) [40.7, 64.4]	44	25 (56.8) [41.0, 71.7]
Non-Asian	118	44 (37.3) [28.6, 46.7]	89	40 (44.9) [34.4, 55.9]
Unspecified	23	16 (69.6) [47.1, 86.8]	16	14 (87.5) [61.7, 98.4]
ECOG performance status				
0	95	43 (45.3) [35.0, 55.8]	68	32 (47.1) [34.8, 59.6]
1	112	53 (47.3) [37.8, 57.0]	75	44 (58.7) [46.7, 69.9]
2	8	3 (37.5) [8.5, 75.5]	6	3 (50.0) [11.8, 88.2]

Source: Study 1001 Table 14.2.2.1.1.1.2.1.s3, Table 14.2.2.1.1.2.2.1.s3, Table 14.2.2.1.2.1.2.1.s3, Table 14.2.2.1.2.2.2.1.s3, Table 14.2.2.1.3.1.2.1.s3, Table 14.2.2.1.3.2.2.1.s3, Table 14.2.2.1.4.1.2.1.s3, Table 14.2.2.1.4.2.2.1.s3, and Table 14.2.2.11.2.s3

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval, ECOG=Eastern Cooperative Oncology Group; IC=intracranial; N/n=number; NSCLC=non-small-cell lung cancer; ORR=objective response rate; QD=once daily.

A trend towards an increased number of responders in the groups of Asians (ORR 54.3%) and Unspecified ethnicity (68.2%) compared with Non-Asians (38.1%) is observed. The efficacy data reported in the cohorts of interest (EXP-3B, EXP-4 and EXP-5) were requested.

Table 60: ORR and IC-ORR by baseline characteristics in patients with ALK-positive NSCLC-ITT population in cohort EXP-3B:EXP-5 (Phase 2)

Baseline Characteristic	N	ORR n (%) [CI][a]	N	IC ORR[b] n (%) [CI][a]
02 Feb 2018				
Race				
Asians	53	26 (49.1) [35.1, 63.2]	22	12 (54.5) [32.2, 75.6]
NonAsians	73	23 (31.5) [21.1, 43.4]	28	13 (46.4) [27.5, 66.1]
Unspecified[c]	13	7 (53.8) [25.1, 80.8]	7	6 (85.7) [42.1, 99.6]
Age				
<65 years	117	46 (39.3) [30.4, 48.8]	51	29 (56.9) [42.2, 70.7]
≥65 years	22	10 (45.5) [24.4, 67.8]	6	2 (33.3) [4.3, 77.7]
15 Mar 2017				
Race				
Asians	53	24 (45.3) [31.6, 59.6]	22	11 (50.0) [28.2, 71.8]
NonAsians	72	20 (27.8) [17.9, 39.6]	28	13 (46.4) [27.5, 66.1]
Unspecified[c]	13	8 (61.5) [31.6, 86.1]	8	7 (87.5) [47.3, 99.7]
Age[d]				
<65 years	-	-	-	-
≥65 years	-	-	-	-

Source: **02 Feb 2018**: Module 5.3.5.3 D120 Supporting Tables ema.125.feb.1.1; ema.125.feb.1.3; Module 5.3.5.3 D120 Supporting Tables mo.171.3; mo.171.5.
15 Mar 2017: Module 5.3.5.3 D120 Supporting Tables ema.125.csr.1.1; ema.125.csr.1.3.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; IC=intracranial; ITT=intention to treat; EXP=expansion (cohort); N/n=number of patients; NSCLC=non-small-cell lung cancer; ORR=objective response rate.

a. Using exact method based on binomial distribution.
b. Patients with at least 1 measureable brain lesion at baseline.
c. Race data were not collected, as per local regulations.
d. Data (15 March 2017 data cutoff) were not provided before.

Supportive study

Phase 1 part of study B7461001

Patients included in the Phase 1 part had advanced ALK/ROS1-positive NSCLC and were either treatment-naïve or experienced disease progression after prior ALK-TKI and any prior chemotherapy.

Thirty-two (32; 59.3%) female patients and 22 (40.7%) male patients were enrolled in Phase 1, and the mean age was 51.9 years old. Most patients enrolled were White (68.5%). Only 17 patients received the relevant dose (100 mg QD). Fifty-two (52;96.3%) Phase 1 patients received prior systemic therapy in any treatment setting and 2 patients (3.7%) were treatment naïve (i.e. no prior chemotherapy in the metastatic disease setting and no prior ALK or ROS1 inhibitor therapy). Of those patients who received prior systemic therapy, 48/52 patients received at least 1 prior ALK or ROS1 TKI. Thirty-five (35;64.8%) patients had prior surgery and 35 (64.8%) had radiation therapy.

Table 61: Baseline Disease Characteristics based on Investigator Assessment (Phase 1) – Safety Analysis Set

	Total (N=54)	100 mg QD (N=17)
Involved disease site		
Bone	26 (48.1)	10 (58.8)
Brain	39 (72.2)	13 (76.5)
Liver	21 (38.9)	8 (47.1)
Lung	44 (81.5)	13 (76.5)
Lymph node	33 (61.1)	12 (70.6)
Other	15 (27.8)	5 (29.4)
Number of involved disease sites		
1	5 (9.3)	1 (5.9)
2	12 (22.2)	2 (11.8)
3	13 (24.1)	6 (35.3)
4	11 (20.4)	3 (17.6)
>4	13 (24.1)	5 (29.4)

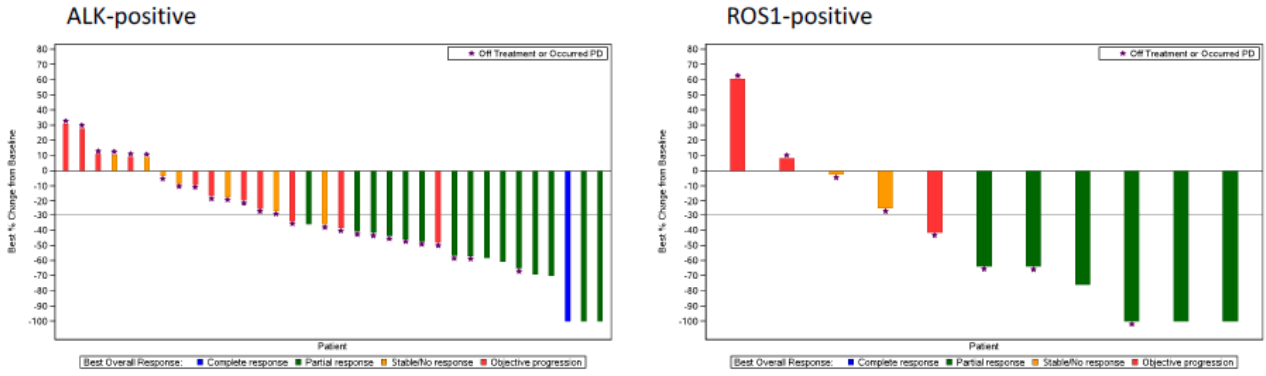
Source: Table 14.1.2.5.1.2.1.
Abbreviations: N/n=number of patients; QD=once daily.
Involved disease sites (per investigator assessment) included both target and non-target lesions. Disease sites with multiple lesions were counted once. Each 'Other' disease site was counted as separate disease site.

The ORR was 39% (95%CI: 24.2-55.5) in the 41 patients with ALK-positive NSCLC, and furthermore 22% of these patients had stable disease. In the CNS, the ORR by IRC was also clinically relevant 41.2% (95%CI: 24.6-53.3) in this setting.

Table 62: Summary of best overall response based on ICR by ALK-positive/ROS-1 positive status (Phase 1)-ITT population

	ALK-Positive NSCLC (N=41)	ROS1-Positive NSCLC (N=12)	Total (N=53)
	n (%)	n (%)	n (%)
Complete response [CR]	1 (2.4)	0	1 (1.9)
Partial response [PR]	15 (36.6)	6 (50.0)	21 (39.6)
Stable dieasea	9 (22.0)	2 (16.7)	11 (20.8)
Objective progression	14 (34.1)	3 (25.0)	17 (32.1)
Indeterminate	2 (4.9)	1 (8.3)	3 (5.7)
Objective response rate: [CR + PR]	16 (39.0)	6 (50.0)	22 (41.5)
95% exact CIb	(24.2, 55.5)	(21.1, 78.9)	(28.1, 55.9)

Source: Table 14.2.1.1.1.1.2.1.
Abbreviations: ALK-positive = anaplastic lymphoma kinase positive; BOR=best overall response; CI = confidence interval; CR=complete response; ITT = intention-to-treat; N/n = number of patients; NSCLC=non small cell lung cancer; PD=progressive disease; SD=stable disease.
a. For a patient to be called having a BOR of stable disease, he/she must have maintained the status of stable disease for at least 6 weeks after treatment start. Patients with only non-measurable disease at baseline and a BOR of non-CR/non-PD were counted as patients with SD.
b. Using exact method based on binomial distribution.



Source: Figure 14.2.1.1.1.1.2.2.2.
Abbreviations: ALK-positive = anaplastic lymphoma kinase positive; ITT=intention-to-treat; PD=progressive disease.

Figure 29: Waterfall plot of best percentage change in tumour size based on ICR (Phase 1) – ITT population

Table 63: Summary of best overall intracranial response based on ICR by ALK-positive or ROS1-positive status (Phase 1) – ITT population in patients with CNS metastases at baseline

	ALK-Positive NSCLC (N=34)	ROS1-positive NSCLC (N=8)	Total (N=42)
	n (%)	n (%)	n (%)
Complete response [CR]	10 (29.4)	3 (37.5)	13 (31.0)
Partial response [PR]	4 (11.8)	1 (12.5)	5 (11.9)
Stable diease[a]	8 (23.5)	0	8 (19.0)
Objective progression	7 (20.6)	3 (37.5)	10 (23.8)
Indeterminate	5 (14.7)	1 (12.5)	6 (14.3)
Objective response rate [CR + PR]	14 (41.2)	4 (50.0)	18 (42.9)
95% exact CI[b]	(24.6, 59.3)	(15.7, 84.3)	(27.7, 59.0)

Source: Table 14.2.1.1.1.2.1.2.1.
Abbreviations: ALK-positive = anaplastic lymphoma kinase positive; BOR=best overall response; CI = confidence interval; CR=complete response; ITT = intention-to-treat; N/n = number of patients; NSCLC=non small cell lung cancer; PD=progressive disease; PR=partial response; SD=stable disease.
a. For a patient to be called having a BOR of SD, he/she must have maintained the status of SD for at least 6 weeks after treatment start. Patients with only non-measurable CNS disease at baseline and a BOR of non-CR/non-PD were counted as patients with SD.
b. Using exact method based on binomial distribution

Time to tumour response

Among the 16 patients with ALK-positive NSCLC with a confirmed objective tumour response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 15.2). Among the 6 patients with ROS1-positive NSCLC with a confirmed objective tumour response by independent assessment, the median TTR was 1.4 months (range: 1.2 to 2.8). The median TTR by investigator assessment was similar to independent assessment for patients with ALK-positive NSCLC and the same for patients with ROS1-positive NSCLC.

For patients with baseline CNS metastases and a confirmed objective response by independent assessment, the median IC-TTR was 1.4 months (range: 1.2 to 20.1) among the 14 patients with ALK-positive NSCLC and 1.4 months (range: 1.1 to 2.8) among the 4 patients with ROS1-positive NSCLC. The analysis included both measurable and non-measurable disease.

DOR

The median follow-up time for DOR by IRC was 27.8 months (95%CI: 20.4, 31.8) for patients with ALK-positive NSCLC.

The duration of response in the CNS for Phase 1 patients with ALK-positive NSCLC was 14.1 months (95%CI: 4.17, NR) with 50% of patients censored. The median intracranial DOR could not be

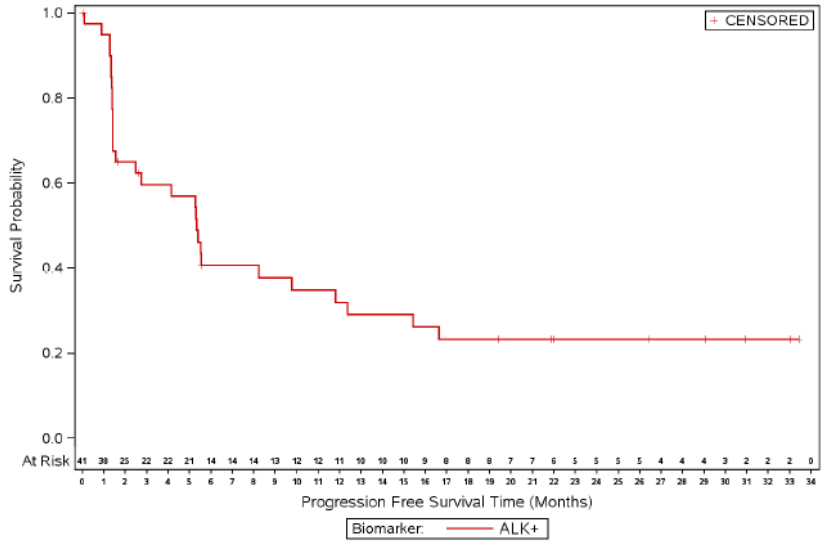
estimated (78.6% of patients censored), however, the lower boundary of the 95%CI was 14.1 months as well.

PFS

Table 64: PFS based on ICR (Phase 1) – ITT population

	ALK-positive NSCLC (N=41)	ROS1-positive NSCLC (N=12)	Total (N=53)
% Censored	29.3	41.7	32.1
Median (months)	5.3	10.1	5.4
(95% CI)[a]	(2.5, 11.8)	(1.6, NR)	(2.7, 11.1)

Source: Table 14.2.1.5.1.1.1.2.1.
Abbreviations: ALK-positive = anaplastic lymphoma kinase positive; CI=confidence interval; ITT=intention to treat; NR=not reached.
a. Using Brookmeyer Crowley method



Source: Figure 14.2.1.5.1.1.1.2.2.
Abbreviations: ALK-positive = anaplastic lymphoma kinase positive; ITT = intention-to-treat.

Figure 30:Kaplan-Meier plot of PFS by ALK-positive status based on ICR (Phase 1) – ITT population

OS

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

2.5.3. Discussion on clinical efficacy

The proposed therapeutic dose was identified in Phase 1, based on a combination of toxicity parameters, mechanism-based PK/PD modelling and also taking into account the pre-clinical anti-tumour activity of lorlatinib against the ALK mutation G1202, which is known to confer resistance to both crizotinib and the second generation ALK-inhibitors alectinib and ceritinib. The approach used for RP2D selection is endorsed. However, other relevant ALK-resistance mutations have been identified for ceritinib (L1152R and F1174C/V) or alectinib (I1171N/T/S) [Muller et al. Onco Targets Ther. 2017; 10: 4535–4541] against which lorlatinib has not been tested *in vitro* using a PK/PD modelling-based approach.

Design and conduct of clinical studies

The efficacy assessment is based on the ongoing Phase 1/2 Study 1001. In the Phase 2 part, 228 patients with ALK-positive NSCLC were included in various cohorts according to prior treatment.

The amendments and protocol violations in the study are deemed unlikely to have had relevant impact on the integrity of study.

The design of the dose escalation study is considered acceptable and standard for a Phase 1 oncology study. The recommended dose of lorlatinib is 100 mg QD orally, and the rationale behind the clinical dose setting and dosing interval has been adequately described and justified. The aims of the Phase 2 part were both efficacy (ORR) and safety, including Patient-related Outcomes (PROs).

Patient demographics were representative of an ALK-positive NSCLC patient population. Most of the patients enrolled in the Phase 2 part were white (48%) or Asian (37.5%) and the age and gender distribution was as could be expected, i.e. a mean age of 53.6 years and 57.1% were female patients. Only 45/334 (13.5%) of patients recruited, were aged >65 years, reflecting that the targeted patient population is generally younger due to the demographics of ALK-positive NSCLC and the study population are considered to be reflective of the patient population regarding age.

Data was not collected regarding smoking history and response. Other studies with ALK-inhibitors have shown some relationship between baseline smoking status and ORR, and although the efficacy was not absent, it seemed to be diminished in patients who were current smokers. The Applicant did not collect data on smoking in the pivotal study, but are doing so in the ongoing Phase 3 study and this is acceptable. The ECOG performance status at baseline was 0-1 in 96.2% of the cases in the Phase 1 part and 96.4% of the cases in the Phase 2 part. This is considered to be expected in the early clinical trial setting, however, more patients with PS 2 are expected in the target population.

The pre-treatment varied a lot between the cohorts and this is now reflected in the final wording of the indication. For example, newly presented data from the EXP-4 and EXP-5 cohorts show that the majority of patients had received prior crizotinib. For the applied indication, results from the EXP-3B to EXP-5 cohort are considered relevant and comprises 139 patients. It is noted that the cohort EXP-4:EXP-5 enrolled a high number of patients with brain metastases at baseline (75%), which is both considered representative of the possible target population and endorsed because efficacy in the CNS can be demonstrated. Overall, the study population is representative of a heavily pre-treated group of NSCLC patients, who became unresponsive to currently available ALK-inhibitors and, therefore, reflects an unmet medical need that can be recognised in clinical practice.

Efficacy data and additional analyses

The primary endpoint of the Phase 2 part was ORR by IRC (RECIST 1.1), while this endpoint was exploratory for the Phase 1 part. However, it is noted that the ORR was 39% (95%CI: 24.2-55.5) in the 41 patients with ALK-positive NSCLC in the Phase 1 study, and furthermore 22% of these patients had stable disease. In the CNS, a similar ORR was observed, which is considered clinically relevant in this setting. The ORR by IRC in the Phase 2 part was 42.9% (95%CI: 24.5-62.8) in EXP-3B and 39.6% (95%CI: 30.5-49.4) in EXP-4:EXP-5. In addition, approximately a third of the patients in both cohorts had stable disease. These results are not outstanding but within an expectable range, considering that the ORRs for other ALK inhibitors are around 50% in the second-line setting and that the ORR generally drops down through the lines of therapy. The magnitude of this effect is difficult to interpret in the absence of a comparator; however, the ability to induce complete remission, although in a very small fraction of subjects, is noted.

Regarding concordance rates, the response disagreement between ICR and Investigator assessments is around 20% for some EXP-groups. Differences are observed in most of the response categories, which compromise the robustness of data and seem larger in the assessment of CNS metastases.

In the CNS, the ORR by IRC was also showing clinically relevant efficacy, even in the later lines of ALK-inhibition therapy. It is noted that only few patients progressed in the CNS on lorlatinib and a stabilisation of CNS disease is also considered highly clinically relevant in this patient population. In the Phase 1 part, the overall discordance rate for objective overall response was 20.8% and 23.8% for intracranial responses. In the Phase 2 part, the overall discordance rate was 16.4% and 29.6% for intracranial responses. These discordance rates are surprisingly high, especially for the assessment of intracranial response in the Phase 2 part of the study, and the applicant suggests that differences may be related to different approaches between local radiologists and ICR to the imaging assessment; rather than providing a reassuring explanation.

Another source of uncertainty in evaluating IC ORR results is prior radiotherapy, since the lapsed period required between the end of radiotherapy and study entry was only 2 weeks for stereotactic or small field brain irradiation and 4 weeks for whole brain radiation. However, data submitted comparing IC-ORR in the efficacy population (pooled EXP-3B, EXP-4, EXP-5) for all patients, and excluding patients with an interval from the end of radiation and the start of lorlatinib treatment <8 weeks and <12 weeks, respectively excluded this bias (data not shown).

Plots of the cumulative incidence function of CNS progression, non-CNS progression, and death have been provided. In all analyses, patients receiving RT for brain metastases up to 8 weeks before lorlatinib were excluded. In the pooled EXP-3B:EXP-5 population, incidence of non-CNS progression was more frequently observed than CNS progression when considering all patient groups (overall efficacy population, patients with brain metastases at baseline, patients without brain metastases at baseline). On the contrary, in the EXP-3B cohort, CNS progression had a higher incidence than non-CNS progression. The interpretation of these data in the context of a single arm trial is intrinsically limited, and need confirmation in a larger cohort, as planned.

The initial data cutoff was 15 March 2017 and results from an updated data cutoff (02 February 2018) have been provided during the procedure with a median duration of follow-up for OS of approximately 20 months in the relevant cohorts. Median PFS with matured data was similar to the prior data cutoff and still considered clinically meaningful. A confirmatory randomised Phase 3 study is ongoing, comparing the efficacy and safety of lorlatinib to crizotinib in the first-line setting and from updated timelines, it is evident that the CSR is at the earliest expected by Q4 2021. The applicant is planning to randomise 280 patients in total and so far approximately 240 of the planned patients have been randomised, hence, full enrollment will be expected and final CSR should be available by the end of 2021.

The proposed confirmatory study is considered acceptable to complete a comprehensive evidence base in respect of safety and confirm the overall efficacy of lorlatinib. In addition, the applicant will conduct a single-arm efficacy study assessing lorlatinib in the second-line setting after disease progression on alectinib or ceritinib, as the CHMP considers that there are no standard of care in this setting. This single-arm efficacy study will confirm the efficacy of lorlatinib in the proposed second-line setting post second generation ALK inhibitors and this study is added to the already proposed confirmatory study of efficacy of lorlatinib in the first-line setting as a special obligation.

Overall, it is considered that mechanisms of on-target resistance to second-generation ALK-i as conferred by ALK-mutations subsequent to treatment are expected to develop regardless of lines of therapy, making the EXP-4:EXP-5 cohorts supportive of the EXP-3B data. The applicant has showed a similar therapeutic activity of lorlatinib in 2L post 2nd generation ALKi and 3L post crizotinib in the first line and a 2nd generation ALKi as 2L in terms of ORR and DOR, as well as a comparable response rate across the different cohorts, when data were analysed by ALK-mutational status, demonstrating benefit of lorlatinib and it's potential to satisfy the requirement for fulfilment of the unmet clinical need in both settings. Considering that the main limitation of the data supporting the 2L currently resides in

the limited sample size of EXP-3B (n=28 vs the 111 patients in EXP-4:EXP-5) the proposed PAES with consequent enlargement of the population of EXP-3B is regarded as confirmatory of the preliminary efficacy data in this population.

Among the secondary endpoints was time to response (TTP), which was approximately 1.4 months and similar in both the Phase 1 and 2 parts of the study. The responses were equally rapid in the CNS, demonstrating clinically relevant efficacy in this patient population with a high frequency of brain metastases. Median DOR in Phase 1 was 14.1 months, and 12.5 months and 7.0 months in the EXP-4 and EXP-5 cohorts respectively. In the CNS, DOR results from the EXP 4:EXP-5 cohort show encouraging results with a median DOR of 12.4 months. Median PFS in the Phase 1 was 5.3 months, but the CIs are wide. PFS data from Phase 2 have matured, and show clinically relevant results for the EXP-4:EXP-5 cohorts (6.9 months (95%CI: 5.4, 9.5). In addition, OS data from Phase 2 have also matured and a median OS of ~20 months in the relevant cohorts are also considered clinically relevant and no obvious selection bias of the results were observed.

The PRO results from the Phase 1 part were generally in line with the Phase 2 results. It is noted that many common cancer symptoms were significantly reduced on treatment but also that peripheral neuropathy at the following time points: Cycles 3 to 14, 16, and 33 was worsened clinically significantly. PRO results from the Phase 2 part showed similar improvements in the general cancer symptoms fatigue, pain, insomnia, and appetite loss. Approximately a third of the patients had worsening of peripheral neuropathy. Overall, PRO results is considered to reflect clinical benefit of lorlatinib and no obvious detrimental effect on QoL was observed.

A trend for lower activity in non-Asian patients was reported, however available data, including PK data, are too limited to draw any definitive conclusion (see Section 5.1 of the SmPC). The applicant will further investigate this observation in the B7461006 Clinical Study Report (see Annex II), in which ethnic origin (Asian vs non-Asian) constitutes a randomisation factor.

Additional efficacy data needed in the context of a conditional MA

Although a positive benefit-risk profile can be concluded, the data have limitations inherent to the non-comparative nature of the pivotal studies supporting the recommendation for a conditional MA. The applicant will submit the results of a Phase 3 study investigating lorlatinib versus crizotinib in the first line setting (CROWN study) which will further confirm the overall efficacy and safety of lorlatinib in ALK-positive NSCLC. Only 28 patients were included in the cohort EXP-3B including patients who have progressed after a second generation ALK inhibitors used as a first line treatment. As a consequence further data are needed to confirm the efficacy of lorlatinib in that setting and the applicant agreed to conduct a prospective observational single arm study to confirm the observed results from EXP-3B.

2.5.4. Conclusions on the clinical efficacy

The data from the pivotal 1001 study show clinically relevant efficacy of lorlatinib in a variation of cohorts according to prior treatments and this has been reflected in the final wording of the indication. The preliminary but clinically relevant efficacy of lorlatinib in the proposed second-line setting can be confirmed by a post-authorisation efficacy study.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to further confirm the overall efficacy of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the Phase 3 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.

- In order to further confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK-TKI therapy, the MAH should conduct a prospective single arm study investigating patients in that same setting. The clinical study report will be submitted by 30 June 2024.

2.6. Clinical safety

One clinical ongoing Phase 1/2 study with lorlatinib 100 mg orally once daily (QD) including adult patients with ALK-positive or ROS1-positive NSCLC was conducted and forms the basis of the safety evaluation. This clinical study consists of 2 portions, Phase 1 and Phase 2:

- The Phase 1 portion of the study was designed to estimate the maximum tolerated dose (MTD) for single-agent lorlatinib and to identify the recommended Phase 2 dose (RP2D). All treated patients (N=54) were included in the safety analysis set. The median duration of lorlatinib treatment in Phase 1 was 10.2 months.

- The Phase 2 portion of the study was designed to evaluate the anticancer activity of single-agent lorlatinib at the identified RP2D from Phase 1 in multiple subpopulations of patients based on ALK/ROS1 status and number of prior therapies. All treated patients (N=275) were included in the safety analysis set. The updated median duration of treatment in Phase 2 was 16.33 months.

Table 65: Summary of Clinical Studies and Datasets Supporting the Registration of Lorlatinib for the Treatment of ALK-Positive NSCLC

Study Title or Dataset Status	Study Design or Dataset Description	Treatment	Safety Population (n)[†]
Studies in Patients with Advanced Cancer			
B7461001 Phase 1/2 Study of PF-06463922 (An ALK/ROS1 Tyrosine Kinase Inhibitor) in Patients With Advanced Non-Small Cell Lung Cancer Harboring Specific Molecular Alterations *Ongoing*	Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamics (PD) and anti-cancer efficacy exploration study	Dose escalation cohorts in 21-day cycles: Phase 1: QD: 10, 25, 50, 75, 100, 150, 200 mg Or BID: 35, 75, 100 mg	54
		Phase 2 cohorts: 100 mg QD in 21-day cycles	275
		LIC (Japan only): 100 mg QD in 21-day cycles	3
		100-mg QD pooled group: 100 mg QD in 21-day cycles	295

The relevant dose of lorlatinib is 100 mg orally once daily (QD) and the safety of this dosing is the main focus of the safety assessment.

Patient exposure

The median duration of treatment was 10.18 months in Phase 1 patients and 17.41 months for the 100 mg QD cohort.

Table 66: Duration of treatment (Phase 1) – safety population

	Total N=54	100 mg QD N=17
Duration category, n (%)		
<3 months	15 (27.8)	5 (29.4)
3 - <6 months	4 (7.4)	0
6 - <9 months	4 (7.4)	1 (5.9)
9 - <12 months	5 (9.3)	2 (11.8)
12 - <15 months	1 (1.9)	0
15 - <18 months	2 (3.7)	1 (5.9)
18 – <21 months	4 (7.4)	2 (11.8)
21 - <24 months	9 (16.7)	3 (17.6)
≥24 months	10 (18.5)	3 (17.6)
Duration of treatment (months)		
Mean	13.84	14.16
Median	10.18	17.41
Range	(0.07, 35.68)	(0.07, 29.07)

Source: Table 14.4.1.1.1
This table is based on descriptive statistics.
The duration of treatment was calculated as (Last dose date - Cycle 1 Day 1 + 1) / 30.44.
Abbreviations: n/N=number of patients; QD=once daily

Table 67: Drug administration (Phase 1) – safety population

	Total N=54	100 mg QD N=17
Relative Dose Intensity[a] (%)		
Median	99.18	98.77
Range	(14.29 - 483.10)[d]	(70.67 - 100.00)
Dose reductions[b], n (%)	14 (25.9)	0
Dose delays[c], n (%)	44 (81.5)	13 (76.5)

Source: Tables 14.4.1.3.1 and Table 14.4.1.4.1
Abbreviations: n/N=number of patients
a. Relative dose intensity (%) = 100 × (overall actual total dose) / (intended total dose per day × number of days from Cycle 1 Day 1 to last dose of study drug).
b. Dose reduction: Prescribed dose is less than previously prescribed dose
c. Dose delay: Any 0 mg dose administered for any duration of time or dose missed on unknown dates
d. Dose increases occurred due to intra-patient dose escalation beyond the initial assigned dose resulting in more than 100% overall relative dose intensity (Table 16.2.5.1.2.1).

The median duration of treatment was 16.33 months in Phase 2 patients. The number of patients still receiving study treatment is 130 (44.1%).

Table 68: Duration of treatment (Phase 2) – safety population

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=60)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=275)
Duration category, n (%)							
<3 months	1 (3.3)	2 (7.4)	13 (21.7)	12 (18.5)	12 (26.1)	11 (23.4)	51 (18.5)
3 - <6 months	2 (6.7)	4 (14.8)	3 (5.0)	10 (15.4)	5 (10.9)	9 (19.1)	33 (12.0)
6 - <9 months	10 (33.3)	9 (33.3)	23 (38.3)	16 (24.6)	16 (34.8)	9 (19.1)	83 (30.2)
9 - <12 months	9 (30.0)	6 (22.2)	11 (18.3)	9 (13.8)	8 (17.4)	6 (12.8)	49 (17.8)
12 - <15 months	2 (6.7)	3 (11.1)	4 (6.7)	10 (15.4)	2 (4.3)	5 (10.6)	26 (9.5)
15 - <18 months	6 (20.0)	3 (11.1)	6 (10.0)	8 (12.3)	3 (6.5)	7 (14.9)	33 (12.0)
Duration of treatment (months)							
Mean	10.17	8.75	7.77	8.15	7.06	7.92	8.13
Median	9.38	8.71	7.98	7.62	7.69	8.74	8.31
Range	(1.68, 17.08)	(0.36, 15.83)	(0.26, 17.77)	(0.23, 17.48)	(0.39, 17.28)	(0.03, 17.51)	(0.03, 17.77)

Source: Table 14.4.1.1.2
This table is based on descriptive statistics.
The duration of treatment was calculated as (Last dose date - Cycle 1 Day 1 + 1) / 30.44.
Abbreviations: n/N=number of patients.

Table 69: Drug administration (Phase 2) – safety population

	EXP-1 (N=30)	EXP-2 (N=27)	EXP-3 (N=60)	EXP-4 (N=65)	EXP-5 (N=46)	EXP-6 (N=47)	Total (N=275)
Relative Dose Intensity[a] (%)							
Median	99.73	98.96	99.22	96.05	97.33	99.61	98.47
Range	63.94 - 100.00	23.38 - 100.36	48.92 - 104.17	30.95- 109.68	37.83 - 100.00	51.43 - 100.43	23.38 - 109.68
Dose reductions[b], n (%)	8 (26.7)	7 (25.9)	15 (25.0)	14 (21.5)	8 (17.4)	12 (25.5)	64 (23.3)
Dose delays[c], n (%)	16 (53.3)	16 (59.3)	36 (60.0)	51 (78.5)	39 (84.8)	30 (63.8)	188 (68.4)

Source: Tables 14.4.1.3.2 and Table 14.4.1.4.2
Abbreviation: n/N=number of patients.
a. Relative dose intensity (%) = 100 × (overall actual total dose) / (intended total dose per day × number of days from Cycle 1 Day 1 to last dose of study drug).
b. Dose reduction: Prescribed dose is less than previously prescribed dose
c. Dose delay: Any 0 mg dose administered for any duration of time or dose missed on unknown dates

In the Phase 1 part, only 17 of 41 patients were exposed to the proposed dose (100mg QD), but of these 12 patients were treated for more than 6 months at a high dose intensity 98.77% (range 70.67-100.00).

Table 70: Duration of treatment (subjects starting lorlatinib 100 mg QD*) – Safety analysis set

	100 mg QD (N=295)	
	n	(%)
Duration of Treatment (Months) - Category [1]		
<3 Months	56	(19.0)
3 Months - < 6 Months	29	(9.8)
6 Months - < 9 Months	25	(8.5)
9 Months - < 12 Months	19	(6.4)
12 Months - < 15 Months	12	(4.1)
15 Months - < 18 Months	34	(11.5)
18 Months - < 21 Months	62	(21.0)
21 Months - < 24 Months	13	(4.4)
>= 24 Months	45	(15.3)
Duration of Treatment (Months) [1]		
Mean	13.78	
Median	16.33	
Min, Max	(0.03, 39.72)	
Days on Drug (Months) - Category [2]		
<3 Months	58	(19.7)
3 Months - < 6 Months	33	(11.2)
6 Months - < 9 Months	22	(7.5)
9 Months - < 12 Months	20	(6.8)
12 Months - < 15 Months	16	(5.4)
15 Months - < 18 Months	42	(14.2)
18 Months - < 21 Months	54	(18.3)
21 Months - < 24 Months	10	(3.4)
>= 24 Months	40	(13.6)
Days on Drug (Months) [2]		
Mean	13.21	
Median	14.68	
Min, Max	(0.03, 39.65)	

* Includes Phase 1, Phase 2 and Japan LIC
[1] The duration is defined as the total number of months =(Last Dose Date - Cycle 1 Day 1 + 1)/30.44.
[2] Days on drug is defined as the total number of months on which the drug was actually administered since cycle 1 day 1.
For patients receiving only lead-in dose, the treatment duration is defined as 1 day. For other patients, the calculations are carried out considering the treatment period in the study except lead-in cycle.
PFIZER CONFIDENTIAL Source Data: Table 16.2.5.1.2.2.ema.1 Date of Reporting Dataset Creation: 20APR2018 Date of Table Generation: 06JUN2018 (03:29)

Adverse events

Table 71: Adverse Events (100-mg QD Pooled Group) - Safety Population

	All-causality (N=295) n (%)	Treatment-Related (N=295) n (%)
Patients evaluable for AEs	295	295
Number of AEs	3392	1835
Patients with AEs	294 (99.7)	280 (94.9)
Patients with SAEs	98 (33.2)	20 (6.8)
Patients with Grade 3 or 4 AEs	184 (62.4)	121 (41.0)
Patients with Grade 5 AEs	33 (11.2)	0
Patients discontinued due to AEs	21 (7.1)[a]	7 (2.4)
Patients with dose reduction due to AEs	65 (22.0)	62 (21.0)
Patients with temporary discontinuation due to AEs	132 (44.7)	89 (30.2)

Source: Study 1001 Table 14.3.1.2.1.2.f1 and Table 14.3.1.3.1.2.f1
Abbreviation: AE=adverse event; n=number of patients; SAE=serious adverse event; N/n=number.
a. One (1) patient discontinued treatment due to progressive disease with fatigue being reported as an AE, which was mistakenly indicated as primary reason of discontinuation.

Table 72: All-Causality and Treatment-Related Adverse Events With Clustering by MedDRA Preferred Terms and Maximum CTCAE Grades (All Grades and Grades 3 and 4 by Decreasing Order of Frequency (> 10%), All Cycles (100-mg QD Pooled Group) - Safety Population
100-mg QD pooled group (N=295)

Preferred Term	All-Causality			Treatment-Related		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any AEs[a]	294 (99.7)	131 (44.4)	24 (8.1)	280 (94.9)	107 (36.3)	14 (4.7)
**HYPERCHOLESTEROLEMIA	243 (82.4)	41 (13.9)	5 (1.7)	241 (81.7)	40 (13.6)	5 (1.7)
**HYPERTRIGLYCERIDEMIA	179 (60.7)	39 (13.2)	7 (2.4)	178 (60.3)	39 (13.2)	7 (2.4)
**EDEMA	151 (51.2)	7 (2.4)	0	129 (43.7)	6 (2.0)	0
**PERIPHERAL NEUROPATHY	129 (43.7)	7 (2.4)	0	88 (29.8)	5 (1.7)	0
Dyspnoea	69 (23.4)	11 (3.7)	3 (1.0)	9 (3.1)	1 (0.3)	0
**COGNITIVE EFFECTS	68 (23.1)	5 (1.7)	0	53 (18.0)	4 (1.4)	0
**FATIGUE	68 (23.1)	1 (0.3)	0	39 (13.2)	1 (0.3)	0
**MOOD EFFECTS	62 (21.0)	4 (1.4)	0	43 (14.6)	2 (0.7)	0
Weight increased	61 (20.7)	7 (2.4)	0	54 (18.3)	6 (2.0)	0
Arthralgia	58 (19.7)	0	0	30 (10.2)	0	0
Diarrhoea	52 (17.6)	2 (0.7)	0	30 (10.2)	1 (0.3)	0
Cough	48 (16.3)	0	0	3 (1.0)	0	0
Dizziness	44 (14.9)	2 (0.7)	0	25 (8.5)	2 (0.7)	0
Headache	44 (14.9)	2 (0.7)	0	16 (5.4)	0	0
Nausea	43 (14.6)	1 (0.3)	1 (0.3)	23 (7.8)	0	0
Constipation	42 (14.2)	0	0	24 (8.1)	0	0
**VISION DISORDER	39 (13.2)	1 (0.3)	0	21 (7.1)	0	0
Anaemia	37 (12.5)	9 (3.1)	0	18 (6.1)	2 (0.7)	0
Aspartate aminotransferase increased	35 (11.9)	2 (0.7)	1 (0.3)	31 (10.5)	1 (0.3)	0
Back pain	35 (11.9)	2 (0.7)	0	5 (1.7)	0	0
Alanine aminotransferase increased	33 (11.2)	2 (0.7)	1 (0.3)	28 (9.5)	2 (0.7)	0
Pain in extremity	33 (11.2)	0	0	12 (4.1)	0	0
Lipase increased	32 (10.8)	15 (5.1)	4 (1.4)	22 (7.5)	10 (3.4)	1 (0.3)
Myalgia	31 (10.5)	0	0	18 (6.1)	0	0

Source: Study Table 14.3.1.2.9.1.2.2.2.f1 and Table 14.3.1.3.9.1.2.2.2.f1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of patients.
Most (25/33) patients who had a Grade 5 event in Phase 2 were due to Disease Progression. Details on remaining patients can be found in Section 2.7.4.2.1.2
* =Cluster terms as indicated (see Table 84)
a= Total number independent of frequency cutoff used in the title
Additional all-causality Grade 3 /4 events (>2 patients) not listed in the table were: Vomiting (3 patients Grade 3), Hyperglycaemia (7 patients Grade 3), Hypertension (10 patients, Grade 3), Pleural effusion (8 patients Grade 3), Pneumonia (7 patients Grade 3), Abdominal pain (3 patients, Grade 3), Hypophosphatemia (6 patients, Grade 3), Fall (3 patients, Grade 3), Hypoxia (4 patients, Grade 3, 1 patient Grade 4), Pericardial effusion 3 patients, Grade 3), Mental status change (4 patients, Grade 3), Pulmonary embolism (4 patients, Grade 3), Respiratory failure (3 patients Grade 3, 2 patients, Grade 4), Superior vena cava syndrome (3 patients, Grade 3), Sepsis (3 patients Grade 4), Amylase increased (7 patients Grade 3 and 1 patient Grade 4), Acute respiratory failure (2 patients Grade 3 and 2 patients Grade 4).

Adverse drug reactions (ADRs)

ADRs were identified based on internal clinical and safety review of available safety data and included AEs and cluster terms of Study 1001 considered as associated to lorlatinib (as listed in the table below)

Table 73: Adverse Drug Reactions in 295 Patients with ALK-positive or ROS1-positive Advanced NSCLC who Received Lorlatinib 100 mg QD in Study B7461001 – Safety Update

System organ class and adverse reaction	Frequency category	All Grades	Grades 3-4
Blood and lymphatic system disorders			
Anaemia	Very common	15.9	5.1
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	84.4	16.6
Hypertriglyceridaemia[b]	Very common	67.1	16.6
Psychiatric disorders			
Mood effects[c]	Very common	22.7	1.7
Hallucinations[d]	Common	7.8	1.0
Nervous system disorders			
Cognitive effects[e]	Very common	28.8	2.0
Peripheral neuropathy[f]	Very common	47.8	2.7
Headache	Very common	18.0	0.7
Speech effects[g]	Common	9.8	0.3
Eye disorders			
Vision disorder[h]	Very common	15.3	0.3
Gastrointestinal disorders			
Diarrhoea	Very common	22.7	1.0
Nausea	Very common	18.3	0.7
Constipation	Very common	15.9	0
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	24.7	0.7
Myalgia[i]	Very common	19.3	0
General disorders and administration site conditions			
Oedema[j]	Very common	54.6	2.4
Fatigue[k]	Very common	28.1	0.7
Investigations			
Weight increased	Very common	26.4	5.4
Lipase increased	Very common	13.9	8.8
Amylase increased	Very common	10.2	3.1
Electrocardiogram PR prolongation	Uncommon	0.7	0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis[l]	Common	1.4	1.0
Skin and subcutaneous tissue disorders			
Rash[m]	Very common	14.2	0.3

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, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress).
[d] Hallucinations (including hallucination, auditory 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, carpal tunnel syndrome, dysaesthesia, formication, gait disturbance, hypoaesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, 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] Myalgia (including musculoskeletal pain, myalgia)
[j] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
[k] Fatigue (including asthenia, fatigue).
[l] Pneumonitis (including interstitial lung disease, pneumonitis).
[m] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).

Adverse events of special interest

Table 74: Prevalence of Treatment-Emergent Adverse Events for Individual MedDRA Preferred Terms and Cluster Terms of Special Interest by Preferred Term and Maximum CTCAE Grade (All-causality, by Cycle) (Phase 2) - Safety Population

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle≥ 8
	N=274	N=263	N=250	N=238	N=225	N=218	N=210	N=208
HYPERCHOLESTEROLEMIA*	180 (65.7)	202 (76.8)	193 (77.2)	182 (76.5)	175 (77.8)	174 (79.8)	167 (79.5)	172 (82.7)
HYPERTRIGLYCERIDEMIA*	115 (42.0)	131 (49.8)	133 (53.2)	131 (55.0)	123 (54.7)	126 (57.8)	119 (56.7)	130 (62.5)
EDEMA*	42 (15.3)	65 (24.7)	81 (32.4)	90 (37.8)	93 (41.3)	91 (41.7)	80 (38.1)	95 (45.7)
PERIPHERAL NEUROPATHY*	15 (5.5)	26 (9.9)	36 (14.4)	57 (23.9)	64 (28.4)	64 (29.4)	74 (35.2)	98 (47.1)
COGNITIVE EFFECTS*	19 (6.9)	21 (8.0)	26 (10.4)	30 (12.6)	30 (13.3)	32 (14.7)	30 (14.3)	49 (23.6)
MOOD EFFECTS*	18 (6.6)	20 (7.6)	27 (10.8)	27 (11.3)	25 (11.1)	22 (10.1)	25 (11.9)	32 (15.4)
SPEECH EFFECTS*	8 (2.9)	7 (2.7)	9 (3.6)	12 (5.0)	14 (6.2)	11 (5.0)	8 (3.8)	12 (5.8)
Weight increased	11 (4.0)	15 (5.7)	23 (9.2)	31 (13.0)	33 (14.7)	36 (16.5)	39 (18.6)	48 (23.1)
VISION DISORDER*	12 (4.4)	10 (3.8)	9 (3.6)	12 (5.0)	12 (5.3)	13 (6.0)	13 (6.2)	23 (11.1)
Hepatic enzyme increased	0	0	1 (0.4)	1 (0.4)	0	0	0	0
Electrocardiogram QT prolonged	10 (3.6)	12 (4.6)	16 (6.4)	11 (4.6)	9 (4.0)	8 (3.7)	8 (3.8)	8 (3.8)
Interstitial lung disease	0	0	0	1 (0.4)	0	0	0	0
Pneumonitis	0	1 (0.4)	0	1 (0.4)	0	1 (0.5)	0	0
Atrioventricular block first degree	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.9)	1 (0.5)	1 (0.5)
Atrioventricular block complete	1 (0.4)	0	0	0	0	0	0	0
Pancreatitis	0	0	1 (0.4)	0	0	0	0	0

*=cluster terms as indicated
Abbreviation: N=number, AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities

Hyperlipidaemia

Table 75: Summary of Treatment-Emergent Hyperlipidaemia Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (Phase 1) - All-causality and Treatment-related - Safety Population

	N = 54											
	All-Causality						Treatment-Related					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
PT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	41	(75.9)	7	(13.0)	4	(7.4)	40	(74.1)	8	(14.8)	3	(5.6)
Hypercholesterolaemia	31	(57.4)	3	(5.6)	3	(5.6)	30	(55.6)	3	(5.6)	3	(5.6)
Hypertriglyceridaemia	17	(31.5)	3	(5.6)	1	(1.9)	17	(31.5)	2	(3.7)	0	(0.0)
Blood cholesterol increased	11	(20.4)	1	(1.9)	0	(0.0)	11	(20.4)	1	(1.9)	0	(0.0)
Blood triglycerides increased	8	(14.8)	2	(3.7)	0	(0.0)	8	(14.8)	2	(3.7)	0	(0.0)

Source: Study 1001 CSR Table 14.3.1.2.9.1.2.4.1 and Table 14.3.1.3.9.1.2.4.1
AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number

Table 76: Summary of Treatment-Emergent Hyperlipidemia Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency(All Cycles) (Phase 2) - All-causality and Treatment-related - Safety Population

	N = 275											
	All-Causality						Treatment-Related					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
PT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	236	(85.8)	61	(22.2)	10	(3.6)	234	(85.1)	60	(21.8)	10	(3.6)
Hypertriglyceridaemia	155	(56.4)	35	(12.7)	7	(2.5)	154	(56.0)	35	(12.7)	7	(2.5)
Hypercholesterolaemia	145	(52.7)	26	(9.5)	1	(0.4)	144	(52.4)	25	(9.1)	1	(0.4)
Blood cholesterol increased	96	(34.9)	16	(5.8)	3	(1.1)	96	(34.9)	16	(5.8)	3	(1.1)
Blood triglycerides increased	17	(6.2)	2	(0.7)	1	(0.4)	17	(6.2)	2	(0.7)	1	(0.4)

Source: Study 1001 CSR Table 14.3.1.2.9.1.2.4.2 and Table 14.3.1.3.9.1.2.4.2
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number

Table 77: Descriptive Summary of Time to Medication to Lower Cholesterol and/ or Triglycerides (Phase 1 and Phase 2) - Safety Population

Time to Start (in Days)	n (%)	Mean	SD	Median	Min, Max
Phase 1 (N=54)					
Medication to Lower Cholesterol and/ or Triglyceride	39 (72.2)	65.2	99.67	28	(8, 580)
Phase 2 (N=275)					
Medication to Lower Cholesterol and/ or Triglyceride	222 (80.7)	27.3	27.07	18	(1, 190)
100-mg QD pooled group (N=295)					
Medication to Lower Cholesterol and/ or Triglyceride	239 (81.0)	27.3	26.92	20	(1, 190)

Source: Study 1001 CSR Table 14.4.2.4.1 and Table 14.4.2.4.2
Medication used to lower cholesterol and/or triglycerides list: Atorvastatin, Atorvastatin Calcium, Bezafibrate, Ezetimibe, Fenofibrate, Fish Oil, Gemfibrozil, Inegy, Lovastatin, Nicotinic Acid, Omega-3 Triglycerides, Omega-3-Acid Ethyl Ester, Pitavastatin, Pitavastatin Calcium, Pravastatin, Pravastatin Sodium, Rosuvastatin, Rosuvastatin Calcium, Simvastatin, Tocopheryl Nicotinate.
Time to start of medication to lower cholesterol and/or triglycerides is calculated from Day -7 and/or C1D1 if this is the first dose, to the start of relevant medications.
Abbreviation: N/n=number; SD=standard deviation; min=minimum; max=maximum

Table 78: Summary of Treatment-Emergent Hyperlipidaemia* Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population – Data cutoff date: 02 February 2018

	N = 295					
	All-Causality			Treatment-Related		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	**259 (87.8)**	**67 (22.7)**	**13 (4.4)**	**256 (86.8)**	**67 (22.7)**	**12 (4.1)**
Hypertriglyceridaemia	183 (62.0)	39 (13.2)	8 (2.7)	181 (61.4)	39 (13.2)	8 (2.7)
Hypercholesterolaemia	164 (55.6)	28 (9.5)	3 (1.0)	162 (54.9)	28 (9.5)	2 (0.7)
Blood cholesterol increased	103 (34.9)	16 (5.4)	3 (1.0)	103 (34.9)	16 (5.4)	3 (1.0)
Blood triglycerides increased	21 (7.1)	3 (1.0)	1 (0.3)	21 (7.1)	3 (1.0)	1 (0.3)

Source: Table 14.3.1.2.9.1.2.4.2.ema.1 and Table 14.3.1.3.9.1.2.4.2.ema.1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/ n=number, QD=once daily.
* Hyperlipidemia includes the cluster terms of HYPERCHOLESTEROLEMIA and HYPERTRIGLYCERIDEMIA

Overall in the 100-mg QD pooled group (n=295), 76.3% of patients were treated with lipid-lowering therapy only; however, in 19.0% and 38.4% of subjects with hypercholesterolemia or hypertriglyceridemia respectively, the AE did not resolve.

The median time to increased levels of cholesterol values of 500 mg/dL or higher and blood triglycerides values of 1,000 mg/dl or higher was 201 days (range 42 – 518 days) and 127 days (range 15 – 358 days), respectively.

Oedema

Table 79: Summary of Treatment-Emergent OEDEMA Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (100-mg QD Pooled Group) - All-causality and Treatment-related -Safety Population

	N = 295											
	All-Causality						Treatment-Related					
	All Grades		Grade 3		Grade 4		All Grades		Grade 3		Grade 4	
PT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	151	(51.2)	7	(2.4)	0	(0.0)	129	(43.7)	6	(2.0)	0	(0.0)
Oedema peripheral	123	(41.7)	4	(1.4)	0	(0.0)	105	(35.6)	4	(1.4)	0	(0.0)
Oedema	22	(7.5)	2	(0.7)	0	(0.0)	19	(6.4)	2	(0.7)	0	(0.0)
Peripheral swelling	18	(6.1)	1	(0.3)	0	(0.0)	13	(4.4)	0	(0.0)	0	(0.0)
Generalised oedema	2	(0.7)	1	(0.3)	0	(0.0)	2	(0.7)	1	(0.3)	0	(0.0)
Swelling	2	(0.7)	0	(0.0)	0	(0.0)	0	0	0	0	0	0

Source: Study 1001 SCS Table 14.3.1.2.9.1.2.10.2.f1 and Table 14.3.1.3.9.1.2.10.2.f1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number

Peripheral neuropathy

Table 80: Summary of Treatment-Emergent Peripheral Neuropathy Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles, all causality) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population - Data cutoff date: 02 February 2018

	(N = 295)					
	All-Causality			Treatment-Related		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AEs	**141 (47.8)**	**8 (2.7)**	**0**	**99 (33.6)**	**6 (2.0)**	**0**
Paraesthesia	42 (14.2)	1 (0.3)	0	31 (10.5)	1 (0.3)	0
Neuropathy peripheral	39 (13.2)	3 (1.0)	0	34 (11.5)	3 (1.0)	0
Peripheral sensory neuropathy	28 (9.5)	1 (0.3)	0	24 (8.1)	1 (0.3)	0
Muscular weakness	17 (5.8)	1 (0.3)	0	3 (1.0)	0	0
Gait disturbance	14 (4.7)	1 (0.3)	0	2 (0.7)	0	0
Carpal tunnel syndrome	10 (3.4)	1 (0.3)	0	4 (1.4)	1 (0.3)	0
Hypoaesthesia	10 (3.4)	0	0	7 (2.4)	0	0
Dysaesthesia	6 (2.0)	0	0	4 (1.4)	0	0
Neuralgia	3 (1.0)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Neurotoxicity	3 (1.0)	0	0	3 (1.0)	0	0
Burning sensation	1 (0.3)	0	0	1 (0.3)	0	0
Formication	1 (0.3)	0	0	1 (0.3)	0	0
Peroneal nerve palsy	1 (0.3)	0	0	0	0	0
Sensory disturbance	1 (0.3)	0	0	0	0	0

Source: Table 14.3.1.2.9.1.2.3.2.ema.1 and Table 14.3.1.3.9.1.2.3.2.ema.1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number, QD=once daily, SCS=summary of clinical safety, SU=safety update.

Events of neuropathy were frequent both in Phase 1 and 2, however, high-grade events were rare. Median time to PERIPHERAL NEUROPATHY was 85 days (range, 1-723) and the median duration was 258 days (range 1-1041) in the 100mg group. Updated data showed a small increase of treatment-related AEs.

Central nervous system (CNS) effects

Events of cognitive effects were frequent in all grades in the Phase 1 part and most events were considered treatment-related. Even though high-grade events were rare, a quarter of the patients were affected and many PTs were used.

An analysis of CNS effects was submitted identifying 4 defined patient populations:

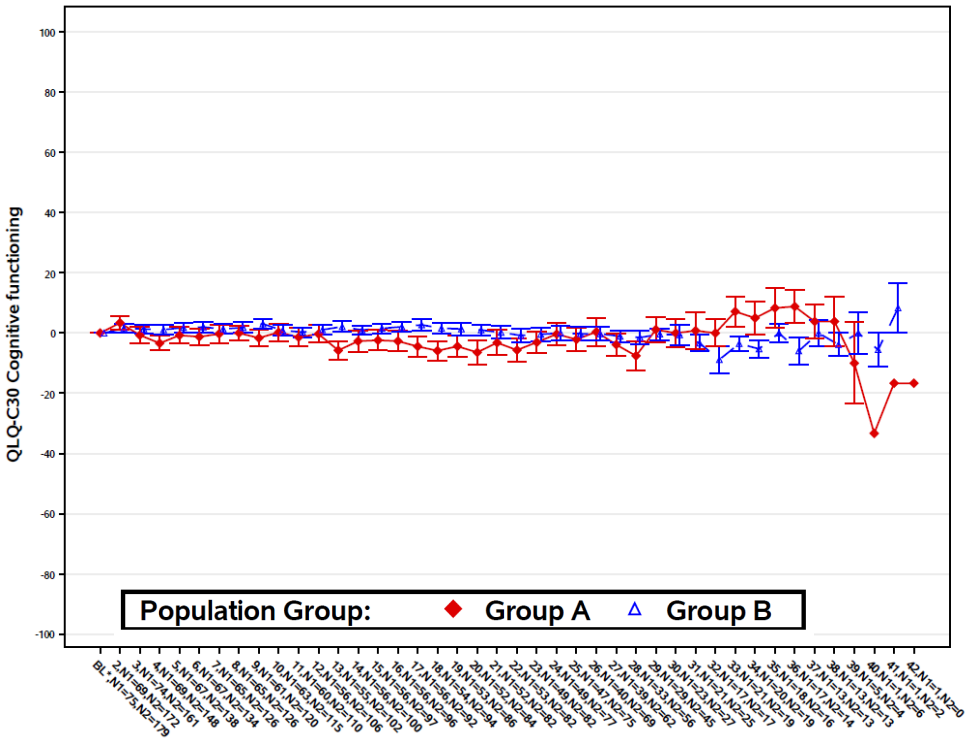
- Group A Patients who reported any Grade (1-4) of Cognitive Effects AEs.

- Subgroup A1 Patients who reported maximum Grade 1 or 2 of Cognitive Effects AEs.

- Subgroup A2 Patients who reported maximum Grade 3 or 4 of Cognitive Effects AEs.

- Group B Patients who reported no Cognitive Effects AEs (control group).

Patients for whom cognitive effect adverse events were reported were not systematically evaluated for radiological alterations, as the focus of the radiological evaluation was on changes in tumour growth. There were no spontaneous reports of radiological alterations in patients with cognitive effect adverse events.



BL*- Baseline is defined as the last PRO assessment prior to first dose, which could be day -7 or C1D1 window. The visit label and visit windows are applied for the analysis of the PRO endpoints. In the case of multiple records for a patient within a particular visit window, then use the assessment which is closest to the target day. Group A is defined as patients who reported any Grade(1-4) of Cognitive Effects AEs. Group B is defined as patients who reported no Cognitive Effects AEs. N1 and N2 are numbers of subjects at risk for Group A and B respectively. It is defined as the number of subjects who completed the scale at baseline and at the respective cycle. A questionnaire is considered complete if at least one question is answered regardless of whether DONE/NOT DONE is checked in the CRF page. Mean Change (+/-) SE was truncated to be in [-100,100]. Figures drawn on a scale of [-100,100] to show trends. In the unlikely event that both (or all) the records are equidistant from the target day the patient's last assessment within that visit window was used.

Source: Module 5.3.5.3 D120 Supporting Table ema.175.1

Figure 31: Plot of Mean Change from Baseline (+/-) SE over time for EORTC QLQ-C30 Cognitive Function (Group A and B) - PRO Evaluable Population, Pooled EXP-1: EXP-6

Comparable degree of variation in emotional functioning can be observed between the 2 groups of people who either suffered or not AEs within the category of mood effects.

Table 81: Summary of EORTC QLQ-C30 Cognitive Function Scales Change (Group A, A1, A2 and B) - PRO Evaluable Population, Pooled EXP-1:EXP-6

Functional scales		Pooled EXP-1: EXP-6 (N=255)							
		Improved [1]		Stable [2]		Worsening [3]		Missing	
		n	(%)	n	(%)	n	(%)	n	(%)
Cognitive functioning	Group A	19	(7.5)	28	(11.0)	28	(11.0)	0	(0.0)
	Group A1	17	(6.7)	26	(10.2)	27	(10.6)	0	(0.0)
	Group A2	2	(0.8)	2	(0.8)	1	(0.4)	0	(0.0)
	Group B	38	(14.9)	107	(42.0)	34	(13.3)	1	(0.4)

% = (n/N)*100. n is the number of distinct patients who met the scale change criterion. N is the number of subjects in PRO population with mean scale scores. A Questionnaire is considered complete if at least one question is answered regardless of whether DONE/NOT DONE is checked in the CRF page. In the case of multiple records for a patient within a particular visit window, use the assessment which is closest to the target day. In the unlikely event that both (or all) the records are equidistant from the target day, use the patient's last assessment within that visit window. [1]In the functioning scales improvement is defined as an increase of at least 10 points. [2]Not improved nor worsened will be considered 'stable'. [3]Worsening is defined as a decrease of at least 10 points. Group A is defined as patients who reported any Grade(1-4) of Cognitive Effects AEs. Group A1 is defined as patients who reported maximum Grade 1 or 2 of Cognitive Effects AEs. Group A2 is defined as patients who reported maximum Grade 3 or 4 of Cognitive Effects AEs. Group B is defined as patients who reported no Cognitive Effects AEs.

Source: Module 5.3.5.3 D120 Supporting Table ema.175.3

A >10-point decline in patient-reported cognitive function was detected in 37.3% of cases among subjects with Cognitive Effect AEs (Group A), compared to 19.0% in Group B.

Table 82: Summary of Treatment-Emergent COGNITIVE EFFECTS Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population - Data cutoff date: 02 February 2018

	(N = 295)					
	All-Causality			Treatment-Related		
PT	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AEs	**85 (28.8)**	**6 (2.0)**	**0**	**68 (23.1)**	**4 (1.4)**	**0**
Memory impairment	34 (11.5)	0	0	29 (9.8)	0	0
Amnesia	25 (8.5)	0	0	21 (7.1)	0	0
Cognitive disorder	21 (7.1)	2 (0.7)	0	19 (6.4)	2 (0.7)	0
Confusional state	13 (4.4)	2 (0.7)	0	5 (1.7)	1 (0.3)	0
Disturbance in attention	10 (3.4)	0	0	10 (3.4)	0	0
Delirium	3 (1.0)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Mental impairment	3 (1.0)	0	0	2 (0.7)	0	0
Attention deficit/ hyperactivity disorder	2 (0.7)	0	0	2 (0.7)	0	0
Dementia	1 (0.3)	0	0	0	0	0
Disorientation	1 (0.3)	1 (0.3)	0	0	0	0
Reading disorder	1 (0.3)	0	0	0	0	0

Source: Table 14.3.1.2.9.1.2.7.2.ema.1 and Table 14.3.1.3.9.1.2.7.2.ema.1

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number, QD=once daily, SCS=summary of clinical safety, SU=safety update.

Mood effects

Table 83: Summary of Treatment-Emergent MOOD EFFECTS Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population - Data cutoff date: 02 February 2018

	(N = 295)					
	All-Causality			Treatment-Related		
PT	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AEs	**67 (22.7)**	**5 (1.7)**	**0**	**46 (15.6)**	**3 (1.0)**	**0**
Irritability	18 (6.1)	3 (1.0)	0	17 (5.8)	2 (0.7)	0
Anxiety	17 (5.8)	1 (0.3)	0	4 (1.4)	0	0
Depression	16 (5.4)	2 (0.7)	0	11 (3.7)	2 (0.7)	0
Affect lability	7 (2.4)	0	0	6 (2.0)	0	0
Affective disorder	5 (1.7)	0	0	4 (1.4)	0	0
Personality change	5 (1.7)	0	0	4 (1.4)	0	0
Mood altered	4 (1.4)	0	0	3 (1.0)	0	0
Agitation	3 (1.0)	1 (0.3)	0	2 (0.7)	1 (0.3)	0
Mood swings	3 (1.0)	0	0	3 (1.0)	0	0
Aggression	2 (0.7)	0	0	2 (0.7)	0	0
Depressed mood	2 (0.7)	0	0	1 (0.3)	0	0
Euphoric mood	1 (0.3)	0	0	1 (0.3)	0	0
Mania	1 (0.3)	0	0	0	0	0
Stress	1 (0.3)	0	0	0	0	0

Source: Table 14.3.1.2.9.1.2.5.2.ema.1 and Table 14.3.1.3.9.1.2.5.2.ema.1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number, QD=once daily, SCS=summary of clinical safety, SU=safety update.

Speech effects

Table 84: Summary of Treatment-Emergent SPEECH EFFECTS Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population - Data cutoff date: 02 February 2018

	(N = 295)					
	All-Causality			Treatment-Related		
PT	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AEs	**29 (9.8)**	**1 (0.3)**	**0**	**25 (8.5)**	**1 (0.3)**	**0**
Dysarthria	12 (4.1)	0	0	9 (3.1)	0	0
Slow speech	10 (3.4)	1 (0.3)	0	10 (3.4)	1 (0.3)	0
Speech disorder	7 (2.4)	0	0	6 (2.0)	0	0

Source: Table 14.3.1.2.9.1.2.6.2.ema.1 and Table 14.3.1.3.9.1.2.6.2.ema.1
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number, QD=once daily, SCS=summary of clinical safety, SU=safety update.

The median time to onset was 42 days (range, 1-727). No patients permanently discontinued treatment associated with this event. One patient required a dose reduction and subsequently a temporary treatment discontinuation for a second event of *Dysarthria*.

Cumulative lorlatinib exposure seems to increase the risk of COGNITIVE EFFECTS AEs, as revealed by the increasing AEs proportions over time.

Weight gain

Phase 1

A total of 12/54 (22.2%) patients had all-causality Weight increased with a median time to first onset of 104 days (Range: 8-559). The median duration was 371 days, most events were Grade 1 (9.3%), Grade 2 (5.6%) or Grade 3 (7.4%) in severity and none required temporary discontinuation or dose reduction. No patients permanently discontinued treatment. Ten (10; 18.5%) patients had treatment-related AEs, none were Grade 4, 3 were Grade 3 and the remainder was Grade 1 or 2 in severity. There were 19 (35.2%) patients with a weight increase of 10 - 20%, and 9 (16.7%) patients with weight increase of ≥20%.

Phase 2

Table 85: Categorical Summary of Postbaseline Vital Sign and Body Weight Data, (100-mg QD Pooled Group) - Safety Population

Parameter	Criteria	100-mg QD pooled group N	100-mg QD pooled group n (%)
Sitting SBP (mmHg)			
Maximum increase from baseline	≥40	290	26 (9.0)
	≥60	290	1(0.3)
Maximum decrease from baseline	≥40	290	10 (3.4)
	≥60	290	0
Sitting DBP (mmHg)			
Maximum increase from baseline	≥20	290	76 (26.2)
	≥40	290	3 (1.0)
Maximum decrease from baseline	≥20	290	42 (14.5)
	≥40	290	0
Sitting pulse rate (bpm)			
Absolute value	<50	293	6 (2.0)
	>120	293	19 (6.5)
Maximum increase from baseline	≥30	289	56 (19.4)
Maximum decrease from baseline	≥30	289	26 (9.0)
Body Weight (kg)			
Maximum increase from baseline	10%-20%	282	87 (30.9)
	≥20%	282	38 (13.5)
Maximum decrease from baseline	≥10%	282	13 (4.6)

Source: Study 1001 SCS Table 14.3.4.2.3.1.2.f1, 14.3.4.2.3.2.2.f1 and Table 14.3.4.2.3.3.2.f1
Abbreviations: BP=blood pressure; DBP=diastolic BP; N=number of subjects evaluated against criteria. n=number of subjects that met criteria; SBP=systolic BP; bpm=beats per minute; mmHg=mm of mercury; kg=kilogram

The risk of increased body weight increased by cycle number i.e. with duration of treatment

Vision disorders

Table 86: Summary of Treatment-Emergent VISION DISORDER Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Cycles, all causality) (100-mg QD Pooled Group) - All-causality and Treatment-related - Safety Population – Data cutoff date: 02 February 2018

	(N= 295)					
	All-Causality			Treatment-Related		
PT	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AEs	**45 (15.3)**	**1 (0.3)**	**0**	**22 (7.5)**	**0**	**0**
Vision blurred	15 (5.1)	0	0	7 (2.4)	0	0
Visual impairment	14 (4.7)	0	0	8 (2.7)	0	0
Diplopia	6 (2.0)	1 (0.3)	0	0	0	0
Photopsia	5 (1.7)	0	0	3 (1.0)	0	0
Visual acuity reduced	5 (1.7)	0	0	2 (0.7)	0	0
Photophobia	2 (0.7)	0	0	2 (0.7)	0	0
Vitreous floaters	2 (0.7)	0	0	2 (0.7)	0	0

Source: Table 14.3.1.2.9.1.2.8.2.ema.1 and Table 14.3.1.3.9.1.2.8.2.ema.1

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, N/n=number, QD=once daily, SCS=summary of clinical safety, SU=safety update.

Median time to first onset was 71 days (range: 1-731). The median duration was 100 days and 1 patient had a Grade 3 event. No SAEs or permanent discontinuations were observed. No clinically relevant differences were observed with updated data.

Liver tests increased

100-mg QD Pooled Group

A total of 43/295 (14.6%) patients had AST increased (Grade 3: 2[0.7%] patients, Grade 4: 2 [0.7%] patients), 40 (13.6%) patients had ALT increased (Grade 3: 3[1.0%] patients, Grade 4: 2 [0.7%] patient), 5 (1.7%) patients had Blood alkaline phosphatase increased (Grade 3:2 patients [0.7%], Grade 4: none), 2 (0.7%) patients had Hepatic function abnormal. The majority of these events were Grade 1 or 2 in severity. None of these AEs resulted in permanent treatment discontinuation. Of note, 1 patient had a Grade 1 AE (treatment-related) of Hepatocellular injury. Some of the patients (<2% in each AE category) required dose reductions or temporary discontinuations due to AEs of liver tests increased. The 2 patients who had liver test increased related SAEs are described above, the additional patients in this pooled group did not result in further SAEs. No clinically relevant differences were observed with updated data.

Liver toxicity resulting in liver tests was considered within an acceptable range and the events do not seem dose-dependent.

QTc prolongation

Table 87: Shift Summary of Maximum Absolute QTcF or QTcB (100-mg QD Pooled Group) - Safety Population – Data cutoff date: 02 February 2018

	Postbaseline Maximum Absolute QTc Results n (%)				
Baseline results (msec) (N=295)	**<450**	**450-<480**	**480-<500**	**≥500**	**Total**
QTcF					
<450	228 (77.3)	47 (15.9)	6 (2.0)	1 (0.3)	282 (95.6)
450 - <480	1 (0.3)	10 (3.4)	1 (0.3)	0	12 (4.1)
480 - <500	0	0	0	0	0
≥500	0	0	0	1 (0.3)	1 (0.3)
Total	229 (77.6)	57 (19.3)	7 (2.4)	2 (0.7)	295(100)
QTcB					
<450	141 (47.8)	92 (31.2)	10 (3.4)	4 (1.4)	247 (83.7)
450 - <480	2 (0.7)	18 (6.1)	19 (6.4)	5 (1.7)	44 (14.9)
480 - <500	0	0	2 (0.7)	1 (0.3)	3 (1.0)
≥500	0	0	0	1 (0.3)	1 (0.3)
Total	143 (48.5)	110 (37.3)	31 (10.5)	11 (3.7)	295 (100)

Source: Tables 14.3.4.4.3.2.ema.1, 14.3.4.4.4.2.ema.1
Abbreviations:N/ n=number of patients meeting specified criterion; N=number of patients evaluated; QTcB=corrected QT interval using Bazett's correction formula; QTcF=corrected QT interval using Fridericia's correction formula, QD=once daily.

Five (5) patients (1.8%) had a change in QTcF from baseline > 60 msec. It has been observed that lorlatinib induced QTc prolongation with a common frequency (5.4% of drug-related events in the pooled 100 mg QD dataset; 1 patient (0.4%) with a shift from normal baseline QT interval to QTcF >500 msec post-baseline (Grade 3 AE) whose causality cannot be ruled out).

Interstitial lung disease or Pneumonitis

100-mg QD Pooled Group

Interstitial lung disease/pneumonitis was reported in 4 patients. The AE of Interstitial lung disease (Grade 3) was reported in 1 (0.3%) patient and the AE of Pneumonitis was reported in 3 (1.0%) patients (1 each at Grade 2, 3 and 4). Lorlatinib was discontinued permanently due to the Grade 4 AE of Pneumonitis (treatment-related) for 1 patient. The 1 patient with Grade 3 AE of Interstitial lung disease (treatment-related) required temporary discontinuation of lorlatinib. No patients required temporary discontinuations or dose reductions due to AE of Pneumonitis. Except the Grade 4 AE of Pneumonitis and Grade 3 AE of Interstitial lung disease, no other AEs of Interstitial lung disease or Pneumonitis were reported as treatment-related. SAEs were Grade 3 and 4 Pneumonitis and Grade 3 Interstitial lung disease. Updated data contains no new cases of ILD or pneumonitis.

Pneumonitis is a class effect of ALK-inhibitors but is not a frequent event with lorlatinib. No patients died due to this event, which was manageable with dose reductions or discontinuations.

Atrioventricular block

In healthy volunteer studies, no AEs associated with AV block were reported, however PR interval prolongation was observed.

100-mg QD Pooled Group

In 295 patients who received lorlatinib at the recommended dose of 100 mg once daily and had an ECG measurement in Study 1001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper CI 19.4 ms). Of these, 7 patients had a baseline PR > 200 ms. Among

the 284 patients with PR interval < 200 ms, 14% had PR interval prolongation ≥200 ms after starting lorlatinib.

Table 88: Shift Summary of Maximum Absolute PR Results (100-mg QD Pooled Group) - Safety Population - Data cutoff date: 02 February 2018

	Maximum Absolute Post-baseline PR Interval n (%)							
Baseline (msec) (N=292)	**<160**	**160-<180**	**180-<200**	**200-<220**	**220-<240**	**240-<260**	**≥260**	**Total**
<160	102 (34.9)	78 (26.7)	18 (6.2)	4 (1.4)	1 (0.3)	3 (1.0)	0	206 (70.5)
160-<180	0	6 (2.1)	36 (12.3)	14 (4.8)	1 (0.3)	0	0	57 (19.5)
180-<200	0	0	4 (1.4)	11 (3.8)	3 (1.0)	2 (0.7)	1 (0.3)	21 (7.2)
200-<220	0	0	0	0	3 (1.0)	1 (0.3)	3 (1.0)	7 (2.4)
220-<240	0	0	0	0	0	0	1 (0.3)	1 (0.3)
240-<260	0	0	0	0	0	0	0	0
≥260	0	0	0	0	0	0	0	0
Total	102 (34.9)	84 (28.8)	58 (19.9)	29 (9.9)	8 (2.7)	6 (2.1)	5 (1.7)	292 (100)

Source: Table 14.3.4.4.2.ema.1
Abbreviations: N/n=number of patients meeting specified criterion; N/n=number of patients evaluated, QD=once daily, msec=millisecond.

AV block first degree was reported in 2 patients (both at Grade 1; treatment-related), and AV block complete was reported by 1 (0.3%) patient (Grade 3, not treatment-related). The median duration for AV block first degree was 141 days. The AV block complete occurred in 2 days. There was 1 temporary treatment discontinuation associated with the Grade 3 event. No other patients required a dose reduction or temporary discontinuations, or permanent treatment discontinuations in association with atrioventricular block. No new case of AV block was observed with updated data.

Higher frequencies of "PR prolonged AE" has been observed with increasing duration of baseline PR interval.

Pancreatitis

100-mg QD Pooled Group

One (1/295) (0.3%) patient had an AE of Pancreatitis. This patient had a treatment-related SAE (Grade 3) from Cycle 3 Day 20, due to which the study treatment was temporarily discontinued. On Cycle 3 Day 21, the AE was considered resolved but another non-serious AE of pancreatic enzymes increased (Grade 1) was reported and while study treatment resumed, it was given at a reduced dose. Lipase increased was reported in 10.8% of patients and Amylase increased was reported in 8.5% of patients. There were no additional cases of pancreatitis with updated data.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 89: All-causality treatment-emergent (≥2 patients) and treatment-related SAEs (≥1 patient) by clustering and MedDRA preferred term (PT) and maximum CTCAE grade, All cycles (100-mg QD pooled group)- safety population- Data cutoff date: 02 February 2018

Preferred Term	100-mg QD Pooled Group (N=295) All-Causality n (%) All Grades	Grade 3	Grade 4	Treatment-Related n (%) All Grades	Grade 3	Grade 4
Any AEs[a]	**112 (38.0)**	**44 (14.9)**	**12 (4.1)**	**23 (7.8)**	**13 (4.4)**	**5 (1.7)**
Disease progression	27 (9.2)	0	0	0	0	0
Dyspnoea	8 (2.7)	6 (2.0)	2 (0.7)	0	0	0
Pyrexia	7 (2.4)	2 (0.7)	0	0	0	0
Pneumonia	6 (2.0)	5 (1.7)	0	1 (0.3)	1 (0.3)	0
Mental status changes	5 (1.7)	4 (1.4)	0	1 (0.3)	1 (0.3)	0
Fall	4 (1.4)	4 (1.4)	0	0	0	0
Pericardial effusion	4 (1.4)	3 (1.0)	0	0	0	0
*COGNITIVE EFFECTS	3 (1.0)	3 (1.0)	0	3 (1.0)	3 (1.0)	0
Pleural effusion	3 (1.0)	3 (1.0)	0	0	0	0
Pulmonary embolism	3 (1.0)	3 (1.0)	0	0	0	0
Respiratory failure	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Vomiting	3 (1.0)	1 (0.3)	0	1 (0.3)	0	0
*EDEMA	2 (0.7)	2 (0.7)	0	0	0	0
*PERIPHERAL NEUROPATHY	2 (0.7)	0	0	1 (0.3)	1 (0.3)	0
Acute respiratory failure	2 (0.7)	2 (0.7)	0	1 (0.3)	1 (0.3)	0
Alanine aminotransferase increased	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Aspartate aminotransferase increased	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Atrial fibrillation	2 (0.7)	1 (0.3)	0	0	0	0
Chest pain	2 (0.7)	1 (0.3)	0	0	0	0
Embolism	2 (0.7)	0	0	0	0	0
Femoral neck fracture	2 (0.7)	1 (0.3)	0	0	0	0
Headache	2 (0.7)	1 (0.3)	0	1 (0.3)	0	0
Lower respiratory tract infection	2 (0.7)	1 (0.3)	0	0	0	0
Lung disorder	2 (0.7)	0	0	0	0	0
Lung infection	2 (0.7)	1 (0.3)	0	0	0	0
Pain	2 (0.7)	2 (0.7)	0	0	0	0
Pneumonitis	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)
Respiratory tract infection	2 (0.7)	1 (0.3)	0	0	0	0
Sepsis	2 (0.7)	0	2 (0.7)	0	0	0
Superior vena cava syndrome	2 (0.7)	2 (0.7)	0	0	0	0
Thrombosis	2 (0.7)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Upper respiratory tract infection	2 (0.7)	1 (0.3)	0	0	0	0
Urinary tract infection	2 (0.7)	1 (0.3)	0	0	0	0
Vertigo	2 (0.7)	2 (0.7)	0	0	0	0
Cerebral infarction	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Coronary artery disease	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)
Dyspnoea exertional	1 (0.3)	0	0	1 (0.3)	0	0
Erysipelas	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Gastritis	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Glossitis	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Hallucination	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)
Interstitial lung disease	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Pancreatitis	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Presyncope	1 (0.3)	0	0	1 (0.3)	0	0
Vagus nerve disorder	1 (0.3)	0	0	1 (0.3)	0	0
*HYPERCHOLESTEROLEMIA	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)
*HYPERTRIGLYCERIDEMIA	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)

Source: Table 14.3.2.2.2.3.ema.1 and Table 14.3.2.2.3.3.ema.1

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of patients; SAE=serious adverse event, QD=once daily.

*= Cluster terms as defined in Table 71

a= Total number independent of cutoff used in the table

Deaths

Phase 1

A total of 7 (13%) of 54 patients died on study treatment or within 28 days of their last dose of lorlatinib, and 20 (37.0%) patients died after 28 days of their last dose of lorlatinib; none of the deaths were treatment-related. Six (6) of 7 deaths, on study treatment or within 28 days, were due to disease progression and 1 death due to Hypoxia (supplemental oxygen dependency). Among the 27 deaths, the majority (24) died due to the disease progression, 1 patient died due to "other" causes specified as hypertension, supplemental oxygen dependency, morbid obesity and diabetes, and 2 patients died due to an unknown cause.

Phase 2

Out of 275 patients, 26 (9.5%) died on study treatment or within 28 days of their last dose of lorlatinib, and 38 (13.8%) patients died after 28 days of their last dose of lorlatinib; none of the deaths were treatment-related. The most frequent reason for death was disease progression (59 patients (21.5%). Four (4) patients died due to "other" causes, and specific reasons included pneumonia (2 patients) probable lung infection (1 patient), and suspected thrombus embolism (1 patient); none of which were considered treatment-related. One patient died due to an unknown cause.

Table 90: Summary of Deaths (Phase 1, Phase 2 and 100-mg QD Pooled Group) - Safety Population

Deaths	Phase 1 (N=54) n (%)	Phase 2 (N=275) n (%)	100-mg QD Pooled Group (N=295) n (%)
Patients who died			
Within 28 days after last dose of study drug	7 (13.0)	26 (9.5)	29 (9.8)
More than 28 days after last dose of study drug	20 (37.0)	38 (13.8)	42 (14.2)
Cause of death			
Disease under study	24 (44.4)	59 (21.5)	65 (22.0)
Unknown/not reported	2 (3.7)	1 (0.4)	2 (0.7)
Study treatment toxicity	0	0	0
Other	1 (1.9)[a]	4 (1.5)[b]	4 (1.4)[b]

a. Specified as hypertension, supplemental oxygen dependency, morbid obesity and diabetes (Table 16.2.6.5.2.1).
b. Specified as pneumonia for 2 patients; Probable lung infection and suspected thrombus embolism for 1 patient each (Table 16.2.6.5.2.2).

The following fatal AEs occurred in 1 patient each: pneumonia, lung infection, acute pulmonary oedema, embolism, general physical health deterioration, myocardial infarction, peripheral artery occlusion, and respiratory distress.

Table 91: Grade 5 AEs (Phase 1, Phase 2 and 100-mg QD Pooled Group) - Safety Population

Preferred Term n (%)	Phase 1 Total AEs (N=54)	Phase 2 Total AEs (N=275)	100-mg QD Pooled Group Total AEs (N=295)
Any AEs	**9 (16.7)**	**30 (10.9)**	**33 (11.2)**
Disease progression	8 (14.8)	22 (8.0)	25 (8.5)
Hypoxia	1 (1.9)	0	0
Pneumonia	0	1 (0.4)	1 (0.3)
Lung Infection	0	1 (0.4)	1 (0.3)
Acute Pulmonary oedema	0	1 (0.4)	1 (0.3)
Embolism	0	1 (0.4)	1 (0.3)
General physical health deterioration	0	1 (0.4)	1 (0.3)
Myocardial infarction	0	1 (0.4)	1 (0.3)
Peripheral artery occlusion	0	1 (0.4)	1 (0.3)
Respiratory distress	0	1 (0.4)	1 (0.3)

Abbreviations: AE=adverse event; N=number of patients evaluable for safety; n=number of patients with AEs

Table 92: Summary of deaths (100 mg QD pooled group) – safety population

	SCS (cutoff 15 March 2017)	SU (cutoff 02 February 2018)
Deaths	100-mg QD Pooled Group (N=295) n (%)	100-mg QD Pooled Group (N=295) n (%)
Patients who died		
Within 28 days after last dose of study drug	29 (9.8)	32 (10.8)
More than 28 days after last dose of study drug	42 (14.2)	69 (23.4)
Cause of death		
Disease under study	65 (22.0)	87 (29.5)
Unknown/not reported	2 (0.7)	6 (2.0)
Study treatment toxicity	0	0
Other	4 (1.4)	8 (2.7)

Source: Table 14.3.2.1.2.2.f1 and Table 14.3.2.1.2.2.ema.1

Laboratory findings

Haematology

Table 93: Summary of haematology post-baseline laboratory results (SU) by maximum CTCAE grade (all cycles) (100 mg QD pooled group) – safety population – Data cutoff date: 02 February 2018

		Grade 1	Grade 2	Grade 3	Grade 4	Total
Parameter	N	n (%)	n (%)	n (%)	n (%)	n (%)
Anemia	293	152 (51.9)	63 (21.5)	16 (5.5)	0	231 (78.8)
Hemoglobin increased	293	7 (2.4)	0	0	0	7 (2.4)
Lymphocyte count decreased	292	52 (17.8)	59 (20.2)	14 (4.8)	0	125 (42.8)
Lymphocyte count increased	292	0	18 (6.2)	0	0	18 (6.2)
Neutrophil count decreased	292	21 (7.2)	12 (4.1)	1 (0.3)	2 (0.7)	36 (12.3)
Platelet count decreased	293	72 (24.6)	1 (0.3)	0	1 (0.3)	74 (25.3)
White blood cell decreased	293	41 (14.0)	7 (2.4)	2 (0.7)	0	50 (17.1)

Source: Table 14.3.4.1.5.1.2.ema.1

Abbreviations: N=total number of patients; n=number of patients with Grade 1, 2, or 3 laboratory parameter, CTCAE=Common Terminology Criteria for AEs, QD=once daily.

Blood chemistry

Table 94: Summary of abnormal clinical chemistry laboratory test results by maximum CTCAE grade (All cycles) (100 mg QD pooled group) – safety population - Data cutoff date: 02 February 2018

		Grade 1	Grade 2	Grade 3	Grade 4	Total
Parameter	N	n (%)	n (%)	n (%)	n (%)	n (%)
ALT increased	292	98 (33.6)	9 (3.1)	4 (1.4)	2 (0.7)	113 (38.7)
ALP increased	292	105 (36.0)	10 (3.4)	3 (1.0)	0	118 (40.4)
AST increased	292	129 (44.2)	7 (2.4)	4 (1.4)	2 (0.7)	142 (48.6)
Blood Bilirubin increased	292	3 (1.0)	0	1 (0.3)	1 (0.3)	5 (1.7)
Creatinine increased	293	195 (66.6)	26 (8.9)	1 (0.3)	0	222 (75.8)
Hypercalcemia	293	24 (8.2)	0	0	0	24 (8.2)
Hyperglycemia	293	121 (41.3)	50 (17.1)	15 (5.1)	1 (0.3)	187 (63.8)
Hyperkalemia	293	60 (20.5)	7 (2.4)	2 (0.7)	1 (0.3)	70 (23.9)
Hypermagnesemia	292	12 (4.1)	0	2 (0.7)	0	14 (4.8)
Hypernatremia	293	31 (10.6)	1 (0.3)	0	0	32 (10.9)
Hypoalbuminemia	291	135 (46.4)	44 (15.1)	3 (1.0)	0	182 (62.5)
Hypocalcemia	293	40 (13.7)	11 (3.8)	0	1 (0.3)	52 (17.7)
Hypoglycemia	293	30 (10.2)	4 (1.4)	0	0	34 (11.6)
Hypokalemia	293	53 (18.1)	0	3 (1.0)	1 (0.3)	57 (19.5)
Hypomagnesemia	292	83 (28.4)	0	0	0	83 (28.4)
Hyponatremia	293	68 (23.2)	0	7 (2.4)	0	75 (25.6)
Hypophosphatemia	292	9 (3.1)	49 (16.8)	20 (6.8)	0	78 (26.7)
Lipase increased	290	38 (13.1)	15 (5.2)	24 (8.3)	7 (2.4)	84 (29.0)
Serum amylase increased	284	52 (18.3)	14 (4.9)	11 (3.9)	1 (0.4)	78 (27.5)

Source: Table 14.3.4.1.6.1.2.ema.1
Abbreviations: N=total number of patients; n=number of patients with Grade 1-4 laboratory parameter; CTCAE=Common Terminology Criteria for Adverse Events; ALT=Alanine aminotransferase; ALP=alkaline phosphatase; AST=Aspartate aminotransferase, QD=once daily.

Lipids

Table 95: Summary Results of Labs by Maximum CTCAE Grade (Others, All Cycles) (100-mg Pooled Group) - Safety Population

			N=292		
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Cholesterol High	71 (24.3)	165 (56.5)	43 (14.7)	6 (2.1)	285 (97.6)
Hypertriglyceridemia	145 (49.7)	82 (28.1)	42 (14.4)	8 (2.7)	277 (94.9)

Source: Study 1001 SCS Table 14.3.4.1.7.1.2.f1
Abbreviations: N is the number of patients who had at least one on-study assessment for the parameter of interest. n is the number of patients whose lab results had met the criteria of CTCAE Grade. CTCAE=Terminology Criteria for Adverse Events

The Grade 3 events of high cholesterol and hypertriglyceridemia were observed in around 15% of the patients. The observed changes in lipid parameters with updated data were of clinically insignificant.

Safety in special populations

Intrinsic factors

Age

Table 96: Safety in patients by age groups -100-mg QD pooled group - Safety Population

MedDRA Terms	Age <65 (N=241)		Age 65-74 (N=41)		Age 75-84 (N=12)		Age 85+ (N=1)	
	n1	n2	n1	n2	n1	n2	n1	n2
Total AEs	3357	13.9	627	15.3	165	13.8	6	6.0
Serious AEs – Total	161	0.7	43	1.0	21	1.8	0	
- Fatal	37	0.2	10	0.2	6	0.5	0	
- Hospitalization/prolong existing hospitalization	125	0.5	32	0.8	16	1.3	0	
- Life-threatening	5	<0.1	0		0		0	
- Disability/incapacity	2	<0.1	0		0		0	
- Other (medically significant)	4	<0.1	3	<0.1	0		0	
AE leading to drop-out	25	0.1	5	0.1	5	0.4	0	
Psychiatric disorders (SOC)	140	0.6	29	0.7	8	0.7	2	2.0
Nervous system disorders (SOC)	390	1.6	66	1.6	17	1.4	0	
Accidents and injuries [1]	46	0.2	6	0.1	10	0.8	0	
Cardiac disorders (SOC)	45	0.2	15	0.4	2	0.2	0	
Vascular disorders (SOC)	55	0.2	10	0.2	3	0.3	0	
Cerebrovascular disorders [2]	1	<0.1	1	<0.1	0		0	
Infections and infestations (SOC)	222	0.9	36	0.9	10	0.8	0	
Anticholinergic syndrome (PT)	0		0		0		0	
Quality of life decreased (PT)	0		0		0		0	
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures +	72	0.3	13	0.3	5	0.4	0	
<other AE appearing more frequently in older patients>	498	2.1	112	2.7	37	3.1	1	1.0
** EDEMA	144	0.6	31	0.8	7	0.6	1	1.0
** COGNITIVE EFFECTS	86	0.4	22	0.5	6	0.5	0	
** FATIGUE	65	0.3	16	0.4	6	0.5	0	
Weight increased	70	0.3	6	0.1	2	0.2	0	
Dyspnoea	62	0.3	14	0.3	6	0.5	0	
Anaemia	33	0.1	9	0.2	5	0.4	0	
Back pain	27	0.1	9	0.2	4	0.3	0	
Dyspnoea exertional	11	<0.1	5	0.1	1	<0.1	0	

Abbreviations: AE= Adverse event; N=number; MedDRA= Medical Dictionary for Regulatory Activities; PT= Preferred term; SOC= System organ class
MedDRA (v20.1) coding dictionary applied.
n1: The number of AEs.
n2: The average number of AEs per patient. n2 = n1/N
* Includes Phase 1, Phase 2 and Japan LIC
** refers to AE cluster terms
[1] PTs from Injury, Poisoning, and Procedural Complications System Organ Class (SOC)
[2] The following PTs were searched: Cerebrovascular accident, Cerebral haemorrhage, Cerebral infarction, Ischaemic cerebral infarction, Cerebral ischaemia, Cerebrovascular disorder, Cerebrovascular insufficiency, Haemorrhagic stroke, Ischaemic stroke, Thrombotic stroke, Embolic stroke, Cerebral arteriosclerosis, Transient ischaemic attack, Cerebral vasoconstriction, Cerebrovascular stenosis, Haemorrhagic transformation stroke
+ The following Preferred Terms (PTs) were searched: Orthostatic hypotension, Dizziness, Dizziness postural, Loss of consciousness, Depressed level of consciousness, Altered state of consciousness, Syncope, Presyncope, Fall, Ataxia. In addition the HLT Fractures and dislocations (NEC) containing the following PTs was used: Atypical fracture, Avulsion fracture, Bone fissure, Bone fragmentation, Comminuted fracture, Complicated fracture, Compression fracture, Fracture, Fracture delayed union, Fracture displacement, Fracture nonunion, Impacted fracture, Joint dislocation, Joint dislocation pathological, Multiple fractures, Open fracture, Osteoporotic fracture, Pathological fracture, Stress fracture, Traumatic fracture, as well as the following reported PTs indicating a fracture: Spinal compression fracture, Ankle fracture, Foot fracture, Humerus fracture, Rib fracture, Femur fracture, Fractured sacrum, Lumbar vertebral fracture, Wrist fracture, Hip fracture, Thoracic vertebral fracture, and Upper limb fracture

Table 97: Most Common (> 10% of Patients <65 years and/ or ≥65 years) All-Causality Adverse Events by Age Category – 100-mg QD pooled group - Safety Population

Preferred Term	Number (%) of Patients	
	< 65 years N= 241	≥ 65 years N= 54
Any AEs	240 (99.6)	54 (100.0)
*HYPERCHOLESTEROLEMIA	200 (83.0)	43 (79.6)
*HYPERTRIGLYCERIDEMIA	151 (62.7)	28 (51.9)
*EDEMA	116 (48.1)	35 (64.8)
*PERIPHERAL NEUROPATHY	104 (43.2)	25 (46.3)
Weight increased	56 (23.2)	5 (9.3)
*COGNITIVE EFFECTS	54 (22.4)	14 (25.9)
Dyspnoea	54 (22.4)	15 (27.8)
*FATIGUE	52 (21.6)	16 (29.6)
*MOOD EFFECTS	52 (21.6)	10 (18.5)
Arthralgia	44 (18.3)	14 (25.9)
Cough	43 (17.8)	5 (9.3)
Headache	41 (17.0)	3 (5.6)
Diarrhoea	40 (16.6)	12 (22.2)
Nausea	40 (16.6)	3 (5.6)
Dizziness	36 (14.9)	8 (14.8)
Constipation	33 (13.7)	9 (16.7)
*VISION DISORDER	32 (13.3)	7 (13.0)
Aspartate aminotransferase increased	31 (12.9)	4 (7.4)
Alanine aminotransferase increased	30 (12.4)	3 (5.6)
Lipase increased	29 (12.0)	3 (5.6)
Pain in extremity	29 (12.0)	4 (7.4)
Anaemia	28 (11.6)	9 (16.7)
Myalgia	26 (10.8)	5 (9.3)
Pyrexia	25 (10.4)	4 (7.4)
Back pain	23 (9.5)	12 (22.2)
*SPEECH EFFECTS	21 (8.7)	7 (13.0)
Vomiting	22 (9.1)	7 (13.0)
Dyspnoea exertional	11 (4.6)	6 (11.1)
Hyperglycaemia	15 (6.2)	6 (11.1)
Insomnia	16 (6.6)	6 (11.1)
Rash	18 (7.5)	6 (11.1)

Source: Study 1001 SCS Table 14.3.1.2.9.1.2.2.3.1.s1
*=Cluster terms as indicated (Table 84)
Abbreviation: N=number

There were more AEs of all causality in patients older than 65 years e.g. anaemia, oedema, dyspnoea, fatigue, arthralgia, and back pain. On the other hand, some incidences of AEs are lower in the elderly population however the number of patients aged ≥65 years was rather limited.

Gender

Table 98: Most Common (> 10% of Patients in Any Category) All-Causality Adverse Events by Gender – 100-mg QD pooled group - Safety Population

	SCS (cutoff 15 March 2017)		SU (cutoff 02 February 2018)	
Preferred Term	**Male N= 125**	**Female N= 170**	**Male N= 125**	**Female N= 170**
Any AEs	124 (99.2)	170 (100)	124 (99.2)	170 (100)
*HYPERCHOLESTEROLEMIA	96 (76.8)	147 (86.5)	99 (79.2)	150 (88.2)
*HYPERTRIGLYCERIDEMIA	83 (66.4)	96 (56.5)	88 (70.4)	110 (64.7)
*EDEMA	56 (44.8)	95 (55.9)	59 (47.2)	102 (60.0)
*PERIPHERAL NEUROPATHY	56 (44.8)	73 (42.9)	60 (48.0)	81 (47.6)
*COGNITIVE EFFECTS	33 (26.4)	35 (20.6)	39 (31.2)	46 (27.1)
*FATIGUE	32 (25.6)	36 (21.2)	38 (30.4)	45 (26.5)
Dyspnoea	32 (25.6)	37 (21.8)	37 (29.6)	45 (26.5)
Weight increased	29 (23.2)	32 (18.8)	35 (28.0)	43 (25.3)
*MOOD EFFECTS	27 (21.6)	35 (20.6)	28 (22.4)	39 (22.9)
Cough	26 (20.8)	22 (12.9)	29 (23.2)	28 (16.5)
Arthralgia	21 (16.8)	37 (21.8)	30 (24.0)	43 (25.3)
Diarrhoea	18 (14.4)	34 (20.0)	23 (18.4)	44 (25.9)
Headache	18 (14.4)	26 (15.3)	18 (14.4)	35 (20.6)
Aspartate aminotransferase increased	16 (12.8)	19 (11.2)	19 (15.2)	24 (14.1)
Dizziness	16 (12.8)	28 (16.5)	19 (15.2)	30 (17.6)
*VISION DISORDER	15 (12.0)	24 (14.1)	20 (16.0)	25 (14.7)
Constipation	15 (12.0)	27 (15.9)	18 (14.4)	29 (17.1)
Lipase increased	15 (12.0)	17 (10.0)	20 (16.0)	21 (12.4)
Myalgia	15 (12.0)	16 (9.4)	16 (12.8)	20 (11.8)
Pyrexia	15 (12.0)	14 (8.2)	17 (13.6)	25 (14.7)
Amylase increased	14 (11.2)	11 (6.5)	17 (13.6)	13 (7.6)
Nausea	14 (11.2)	29 (17.1)	20 (16.0)	34 (20.0)
*SPEECH EFFECTS	13 (10.4)	15 (8.8)	14 (11.2)	15 (8.8)
Alanine aminotransferase increased	13 (10.4)	20 (11.8)	16 (12.8)	24 (14.1)
Pain in extremity	12 (9.6)	21 (12.4)	13 (10.4)	27 (15.9)
Vomiting	11 (8.8)	18 (10.6)	15 (12.0)	21 (12.4)
Anaemia	9 (7.2)	28 (16.5)	12 (9.6)	35 (20.6)
Back pain	9 (7.2)	26 (15.3)	13 (10.4)	27 (15.9)
Upper respiratory tract infection	12 (9.6)	12 (7.1)	18 (14.4)	17 (10.0)
Chest pain	12 (9.6)	7 (4.1)	16 (12.8)	11 (6.5)
Hypertension	12 (9.6)	9 (5.3)	15 (12.0)	14 (8.2)
Disease progression	12 (9.6)	13 (7.6)	13 (10.4)	14 (8.2)
Rash	12 (9.6)	12 (7.1)	13 (10.4)	17 (10.0)
Urinary tract infection	0	11 (6.5)	0	20 (11.8)
Tinnitus	7 (5.6)	15 (8.8)	8 (6.4)	18 (10.6)

Source: SCS Table 14.3.1.2.9.1.2.2.2.1.s1 and Table 14.3.1.2.9.1.2.2.2.2.ema.1
*=Cluster terms as indicated (Table 71)
Abbreviation: N=number

All-causality AEs were generally balanced between genders.

Race

Table 99: Most Common (> 10% of Patients in Any Category) All-Causality Adverse Events by Race Category – 100-mg QD pooled group - Safety Population

	SCS (cutoff 15 March 2017)		SU (cutoff 02 February 2018)	
Preferred Term	**Asian N= 108**	**Non-Asian N= 161**	**Asian N= 108**	**Non-Asian N= 161**
Any AEs	107 (99.1)	161 (100)	107 (99.1)	161 (100)
*HYPERCHOLESTEROLEMIA	87 (80.6)	133 (82.6)	90 (83.3)	135 (83.9)
*HYPERTRIGLYCERIDEMIA	73 (67.6)	86 (53.4)	82 (75.9)	92 (57.1)
*EDEMA	48 (44.4)	94 (58.4)	52 (48.1)	97 (60.2)
*PERIPHERAL NEUROPATHY	37 (34.3)	76 (47.2)	41 (38.0)	82 (50.9)
Constipation	20 (18.5)	20 (12.4)	20 (18.5)	25 (15.5)
Dizziness	20 (18.5)	23 (14.3)	21 (19.4)	27 (16.8)
Dyspnoea	20 (18.5)	43 (26.7)	24 (22.2)	47 (29.2)
Arthralgia	19 (17.6)	31 (19.3)	21 (19.4)	43 (26.7)
Nausea	16 (14.8)	23 (14.3)	17 (15.7)	30 (18.6)
Diarrhoea	14 (13.0)	30 (18.6)	17 (15.7)	38 (23.6)
Myalgia	14 (13.0)	14 (8.7)	14 (13.0)	19 (11.8)
*COGNITIVE EFFECTS	13 (12.0)	45 (28.0)	18 (16.7)	53 (32.9)
Alanine aminotransferase increased	13 (12.0)	19 (11.8)	14 (13.0)	25 (15.5)
Back pain	13 (12.0)	17 (10.6)	15 (13.9)	18 (11.2)
Cough	13 (12.0)	27 (16.8)	13 (12.0)	35 (21.7)
Headache	13 (12.0)	23 (14.3)	18 (16.7)	26 (16.1)
Aspartate aminotransferase increased	12 (11.1)	22 (13.7)	13 (12.0)	29 (18.0)
*MOOD EFFECTS	11 (10.2)	44 (27.3)	13 (12.0)	45 (28.0)
Disease progression	11 (10.2)	14 (8.7)	11 (10.2)	16 (9.9)
Vomiting	11 (10.2)	11 (6.8)	13 (12.0)	15 (9.3)
Lipase increased	10 (9.3)	20 (12.4)	11 (10.2)	24 (14.9)
Pyrexia	10 (9.3)	17 (10.6)	13 (12.0)	26 (16.1)
Weight increased	10 (9.3)	36 (22.4)	15 (13.9)	46 (28.6)
*VISION DISORDER	9 (8.3)	24 (14.9)	9 (8.3)	29 (18.0)
*FATIGUE	5 (4.6)	51 (31.7)	8 (7.4)	59 (36.6)
Anaemia	5 (4.6)	31 (19.3)	7 (6.5)	35 (21.7)
*SPEECH EFFECTS	4 (3.7)	17 (10.6)	4 (3.7)	17 (10.6)
Pain in extremity	5 (4.6)	27 (16.8)	7 (6.5)	30 (18.6)
Upper respiratory tract infection	8 (7.4)	16 (9.9)	15 (13.9)	20 (12.4)
Rash	9 (8.3)	14 (8.7)	11 (10.2)	17 (10.6)
Tinnitus	9 (8.3)	9 (5.6)	11 (10.2)	10 (6.2)
Hypertension	5 (4.6)	16 (9.9)	9 (8.3)	20 (12.4)
Amylase increased	9 (8.3)	16 (9.9)	9 (8.3)	18 (11.2)

Source: SCS Table 14.3.1.2.9.1.2.2.1.1.s1 and Table 14.3.1.2.9.1.2.2.1.2.ema.1
*=Cluster terms as indicated (Table 71)
Abbreviation:, N=number

Extrinsic factors

Food effect

There was no clinically significant effect of food on lorlatinib exposure. Therefore, lorlatinib may be administered without regard to food.

Safety related to drug-drug interactions and other interactions

See Section 2.4.2.

Discontinuation due to adverse events

AEs leading to Permanent Discontinuation

Table 100: Adverse Events leading to Permanent Discontinuation by MedDRA Preferred Terms (PT), All CTCAE Grades, All Cycles (100-mg QD Pooled Group) - Safety Population

	Number (%) of Patients (N=295)	
PT	**All-causality**	**Treatment-Related**
Any AEs	21 (7.1)[a]	7 (2.4)
Acute respiratory failure	2 (0.7)	0
Dyspnoea	2 (0.7)	0
Respiratory failure	2 (0.7)	0
Affect lability	1 (0.3)	1 (0.3)
Anxiety	1 (0.3)	0
Brain compression	1 (0.3)	0
Cognitive disorder	1 (0.3)	1 (0.3)
Confusional state	1 (0.3)	1 (0.3)
Disease progression	1 (0.3)	0
Embolism	1 (0.3)	0
Fatigue	1 (0.3)	0
Hallucination, auditory	1 (0.3)	1 (0.3)
Hallucination, visual	1 (0.3)	1 (0.3)
Hydrocephalus	1 (0.3)	1 (0.3)
Hypoxia	1 (0.3)	0
Leukocytosis	1 (0.3)	1 (0.3)
Loss of consciousness	1 (0.3)	0
Lung infection	1 (0.3)	0
Mental state changes	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Parkinsonian gait	1 (0.3)	0
Peripheral swelling	1 (0.3)	0
Pneumonitis	1 (0.3)	1 (0.3)
Tinnitus	1 (0.3)	1 (0.3)
Vomiting	1 (0.3)	0

MedDRA (version 20.0) coding dictionary was applied.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients;
a. One (1) patient discontinued treatment due to progressive disease with fatigue being reported as an AE. The Fatigue AE was mistakenly used as the primary reason of discontinuation.

Table 101: Discontinuations from treatment (subjects starting lorlatinib 100 mg QD*) – safety analysis set - Data cutoff date: 02 February 2018

Number (%) of Subjects	100 mg QD 295	
Discontinuations from Treatment		
Subject Died	9	(3.1)
Relation to Study Drug not Defined	130	(44.1)
Global deterioration of health status	10	(3.4)
No longer willing to participate in study	14	(4.7)
Objective progression or relapse	103	(34.9)
Other	2	(0.7)
Protocol violation	1	(0.3)
Related to Study Drug	9	(3.1)
Adverse event	9	(3.1)
Not Related to Study Drug	17	(5.8)
Adverse event	17	(5.8)
Total	165	(55.9)

* Includes Phase 1, Phase 2 and Japan LIC

Table 102: Adverse Events leading to Permanent Discontinuation by MedDRA PT in decreasing frequency, All CTCAE Grades, All Cycles (100-mg QD Pooled Group) - Safety Population – Data cutoff date: 02 February 2018

	Number (%) of Patients (N=295)	
PT	All-causality	Treatment-Related
Any AEs	**26 (8.8)**	**9 (3.1)**
Acute respiratory failure	2 (0.7)	0
Dyspnoea	2 (0.7)	0
Respiratory failure	2 (0.7)	0
Acute leukaemia	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	0
Affect lability	1 (0.3)	1 (0.3)
Anxiety	1 (0.3)	0
Asphyxia	1 (0.3)	0
Brain compression	1 (0.3)	0
Cognitive disorder	1 (0.3)	1 (0.3)
Confusional state	1 (0.3)	1 (0.3)
Disease progression	1 (0.3)	0
Embolism	1 (0.3)	0
Hallucination	1 (0.3)	1 (0.3)
Hallucination, auditory	1 (0.3)	1 (0.3)
Hallucination, visual	1 (0.3)	1 (0.3)
Headache	1 (0.3)	1 (0.3)
Hydrocephalus	1 (0.3)	1 (0.3)
Hypoxia	1 (0.3)	0
Leukocytosis	1 (0.3)	1 (0.3)
Loss of consciousness	1 (0.3)	0
Lung infection	1 (0.3)	0
Mental status changes	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Parkinsonian gait	1 (0.3)	0
Peripheral swelling	1 (0.3)	0
Pneumonitis	1 (0.3)	1 (0.3)
Renal cyst haemorrhage	1 (0.3)	0
Seizure	1 (0.3)	0
Thrombocytopenia	1 (0.3)	0
Tinnitus	1 (0.3)	1 (0.3)
Vomiting	1 (0.3)	0

Source: Table 14.3.1.1.3.1.2.2.ema.1and Table 14.3.1.1.3.2.2.2.ema.1
MedDRA (version 20.1) coding dictionary was applied.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for AEs; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients, QD=once daily.

AEs leading to temporary discontinuations and dose reductions

Table 103: Most frequent (≥2% of patients) treatment-emergent all-causality and TRAEs associated with temporary discontinuation of lorlatinib (100 mg QD pooled group) safety population - Data cutoff date: 2 February 2018

	100-mg QD Pooled Group (N = 295) n (%)	
Preferred Term	All-Causality n (%)	Treatment-Related n (%)
Any AEs[a]	**147 (49.8)**	**99 (33.6)**
*HYPERTRIGLYCERIDEMIA	19 (6.4)	19 (6.4)
*EDEMA	18 (6.1)	17 (5.8)
*PERIPHERAL NEUROPATHY	15 (5.1)	12 (4.1)
*COGNITIVE EFFECTS	14 (4.7)	14 (4.7)
Lipase increased	12 (4.1)	9 (3.1)
*HYPERCHOLESTEROLEMIA	11 (3.7)	11 (3.7)
*MOOD EFFECTS	9 (3.1)	8 (2.7)

Source: Table 14.3.1.1.2.1.3.2.ema.1 and Table 14.3.1.1.2.2.3.2.ema.1
Abbreviation: N/n=number; AE=adverse Event, QD=once daily.
*=Cluster terms as defined in **Table 71**
a= Total number independent of frequency cutoff used in the table

Table 104: Most frequent (≥2% of patients) treatment-emergent all-causality and TRAEs associated with dose reductions (100 mg QD pooled group) safety population - Data cutoff date: 2 February 2018

	100-mg QD Pooled Group (N 295) n (%)	
Preferred Term	All-Causality	Treatment-related
Any AEs[a]	73 (24.7)	69 (23.4)
*EDEMA	18 (6.1)	18 (6.1)
*PERIPHERAL NEUROPATHY	14 (4.7)	13 (4.4)
*COGNITIVE EFFECTS	13 (4.4)	12 (4.1)
*MOOD EFFECTS	10 (3.4)	10 (3.4)

Source: Table 14.3.1.1.2.1.3.2.ema.1 and Table 14.3.1.1.2.2.3.2.ema.1
Abbreviation: N/n=number; AE=adverse Event, QD=once daily.
*=Cluster terms as defined in Table 71.
a= Total number independent of frequency cutoff used in the table

Approximately half of the patients in the 100-mg group experienced temporary dose discontinuations, most frequently due to oedema, hypertriglyceridemia and neuropathy. Almost a quarter of the patients were dose reduced due to treatment-related AEs.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety database comprises 332 patients, and of these, 295 patients received the proposed dose for marketing (100mg QD). The median duration of treatment was 10.2 months in Phase 1 and approximately 16 months in the Phase 2 patients. All patients experienced at least one AE, and most of these were treatment-related. The most common TEAEs were hyper-cholesteremia/hypertriglyceridemia, oedema, peripheral neuropathy, fatigue, cognitive and mood effects, dyspnoea, and increased weight. The most common Grade 3-4 events were also hypercholesterolemia/hypertriglyceridemia.

Adverse events of special interest include hyperlipidaemia, oedema, peripheral neuropathy, CNS effects, weight gain, vision disorders, etc.

The risk of increases in serum cholesterol and triglycerides is relatively high with lorlatinib and more than 80% of the patients in Phase 2/100-mg group were treated medically. Median time of occurrence of severe increase in serum cholesterol and triglycerides is 201 days (range: 42 to 518 days) and 127 days (range: 15 to 358 days), respectively. Serum cholesterol and triglycerides should be monitored before initiation of lorlatinib; 2, 4 and 8 weeks after initiating lorlatinib; and regularly thereafter. Lipid-lowering medicinal products should be initiated or their dose increased, if indicated (see Sections 4.2, 4.4 and 4.8 of the SmPC).

CNS effects have been observed in patients receiving lorlatinib, including changes in cognitive function, mood or speech (see Sections 4.4 and 4.8 of the SmPC). The risk of an event is less frequent in the Phase 2 part and these events may therefore be dose- and exposure related. Despite the relatively low rate of Grade 3 events, the impact of the reported cognitive disorders (neurological and psychiatric) may be important for the patient's quality of life. Such events included confusion, delirium, mental impairment, amnesia, dementia, disturbance in attention, etc., which are considered clinically relevant also at a Grade 2 of severity. Their impact on patient's quality of life was discussed by the Applicant, however as CNS effects and their origin are very complex and challenging both to diagnose and evaluate the degree of impact on patient functioning may be equally difficult to assess. CNS effects are an identified risk in the RMP and will be monitored via routine pharmacovigilance. Dose modification or

discontinuation may be required for those patients who develop CNS effects (see Sections 4.2, 4.4 and 4.8).

Lorlatinib was studied in a population of patients that excluded those with second-degree or third-degree AV block (unless paced) or any AV block with PR interval > 220 msec. PR interval prolongation and AV block have been reported in patients receiving lorlatinib. ECG should be monitored prior to initiating lorlatinib and monthly thereafter, particularly in patients with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those patients who develop PR prolongation or AV block (see Sections 4.2, 4.4 and 4.8 of the SmPC). AV block is identified as an important potential risk in the Risk Management Plan.

Left ventricular ejection fraction (LVEF) decrease has been reported in patients receiving lorlatinib who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, it is not possible to determine a causal relationship between effects on changes in cardiac contractility and lorlatinib. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including LVEF assessment at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring, including LVEF assessment should be considered.

Elevations of lipase and/or amylase have occurred in patients receiving lorlatinib. Median time of occurrence of increase in serum lipase and amylase is 70 days (range: 7 to 696 days) and 41 days (range: 7 to 489 days), respectively. Risk of pancreatitis should be considered in patients receiving lorlatinib due to concomitant hypertriglyceridemia and/or a potential intrinsic mechanism. Patients should be monitored for lipase and amylase elevations prior to the start of lorlatinib treatment and regularly thereafter as clinically indicated (see Sections 4.2, 4.4 and 4.8 of the SmPC).

Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis have occurred with lorlatinib. Any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough and fever) should be promptly evaluated for ILD/pneumonitis. Lorlatinib should be withheld and/or permanently discontinued based on severity (see Sections 4.2, 4.4 and 4.8 of the SmPC).

In Phase 1, 27 patients have died, and no deaths were considered treatment-related. In Phase 2, 30 patients died and although none of the deaths were considered treatment-related, after a clarification, 2 deaths were re-categorised as death from disease progression and one death remains due to unknown causes.

Most of the SAEs are cases of disease progression, or due to other known risks associated with disseminated cancer-disease such as pulmonary embolism and super vena cava syndrome that are present in an expected number for this patient population.

There was generally more toxicity in non-Asian patients and clinically significant differences regarding hypertriglyceridemia, oedema, peripheral neuropathy, cognitive and mood effects, increased weight, fatigue, and anaemia. This result correlates with other findings in clinical trials; however, although all causality treatment-emergent AEs showed a similar incidence among Asian and non-Asian patients (99.1% versus 100%), the Grade 3-4 or Grade 5 adverse events were found respectively in 57.4% and 12.0% in the Asian group versus 48.4% and 14.9% in the non-Asian group. The greatest differences in incidence among the 2 race groups was found for: fatigue (Asian 7.4% versus non-Asian 36.6%), and anaemia (Asian 6.5% versus non-Asian 21.7%). Only minor differences in all causality AEs were observed for Phase 1 and Phase 2 receiving RP2D after stratification by race and cumulating all cycles with regards to incidence or to severity.

Less than 10% of the patients discontinued lorlatinib permanently, but it is noted that only a third of the discontinuations were assessed to be due to treatment-related AEs and these AEs were mostly related to cognitive effects, even at the 100 mg dose.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional safety data needed in the context of a conditional MA

There are inherent limitations to the interpretation of the safety profile based on a single arm non-comparative trial. The safety data from the ongoing controlled Phase 3 CROWN study (1006) will be important to further characterise the safety profile of lorlatinib post authorisation (see Annex II).

2.6.2. Conclusions on the clinical safety

The safety profile of lorlatinib is in line with what could be expected from an ALK-inhibitor. Most toxicities were clinically manageable with dose modifications, and only few uncertainties regarding the safety profile remain (see SmPC and RMP). The ongoing confirmatory Phase 3 trial is expected to provide comprehensive evidence in respect to safety, in particular, regarding the CNS effects. The discontinuation rate was below 10% and is considered relatively low and acceptable in the palliative setting. Overall, the safety profile of lorlatinib is manageable and in line with other ALK-inhibitors.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- In order to further confirm the safety of lorlatinib in the treatment of patients with ALK-positive NSCLC, the MAH should submit the clinical study report of the Phase 3 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.

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	CNS Effects
	Interstitial lung disease/pneumonitis
Important Potential Risks	Atrioventricular block
	Pancreatitis
	Embryo-foetal toxicity
Missing Information	Patients with moderate or severe hepatic impairment
	Patients with severe renal impairment

Pharmacovigilance plan

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:	07/09/2018 03/31/2023 02/28/2024
Lorlatinib Renal Impairment Trial (B7461010)	To determine an appropriate dose of lorlatinib to minimize toxicity in patients with renal impairment.	Missing information on patients with severe renal impairment	Final Protocol Submission: Study/Trial Completion: Final Report Submission:	04/12/2018 05/31/2020 01/31/2021

Risk minimisation measures

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
Interstitial lung disease/pneumonitis	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks		
Atrioventricular block	Routine risk minimisation measures: SmPC sections 4.2, 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		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)
Patients with severe renal 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 Renal Impairment Trial (B7461010)

Conclusion

The CHMP and Pharmacovigilance Risk Assessment Committee (PRAC) considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the Periodic

Safety Update Report (PSUR) cycle with the international birth date (IBD). The IBD is 21.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of lorlatinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers lorlatinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lorviqua (lorlatinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14(7)]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is as follows:

"*Lorlatinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (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 survival and improve overall response rate (ORR), especially for in the CNS, as brain metastases are a major clinical problem in this patient population. The primary endpoint of the pivotal trial is ORR by investigator and can be considered an early surrogate for clinical benefit.

3.1.2. Available therapies and unmet medical need

ALK-inhibitors are currently the main treatment options for ALK-positive NSCLC. The first ALK inhibitor to be approved was crizotinib in 2012, but since then alectinib and ceritinib have been approved as first- and second-line therapies.

There is an unmet medical need for further targeted therapy in patients who have already received the approved ALK-inhibitors (crizotinib, ceritinib, and alectinib) as few treatment options are available once patients become resistant to approved therapies. Currently, there are no standard of care for patients in the second-line after alectinib or ceritinib nor in the third- or later line setting as treatment with chemotherapy has a very modest efficacy in both settings in addition to poor penetrance to the CNS. There is a particular need for therapies active in the CNS, as brain metastases is a major clinical problem in this patient population, reflected by an incidence of brain metastases of 75% of patients in cohort EXP-4 and 5 of the pivotal study. Therefore there is a high unmet medical need for further treatment options in patients with CNS metastases. The data is currently limited on the use of checkpoint inhibitors in the second- and third line setting (small sample sizes) in patients with ALK-positive NSCLC and represented in small subgroups of larger randomised trials. In addition, the efficacy results with immunotherapy are not of high clinical relevance in this setting. In conclusion, there is currently no effective standard of care for patients neither in the proposed second-line setting after alectinib or ceritinib nor in the third-or later line setting.

The unmet medical need also includes prevention of CNS metastases as this is a potential risk for all patients with ALK-positive advanced NSCLC, who have received available targeted therapies.

3.1.3. Main clinical studies

Data from a pivotal Phase 1-2 study are provided. Both parts of the study were open-label, non-randomised, single-arm study with no comparator. In the Phase 1 part, 41 patients were included, and in the Phase 2 part, 197 patients with ALK-positive NSCLC were included across 5 cohorts. However, the relevant study population for the sought indication were cohort 3B-5, which consisted of patients with:

- Diagnosis of advanced ALK-positive NSCLC;
- Previously treated with a prior second-generation ALK-TKI with or without chemotherapy (EXP-3B);
- Previously treated with 2 or more ALK-TKIs (pooled cohorts EXP-4 and EXP-5)

3.2. Favourable effects

Primary endpoint: Confirmed ORR by IRC was 42.9% (95%CI: 54.5, 62.8) in cohort EXP-3B and among patients treated with 2 or 3 prior ALK-TKIs (pooled cohort EXP-4:EXP-5), the ORR was 38.7% (95%CI: 29.6, 48.5). Per cohort, the ORRs were 41.5% (CI 29.4, 54.4) in EXP-4 and 37.0% (23.2, 52.5) in EXP-5. A partial response was obtained in 39.3% in cohort EXP-3B and 37.8% in cohort EXP-4-5, while complete responses were observed in 3.6% and 1.8% of the patients, respectively.

Key secondary endpoints: Intracranial ORR by IRC, and results are also presented by cohort. Among the 9 patients with baseline brain metastases in EXP-3B, the IC ORR was 66.7% (95%CI: 29.9, 92.5) and among the 48 patients with baseline brain metastases in EXP-4:EXP-5, the IC ORR was 52.1% (95%CI: 37.2, 66.7). The CR/PR rates were 22.2/44.4% and 20.8/31.3%, respectively. Two patients (22.2%) and 8.3% of the patients from these subgroups, respectively, had progressive disease and no and 35.4%, respectively, had stable disease.

Median duration of response was 5.6 months (4.17-NR) in cohort EXP-3B and 9.9 months (5.65-24.44) in the pooled cohorts EXP-4 and 5, while time to tumour response were approximately 1.4 months across the cohorts. Median PFS by ICR was 5.5 months (95%CI: 2.9, 8.2) for EXP-3B and 6.9 months (95%CI: 5.4, 9.5) for EXP-4:EXP-5. The median OS for the 28 patients with ALK-positive NSCLC in EXP-3B was 19.5 months (95%CI: 18.3, 21.0) while it was 20.5 months (95%CI: 19.6, 23.3 for EXP-4:EXP-5.

There were no detrimental effects on quality of life in the pivotal study.

3.3. Uncertainties and limitations about favourable effects

Although the results from the presented study are considered mature, they are not considered comprehensive as based on uncontrolled data with limited sample size. Thus confirmatory studies are needed.

The ongoing confirmatory Phase 3 study compares lorlatinib to crizotinib in the first-line treatment of ALK-positive NSCLC and results will be available by Q4 2021. This proposed confirmatory study is considered acceptable for confirming the overall efficacy and safety of lorlatinib. In view of the preliminary evidence for the benefit of lorlatinib in the proposed second-line setting in patients progressing on/resistant to currently approved second-generation ALK-inhibitors, an observational efficacy study adequately powered to confirm the observed results in the limited sample size from EXP-3B will be conducted as a specific obligation to the CMA. The PAES will confirm the efficacy of lorlatinib in the second-line setting after disease progression on alectinib or ceritinib. The primary endpoint is ORR, the estimated sample size is 70 patients, and the results will be available in Q2 2024.

3.4. Unfavourable effects

All of the patients experienced at least one AE, and most of these were treatment-related. The most common TEAEs were hypercholesterolemia/hypertriglyceridemia, oedema, peripheral neuropathy, fatigue, cognitive and mood effects, dyspnoea, and increased weight. The most common Grade 3-4 events were also hypercholesterolemia/hypertriglyceridemia.

Adverse events of special interest include hyperlipidaemia, oedema, peripheral neuropathy, CNS effects, weight gain, and vision disorders.

Less than 10% of the patients discontinued lorlatinib permanently, but it is noted that only a third of the discontinuations were assessed to be treatment-related and these AEs were mostly related to cognitive effects, even at the 100 mg dose.

3.5. Uncertainties and limitations about unfavourable effects

There are inherent limitations to the interpretation of the safety profile based on a single arm non-comparative trial. The safety data from the ongoing controlled Phase 3 study 1006 will be important to further characterise the safety of lorlatinib post authorisation (see Annex II).

The CNS effects include e.g. mood effects, speech effects, and cognitive effects and looking at each effect individually may cause an underestimation of the overall risk of CNS effects with lorlatinib. Despite the relatively low rate of Grade 3 events, the reported cognitive disorders (neurological and psychiatric) may impact the patient's quality of life. CNS effects and their origin are very complex and challenging both to diagnose and evaluate, and the impact on patient functioning may be equally difficult to estimate. Therefore, safety results from the ongoing confirmatory Phase 3 study comparing lorlatinib to crizotinib in the first-line treatment of ALK-positive NSCLC (see Annex II) are especially important regarding the assessment of CNS effects in the first-line setting as fewer patients would have metastases to the CNS at that point in time.

3.6. Effects Table

Table 105: Effects Table for lorlatinib (data cutoff: 02 February 2018).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR by IRC	Proportion of patients with a confirmed CR or PR	%	EXP-3B: 42.9% EXP-4:EXP-5: 38.7%	N/A		
ORR IC	CR or PR in the CNS	%	EXP-3B: 66.7% EXP-4:EXP-5: 52.1%	N/A		
TTR	Time to tumour response	Months	EXP-3B: 1.4 EXP-4:EXP-5: 1.4	N/A		
DOR	Duration of response in patients with a RECIST Version 1.1 CR or PR	Months	EXP-3B: 5.6 EXP-4:EXP-5: 9.9	N/A		
PFS	Progression free survival	Months	EXP-3B: 5.5 EXP-4:EXP-5: 6.9	N/A		
OS	Overall survival	Months	EXP-3B: 19.5 EXP-4:EXP-5: 20.5	N/A		
Unfavourable Effects: safety population (n=295)						
Treatment-related Grade ≥ 3 TEAE		%	38.6	N/A		
Hypercholesterolemia	Treatment-related All grades	%	84.4	N/A		
Hypertriglyceridemia	Treatment-related All grades	%	67.1	N/A		
Oedema	Treatment-related All grades	%	54.6	N/A		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Peripheral neuropathy	Treatment-related All grades	%	47.8	N/A		
Cognitive effects	Treatment-related All grades	%	28.8	N/A		
Fatigue	Treatment-related All grades	%	28.1	N/A		
Mood effects	Treatment-related All grades	%	22.7	N/A		
Weight increased	Treatment-related All grades	%	26.4	N/A		
Diarrhoea	Treatment-related All grades	%	22.7	N/A		
Vision disorders	Treatment-related All grades	%	15.3	N/A		

Abbreviations: TAE: Treatment Emergent Event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is a recognised unmet medical need in ALK-positive NSCLC patients who progressed after currently available ALK-targeted agents (crizotinib, alectinib, and ceritinib).

Treatment with lorlatinib results in clinically relevant response rates and duration of response in the proposed second- and third or later line indication. The efficacy in brain metastases is clinically meaningful and lorlatinib is considered an effective treatment option for patients with brain metastases.

A major therapeutic advantage of lorlatinib over treatment alternatives (platinum-based chemotherapy and immunotherapies, etc.) can therefore be agreed upon for the proposed indication.

Although the number of patients included in the cohort EXP-3B supporting the 2nd line indication is limited, the totality of the data in the post 2nd generation ALK-inhibitors setting can support a positive B/R in that indication. The pivotal study is a single arm study with no comparator. However, as ALK is a driver mutation in ALK-positive NSCLC and lorlatinib is a targeted treatment against a well-known target, a randomisation to chemotherapy, immunotherapy or placebo is not considered ethical in a situation, when the disease progresses after use of the available ALK-inhibitors, due to the poor efficacy of these treatment options. Furthermore, all of the developed ALK-inhibitors have been superior in efficacy compared to chemotherapy and immunotherapy so far, both regarding ORR and duration of response and there is an unmet medical need in patients who progressed after second generation ALKi in the 2nd or 3rd line setting. However, given the limited sample size the applicant will conduct and submit an efficacy study post authorisation to further confirm the positive B/R in the 2nd line post 2nd generation ALK-inhibitor setting (see Section 3.7.3). The applicant's proposal for the study design is considered acceptable and results from approximately 70 patients treated in the proposed second-line setting will be available in Q2 2024.

Efficacy data presented according to the initial lines of ALK-targeted therapy from the EXP-4 and 5 cohorts show that almost all of the patients had crizotinib as first-line therapy and that lorlatinib as 3rd line treatment only induced responses in patients, who have had previous treatment with crizotinib and this is reflected in the wording of the indication. Time to tumour response of 1.4 months is in line with other ALK-inhibitors and is also considered clinically meaningful. It is also noted that the median OS was 20.5 months in the EXP4-5 cohort, which is considered highly clinically relevant in the third-or

later line setting. There was no obvious selection bias of subsequent therapies, the results are therefore considered clinically relevant and meaningful.

Reported adverse reactions appear manageable and for the most part reversible and unlikely to affect the tolerability of lorlatinib in the proposed dose. Lorlatinib causes multiple CNS effects which may have a negative impact on the patient's quality of life. However, it should be noted that only 7.1% of patients discontinued lorlatinib at the proposed dose regimen.

Finally, as part of the requirements for granting CMA, the applicant will provide results from an ongoing confirmatory Phase 3 trial in Q4 2021 at the earliest. Such data will confirm the overall efficacy and further characterise the safety profile of lorlatinib in the authorised indication. In addition, the applicant will conduct a PAES in the 2nd line post 2nd generation ALK inhibitors to confirm the efficacy of lorlatinib in that setting. The results will be submitted by Q2 2024 (see Annex II).

3.7.2. Balance of benefits and risks

The B/R is positive in the claimed indication. It is agreed that lorlatinib represents a major therapeutic advantage in patients who have been previously treated with the 2nd generation ALK-inhibitors alectinib or ceritinib and/or crizotinib who currently have very limited treatment options with limited efficacy and no standard of care. The ORR and DOR are considered clinically relevant in this setting and outweigh the risks related to the use of lorlatinib. Lorlatinib is a valuable treatment option with clinically meaningful efficacy in the CNS and results show similar response rates both systemically and in the CNS.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of advanced ALK-positive NSCLC which is a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed. Treatment with lorlatinib has demonstrated a positive benefit-risk balance for the treatment of ALK-positive NSCLC in the proposed indication.
- It is likely that the applicant will be able to provide comprehensive data. The data package is not considered comprehensive and the applicant will submit a Phase 3 confirmatory study in the 1st line setting to further characterise the overall efficacy and safety profile of lorlatinib. Although the Phase 3 study will be conducted in the 1L setting it will provide additional evidence to support the overall efficacy of lorlatinib in ALK-positive NSCLC and will allow putting safety data into context. In addition, in view of the limited sample size of cohort EXP-3B, the applicant will conduct and submit the results from an efficacy study to confirm efficacy in the proposed 2L ALK-positive NSCLC post 2nd generation ALKi setting. These are specific obligations to the CMA. The SOB is considered feasible as there is a high unmet medical need and to date no standard of care is available in the proposed second-line setting i.e. after alectinib and ceritinib and results are awaited by Q2 2024. The confirmatory Phase 3 trial is also considered

feasible as it is almost fully recruited and results are awaited in Q4 2021.

- Unmet medical needs will be addressed, as to date there is no standard of care in the proposed second- or later line setting. Patients who have progressed after a second generation ALKi in the 2L or 3L setting patients have a poor long-term prognosis. Lorlatinib represents a major therapeutic advantage over potential alternative treatment options for the proposed indication i.e. chemotherapy and immunotherapy. No targeted therapies (ALK-TKIs) have been approved for the applied indication.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required, as the available data show that lorlatinib is an effective CNS-penetrative therapy option in patients who progressed after treatment with a second generation ALK-inhibitors such as alectinib and ceritinib, a clinical setting where currently no treatments are authorised.

3.8. Conclusions

The overall B/R of lorlatinib for the treatment of adult patients with ALK positive advanced NSCLC whose disease has progressed after: alectinib or ceritinib as the first ALK TKI therapy; or crizotinib and at least one other ALK-TKI is positive.

A divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Lorviqua is favourable in the following 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) 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 CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, Section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

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

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

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
In order to further confirm the efficacy of lorlatinib in patients who progressed after alectinib or ceritinib as the first ALK-TKI therapy, the MAH should conduct a prospective single arm study investigating patients in that same setting. The clinical study report will be submitted by:	30 June 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lorlatinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

APPENDIX

DIVERGENT POSITION DATED 28 February 2019

DIVERGENT POSITION DATED 28 February 2019

Lorviqua EMEA/H/C/004646/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Lorviqua indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (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 reason for divergent opinion was the following:

Divergent position

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the conditional marketing authorisation of Lorviqua 25 & 100 mg film-coated tablets indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) after treatment with at least one second-generation ALK tyrosine kinase inhibitor (TKI).

In line with the requirements for a conditional marketing authorisation, the applicant must ensure that a major therapeutic advantage has been shown for the product applied for. In the view of the divergent CHMP members, these requirements have not been fulfilled for the following reasons:

- Major therapeutic advantage has not been shown for the entire claimed indication, as efficacy in the second-line setting (i.e. after a previous treatment with a second-generation ALK tyrosine kinase inhibitor) is currently not sufficiently established. The number of patients in the second line (n=28) does not allow for a proper evaluation of the efficacy data.
- The major therapeutic advantage shown in terms of efficacy in third or further lines cannot be extrapolated to the second-line setting, as the Applicant has not provided (non)-clinical data in support for such extrapolation approach.

Thus, the efficacy of Lorviqua 25 & 100 mg film-coated tablets in the claimed indication has not been sufficiently demonstrated rendering the B/R relationship of this product undetermined.

CHMP Members expressing a divergent opinion:

- HR – Katarina Vučić
- ES - Concepcion Prieto Yerro
- FR - Alexandre Moreau
- NL - Johann Lodewijk Hillege
- Co-opted member - Sol Ruiz