27 February 2025
EMA/210106/2025

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lorviqua

International non-proprietary name: Lorlatinib

Procedure No. EMEA/H/C/004646/R/0040

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure:	02 Dec 2024	02 Dec 2024	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	02 Jan 2025	23 Dec 2024	☐
☐	CHMP and PRAC members comments	06 Jan 2025	n/a	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	09 Jan 2025	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 Jan 2025	16 Jan 2025	☐
☐	Request for supplementary information	30 Jan 2025	30 Jan 2025	☐
	Submission of responses	04 Feb 2025	04 Feb 2025	
☐	Start of procedure:	05 Feb 2025	05 Feb 2025	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	12 Feb 2025	12 Feb 2025	☐
☐	PRAC endorsed relevant sections of the assessment report	13 Feb 2025	13 Feb 2025	☐
☐	CHMP and PRAC members comments	17 Feb 2025	17 Feb 2025	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	20 Feb 2025	n/a	☐
☒	Opinion	27 Feb 2025	27 Feb 2025	☐

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1. Background information on the annual renewal

The European Commission issued on 6 May 2019, a conditional marketing authorisation (MA) for Lorviqua. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Pfizer Europe MA EEIG, submitted to the Agency on 31 October 2024 an application for renewal of the conditional MA for Lorviqua. The expiry date of the MA is 8 May 2025.

The period covered by this annual renewal is 06 August 2023 to 05 August 2024.

The application contained a justification in support of the possible granting of a marketing authorisation no longer subject to specific obligations.

2. Overall conclusions and benefit-risk balance

The MAH is seeking renewal for two authorised Lorviqua presentations 100 mg and 25 mg film-coated tablet.

The MAH submitted the **B7461027** clinical study report within the current annual renewal to fulfil the last outstanding specific obligation and consequently to request the granting of a full marketing authorisation, no longer subject to specific obligations, in accordance with Article 14(1) of Regulation (EC) No 726/2004.

Efficacy

The final CSR from study B7461027 was submitted. This is a non-comparative study of use of lorlatinib in patients with advanced ALK-positive NSCLC, who had disease progression after one prior second-generation ALK-TKI (alectinib or ceritinib as first line of treatment) for metastatic disease. The study was designed to substantiate the clinical efficacy in that particular population with a larger sample size (N=71) compared to pivotal Study 1001 (EXP-3B cohort; N=28).

A total of 71 participants were treated with lorlatinib at 23 centres in 7 countries. The first participant was enrolled on 29 September 2020 and enrollment was completed on 13 June 2023. The primary completion date (PCD) was 29 May 2024. All treated patients had at least 1 prior anti-cancer drug therapy, 16.9% received prior chemotherapies, 84.5% received alectinib as prior ALK inhibitor and 15.5% received ceritinib as prior ALK inhibitor. Moreover, 47.9% had at least 1 prior anti-cancer radiotherapy and 14.1% underwent at least 1 prior anti-cancer surgery. The median duration of study intervention was 9.69 months.

The primary efficacy endpoint was ORR by independent review (ICR). The ITT analysis showed that 4 (5.6%) patients had a confirmed CR and 36.6% had a confirmed PR, resulting in an ORR of 42.3% (95%CI: 30.6%, 54.6%). The study met its primary endpoint as the lower limit of the 95%CI around the estimated ORR exceeded 30%. Of note, the ORR was slightly higher in patients who had received prior ceritinib (45.5%) versus those who had prior alectinib; however, no firm conclusions could be made due to the small sample size of patients who had prior ceritinib.

Safety

No new safety signals were observed in the study therefore no new safety concerns are raised. Frequencies of adverse reactions were updated in sections 4.8 and 4.4 to reflect the updated safety data set including the additional 71 patients from study B7461027. They remain largely in line with existing frequencies.

In summary, the ORR of 42.3% shown from single-arm study B7461027 is in line with what has previously been reported (42.9%) and the efficacy in the second-line setting after a second-generation ALK-TKI is considered to be confirmed with a reasonable sample size (N=99). Section 5.1 of the SmPC has been adequately updated with the final results of study B7461027.

The remaining Specific Obligation is considered fulfilled, and its deletion from the Annex II is recommended.

The marketing authorisation of Lorviqua can be switched from conditional marketing authorization to full marketing authorization.

Within this renewal the MAH also requested a change to the proposed due date for submitting the CSR of the study B7461006 (CROWN) (Annex II.D condition). The originally agreed due date of 30 June 2025 was estimated based on the total number of OS events available at the time of the first interim analysis of OS (51 OS events, 26% information fraction (IF), data cutoff date 20 March 2020). Since that time, OS events in the CROWN study have accrued more slowly than originally projected, making this due date no longer tenable. Based on a revised OS prediction the MAH expects that the 139 OS events required for the pre-specified second interim analysis of OS (at 70% IF) will be met in Apr 2027 (95%CI Apr 2026-Jul 2028). The proposal to change the CSR submission due date to 01 Dec 2027 is considered acceptable.

Minor updates to the product information were also made, in line the latest QRD template.

The Benefit risk of Lorviqua remains positive and unchanged.

Risk Management Plan

The updated RMP v5.3 was found acceptable.

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal, data on the SOBs have been submitted that are overall compliant in terms of adherence to deadlines and in terms of acceptability of data submitted.

As part of this annual renewal the CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

Study B7461027: Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Whose Ongoing Disease Progressed After One Prior Second Generation ALK Tyrosine Kinase Inhibitor (TKI). This is a Phase 4 open-label, multicenter, multi-national, non-randomized, prospective, single-arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease.

Updated list of specific obligations (SOBs)

The last SOB has been fulfilled and the data available concerning this product is considered comprehensive; therefore, there are no remaining Specific Obligations.

2.2. Benefit-risk Balance

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the benefit-risk of Lorviqua in the approved indications.

The data collected as part of the specific obligation for Lorviqua during the period covered by this annual renewal supported its positive benefit-risk balance in the approved indications.

The MAH has submitted data from the requested single-arm study B7461027, which was a SOB for the CMA of lorlatinib and the main objective was to substantiate the clinical efficacy in the second-line setting after a second-generation ALK-TKI with a larger sample size (N=71) compared to pivotal Study 1001 (EXP-3B cohort; N=28).

Since the results show an ORR of 42.3%, which is fully in line with what has been previously reported (42.9%), the efficacy in the second-line setting after a second-generation ALK-TKI is considered to be confirmed with a reasonable sample size (N=99). Moreover, no new safety signals were observed in the study.

Therefore, the benefit-risk balance of Lorviqua in the approved indications remains positive.

No new post-authorisation measures are requested.

3. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Lorviqua in its approved indication(s) (please refer to the Summary of Product Characteristics) continues to be favourable and all specific obligations have been fulfilled, and therefore the granting of a marketing authorisation no longer subject to specific obligations is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application amendments to Annexes I, II and IIIB are recommended

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

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

- ***Obligation to conduct post-authorisation measures***

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

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of lorlatinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor, the MAH will submit the results including overall survival (OS) data of the Phase III CROWN study **(B7461006)** comparing lorlatinib versus crizotinib in that same setting.	Dec 2027

PSUR cycle

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

4. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation.

Summary

Please refer to Scientific Discussion 'Lorviqua-H-C-004646-R-0040'.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☒	☐
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☒
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☒

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Full list of SOBs as adopted with the initial marketing authorisation

Description	Due date
001: 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 Fulfilled
002: Study B7461027 - 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 Submitted here

Since the granting of the conditional MA, the MAH has submitted the following SOB:

001: 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.

This was fulfilled via variation II/0015 for which an EC decision was issued in January 2022. Some further update has been provided with this submission, see section 6.1.

5.2. Outstanding Specific Obligations – status report for period covered

With this submission the MAH provided the final report for:

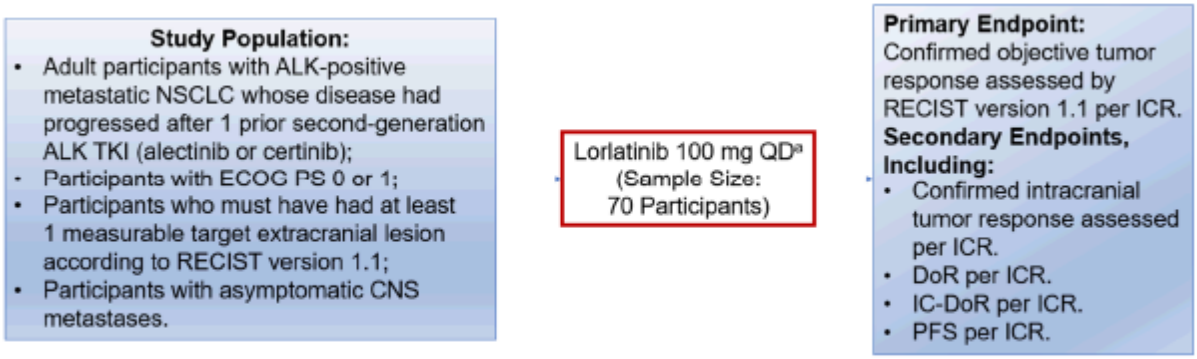
Study B7461027: Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Whose Ongoing Disease Progressed After One Prior Second Generation ALK Tyrosine Kinase Inhibitor (TKI) - a Phase 4 open-label, multicenter, multi-national, non-randomized, prospective, single-arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease.

Efficacy

Methods

Study 1027 is a Phase 4 open-label, multicenter, multinational, non-randomized, prospective, single-arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first-line of treatment for metastatic disease (Figure 1). The study was designed to fulfil the SOB for the CMA with the goal to substantiate the clinical efficacy in this particular population with a larger sample size (N=71) compared to pivotal Study 1001 (EXP-3B cohort; N=28).

Figure 1: Study Schema



Source: Appendix 16.1.1, Protocol Section 1.2
a. Treatment until disease progression, patient refusal/lost to follow-up, or unacceptable toxicity.

The objectives were to assess the overall and intracranial activity of single-agent lorlatinib in patients with advanced ALK-positive NSCLC evaluated by independent central review (ICR) and by Investigators as well as the Safety of the compound. Approximately 85 participants were to be screened to achieve 70 participants assigned to study intervention.

Results

A total of 71 participants were treated with lorlatinib at 23 centers in 7 countries. A total of 85 participants signed the informed consent and were screened in the study, and 71 participants completed screening and were treated with lorlatinib. The first participant was enrolled on 29 September 2020. Enrolment was completed on 13 June 2023 with 71 subjects dosed. The study reached the Primary Completion Date (PCD) on 29 May 2024.

Figure 2: Participant Disposition

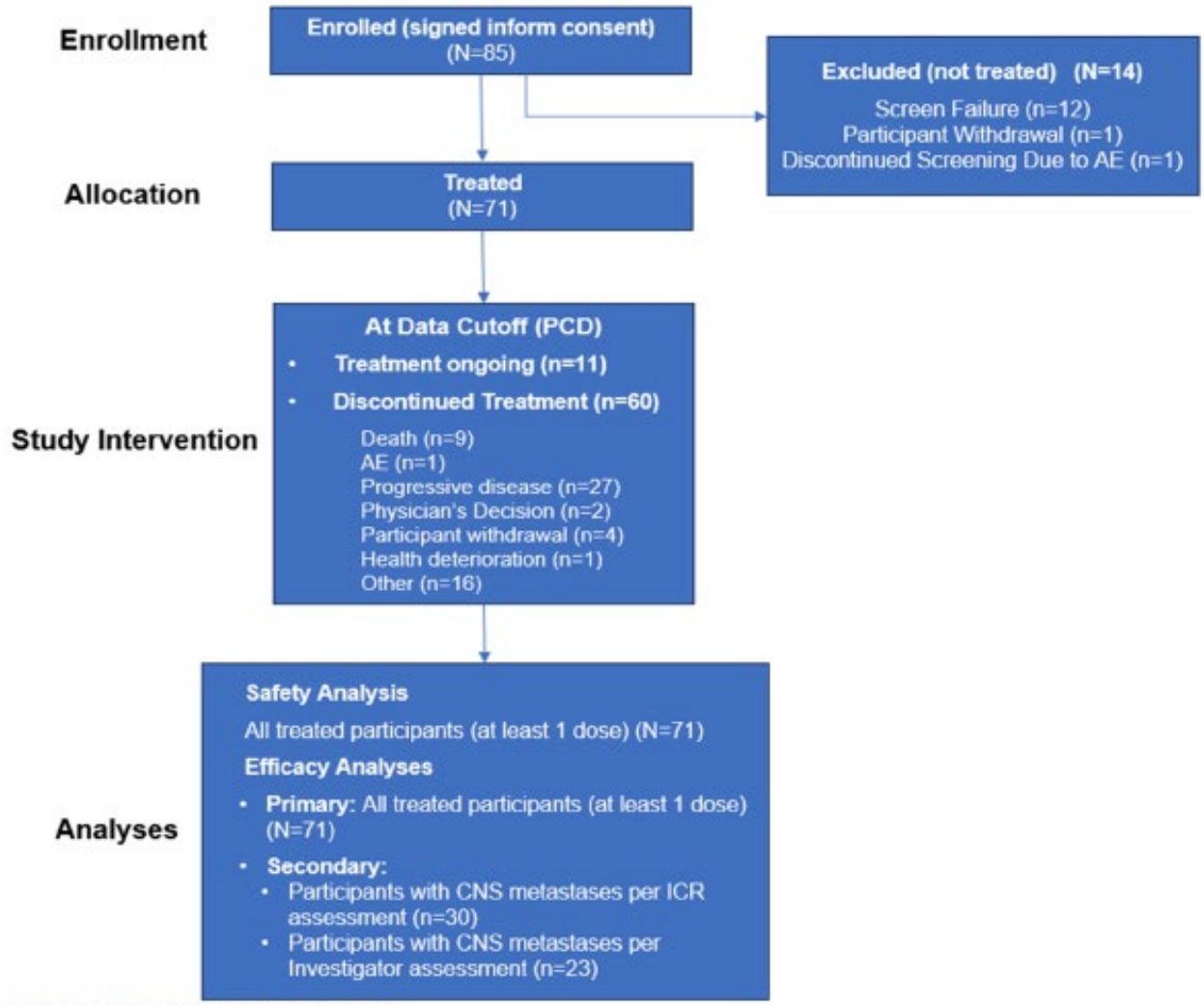


Table 1: Participant Evaluation Groups (Protocol B7461027)

	Lorlatinib (N=71) n (%)
Screened (Enrolled Analysis Set[a]): 85	
Screen Failure: 12	
Discontinued without treatment for other reasons[b]: 2	
Treated (Intent to Treat[c])	71 (100.0)
Safety Analysis Set[d]	71 (100.0)
Per Protocol Analysis Set based on Independent Central Review[e]	30 (42.3)
Per Protocol Analysis Set based on Investigator Assessment[f]	23 (32.4)

a. Enrolled Analysis Set: Participants who sign the Inform Consent Form.
b. Discontinued screening phase due to adverse event (1 participant) and withdrawal of consent (1 participant).
c. Intent to Treat: ITT.
d. Safety Analysis Set: Participants who take at least 1 dose of Lorlatinib.
e. Per Protocol Analysis Set based on Independent Central Review (PPICR): Participants with CNS metastases at study entry according to central neuroradiological review.
f. Per Protocol Analysis Set based on Investigator Assessment (PPINV): Participants with CNS metastases at study entry (at least one brain lesion) according to investigator assessment.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adsl Table Generation: 19JUL2024 (16:55) (Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746_US/B7461027_CSR/adsl_s002 Table 14.1.1.1 PF-06463922 is for Pfizer internal use.

Baseline data

Table 2: Demographic Characteristics – ITT Analysis Set (Protocoal B7461027)

	Lorlatinib (N=71)
Age (Years), n (%)	
18 - 44	13 (18.3)
45 - 64	35 (49.3)
≥ 65	23 (32.4)
Mean (SD)	58.1 (12.9)
Median (Range)	59.0 (26.0, 87.0)
(Q1,Q3)	(48, 68)
Gender, n (%)	
Male	41 (57.7)
Female	30 (42.3)
Race, n (%)	
White	54 (76.1)
Asian	15 (21.1)
Not reported	2 (2.8)
ECOG performance status, n (%)	
0	37 (52.1)
1	34 (47.9)

Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
The denominator to calculate percentages is N, the number of participants in the ITT analysis set.
Baseline ECOG is defined as the last assessment performed on or prior to date of the first dose of lorlatinib.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adsl Table Generation: 09JUL2024 (12:59) (Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/adsl s001 Table 14.1.2 PF-06463922 is for Pfizer internal use.

Medical History and Concurrent Illnesses

A total of 37 (52.1%) participants had at least 1 disease/syndrome of prior medical history, and 60 (84.5%) participants had ongoing medical histories.

- The most frequently reported prior medical histories included Cholecystectomy (5 [7.0%]), Tonsillectomy (4 [5.6%]) and Chest pain (4 [5.6%]).
- The most frequently reported ongoing medical history was Hypertension (24 [33.8%]).

Primary Diagnosis

All treated participants had primary diagnosis of ALK-positive NSCLC, and the median duration since initial diagnosis was 23.1 (range: 4.0 – 248.5) months.

- Most participants (69 [97.2%] participants) had histopathological classification of adenocarcinoma with 59 (83.1%) participants having adenocarcinoma NOS. Two (2.8%) participants had non-adenocarcinoma histopathological classification.
- At initial diagnosis, most participants (63 [88.7%]) had TNM Stage IV.

ALK Tests

Most participants (54 [76.1%]) used IHC, and 5 (7.0%) participants each used FISH, NGS and RT-PCR. The ALK analytical methods of 2 (2.8%) participants were missing in the absence of a validated ALK status assessment.

Prior, Concomitant and Post-Interventional Therapy

Prior Anti-Cancer Therapies

All 71 treated participants had at least 1 type of prior anti-cancer treatment.

- All 71 treated participants had at least 1 prior anti-cancer drug therapy.
  - o 12 (16.9%) participants received prior chemotherapies.
  - o 60 (84.5%) participants received alectinib as prior ALK inhibitor and 11 (15.5%) participants received ceritinib as prior ALK inhibitor.
- 34 (47.9%) participants had at least 1 prior anti-cancer radiotherapy.
- 10 (14.1%) participants underwent at least 1 prior anti-cancer surgery.

Objective Response to Prior ALK-TKI

The ORR of the 71 treated participants to prior ALK-TKI was 67.6% (95% CI: 55.5%, 78.2%)

- For the 60 participants with prior ALK-TKI of alectinib, the ORR was 76.7% (95% CI: 64.0%, 86.6%)
- For the 11 participants with prior ALK-TKI of ceritinib, the ORR was 18.2% (95% CI: 2.3%, 51.8%)

All 71 treated participants discontinued from prior ALK-TKI, and the Kaplan-Meier estimate of median time of prior ALK treatment duration was 20.0 (95% CI: 15.9, 22.8) months.

Concomitant Treatments

A total of 70 (98.6%) participants received at least 1 concomitant medication with the most frequently used concomitant medications being furosemide (20 [28.2%] participants) and rosuvastatin (17 [23.9%] participants).

A total of 10 (14.1%) participants received at least 1 concomitant non-drug treatment/procedure. All concomitant non-drug treatments/procedures are reported in single participants except for Oxygen therapy reported in 3 (4.2%) participants.

Subsequent Anti-Cancer Therapies

A total of 18 (25.4%) participants received at least 1 type of subsequent anti-cancer treatment: 18 (25.4%) participants received at least 1 subsequent anti-cancer drug therapy, and 1 (1.4%) participant received at least 1 subsequent anti-cancer radiotherapy; no participant underwent subsequent anti-cancer surgery.

Exposure and Study Intervention Compliance

Exposure

Of the 71 treated participants, the median duration of study intervention was 9.69 (range: 0.33, 42.78) months. Most participants (53 [74.6%]) had duration of study intervention ≥91 days.

Of the 71 treated participants, the median cumulative lorlatinib dose was 27200 (range: 1000,130250) mg, the median dose intensity was 100 (range: 62.1, 100) mg/day, and the median relative dose intensity was 100% (range: 62.1%, 100%).

A total of 47 (66.2%) participants discontinued lorlatinib. Kaplan-Meier estimate of median duration of study intervention was 9.7 (95%CI: 7.3, 18.2) months. Participants who remained on study intervention or continued receiving lorlatinib off study were censored at the last known lorlatinib dose date.

Dose Modification

11 (15.5%) participants had 1 dose reduction and 2 (2.8%) participants had 2 dose reductions based on investigator prescription. All these 13 (18.3%) participants had dose reductions due to AEs, of whom 1 participant also had other reasons for dose reduction.

30 (42.3%) participants had dose interruptions, and most participants (16 [22.5%]) had 1 interruption. A total of 21 (29.6%) participants had dose interruptions due to AEs, and 11 (15.5%) participants had dose interruptions due to other reasons.

Outcomes and estimation

Efficacy

Primary Efficacy Endpoint: Confirmed Objective Tumor Response Assessed by ICR

Based on the ICR assessment of ITT Analysis Set (N=71), 4 (5.6%) participants had a confirmed CR and 26 (36.6%) participants had a confirmed PR, resulting in an ORR of 42.3% (95%CI: 30.6%, 54.6%) (Table 7). The study met its primary endpoint as the lower limit of the 95%CI around the estimated ORR exceeded 30%.

- Of the 60 participants who received prior ALK-TKI of alectinib, the ORR was 41.7% (95%CI: 29.1%, 55.1%) per ICR assessment. Of the responders, 2 participants received prior alectinib + chemotherapies.
- Of the 11 participants who received prior ALK-TKI of ceritinib, the ORR was 45.5% (95% CI: 16.7%, 76.6%) per ICR assessment. Of the responders, 3 participants received prior ceritinib + chemotherapies.

In a post-hoc analysis, the ORR of the participants with measurable disease at baseline per ICR assessment (N=64) was evaluated. Of the 64 participants with measurable diseases at baseline, 3 (4.7%) participants had a confirmed CR and 26 (40.6%) participants had a confirmed PR, with the ORR of 45.3% (95%CI: 32.8%, 58.3%).

Table 3: Summary of Best Overall Response and Objective Response (Confirmed) based on ICR Assessment (RECIST v1/1) – ITT Analysis Set (Protocol B7461027)

	Lorlatinib (N=71)
Confirmed Best Overall Response, n (%)	
Complete response (CR)	4 (5.6)
Partial response (PR)	26 (36.6)
Stable disease (SD)	14 (19.7)
Non-CR/Non-PD	6 (8.5)
Progressive disease (PD)	13 (18.3)
Not evaluable (NE)	8 (11.3)
Reason for NE, n (%)	
No post-baseline assessments due to early death	3 (4.2)
No post-baseline assessments due to other reasons	3 (4.2)
SD too early [< 6 weeks after treatment start date]	2 (2.8)
Objective Response (CR+PR), n (%)	30 (42.3)
95% CI [a]	30.6, 54.6

The denominator to calculate percentages is N, the number of participants in the ITT analysis set.
a. Clopper-Pearson method used.

Secondary Efficacy Endpoints

Confirmed Objective Tumor Response Assessed by Investigator

Based on the investigator assessment of ITT Analysis Set (N=71), 1 (1.4%) participant had a confirmed CR and 25 (35.2%) participants had a confirmed PR, resulting in an ORR of 36.6% (95%CI: 25.5%, 48.9%) (Table 8). The confirmed ORR assessed by the investigator was consistent with the ORR assessed by ICR, further corroborating the robustness of the estimation of the ORR.

- Of the 60 participants who received prior ALK-TKI of alectinib, the ORR was 36.7% (95%CI: 24.6%, 50.1%) per investigator assessment.
- Of the 11 participants who received prior ALK-TKI of ceritinib, the ORR was 36.4% (95%CI: 10.9%, 69.2%) per investigator assessment.

The agreement rate between investigator- and ICR-assessed ORR was 74.6%.

Table 4: Summary of Best Overall Response and Objective Response (Confirmed) based on Derived Investigator Assessment (RECIST v1/1) – ITT Analysis Set (Protocol B7461027)

	Lorlatinib (N=71)
Confirmed Best Overall Response, n (%)	
Complete response (CR)	1 (1.4)
Partial response (PR)	25 (35.2)
Stable disease (SD)	24 (33.8)
Non-CR/Non-PD	0
Progressive disease (PD)	12 (16.9)
Not evaluable (NE)	9 (12.7)
Reason for NE, n (%)	
No adequate baseline assessment	1 (1.4)
No post-baseline assessments due to early death	3 (4.2)
No post-baseline assessments due to other reasons	3 (4.2)
SD too early [< 6 weeks after treatment start date]	2 (2.8)
Objective Response (CR+PR), n (%)	26 (36.6)
95% CI [a]	25.5, 48.9

The denominator to calculate percentages is N, the number of participants in the ITT analysis set.
a. Clopper-Pearson method used.
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(Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File:
./B746 US/B7461027 CSR/adrsd borc s001
Table 14.2.1.5 PF-06463922 is for Pfizer internal use.

Confirmed Intracranial Tumor Response Assessed by ICR and Investigator

Based on the ICR assessment of the PPICR Analysis Set (N=30), 10 (33.3%) participants had a confirmed intracranial CR and 4 (13.3%) participants had a confirmed intracranial PR, with the intracranial ORR of 46.7% (95%CI: 28.3%, 65.7%) (Table 9).

- Of the 21 participants in PPICR Analysis Set who received prior ALK-TKI of alectinib, the intracranial ORR was 47.6% (95% CI: 25.7%, 70.2%) per ICR assessment.
- Of the 9 participants in PPICR Analysis Set who received prior ALK-TKI of ceritinib, the intracranial ORR was 44.4% (95% CI: 13.7%, 78.8%) per ICR assessment.

Based on the investigator assessment of PPINV Analysis Set (N=23), 6 (26.1%) participants had a confirmed intracranial CR and 7 (30.4%) participants had a confirmed intracranial PR, with the intracranial ORR of 56.5% (95% CI: 34.5%, 76.8%).

- Of the 14 participants in PPINV Analysis Set who received prior ALK-TKI of alectinib, the intracranial ORR was 42.9% (95%CI: 17.7%, 71.1%) per investigator assessment.
- Of the 9 participants in PPINV Analysis Set who received prior ALK-TKI of ceritinib, the intracranial ORR was 77.8% (95%CI: 40.0%, 97.2%) per investigator assessment.

Table 5: Summary of Intra-Cranial Best Overall Response and Objective Response (Confirmed) based on ICR Assessment (RECIST v1/1) – PPICR Analysis Set (Protocol B7461027)

	Lorlatinib (N=30)
Confirmed Best Overall Response, n (%)	
Complete response (CR)	10 (33.3)
Partial response (PR)	4 (13.3)
Stable disease (SD)	1 (3.3)
Non-CR/Non-PD	10 (33.3)
Progressive disease (PD)	2 (6.7)
Not evaluable (NE)	3 (10.0)
Reason for NE, n (%)	
No post-baseline assessments due to other reasons	2 (6.7)
SD too early [< 6 weeks after treatment start date]	1 (3.3)
Objective Response (CR+PR), n (%)	14 (46.7)
95% CI [a]	28.3, 65.7

The denominator to calculate percentages is N, the number of participants in the Per Protocol Analysis Set based on Independent Central Review (PPICR).
a. Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adrsbi Table Generation: 22JUL2024 (11:46) (Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/adrsbi borc s001
Table 14.2.1.6 PF-06463922 is for Pfizer internal use.

Time to Tumor Response (TTR) per ICR and Investigator Assessment

Based on the ICR assessment of ITT Analysis Set, of the 30 treated participants with confirmed CRs or PRs, the median TTR was 1.5 (range: 1.2, 8.4) months, corresponding with the timing of the first scheduled tumor scan.

- Based on the ICR assessment of PPICR Analysis Set, of the 14 participants with confirmed intracranial objective responses, median time to intracranial tumor response was 2.8 (range: 1.3, 12.6) months.

Based on the investigator assessment of ITT Analysis Set, of the 26 treated participants with confirmed CRs or PRs, the median TTR was 1.6 (range: 1.2, 8.3) months.

- Based on the investigator assessment of PPINV Analysis Set, of the 13 participants with confirmed intracranial objective responses, median time to intracranial tumor response was 2.8 (range: 1.3, 15.3) months

Duration of Response (DoR) per ICR and Investigator Assessment

Based on the ICR assessment in the ITT Analysis Set, of the 30 participants with confirmed CRs or PRs, over 50% of responders (16 [53.3%] participants) remained in response at the time of PCD data-cut. Overall, 9 (30.0%) of the responders experienced an event due to disease progression and 1 (3.3%) due to death.

- Kaplan-Meier estimate of the median duration of follow-up for response was 18.0 (95%CI: 9.6, 22.1) months.
- The median DoR was not reached (95%CI: 8.6 months, NE).
- The range of DoR was 1.4 to 25.2 months.
- The probability of being event-free at 12 months was 0.652 (95%CI: 0.434, 0.803).

Based on the investigator assessment in the ITT Analysis Set, of the 26 participants with confirmed CRs or PRs, 12 (46.2%) participants were ongoing at the PCD data-cut. Overall, 12 (46.2%) of the responders experienced an event due to disease progression.

- The median DoR was 20.9 (95%CI: 9.9, NE) months.
- The range of DoR was 1.4 to 27.2 months.
- The probability of being event-free at 12 months was 0.657 (95%CI: 0.428, 0.812).

Duration of Intracranial Response (IC-DoR) per ICR and Investigator Assessment

Based on the ICR assessment of PPICR Analysis Set, of the 14 participants with confirmed intracranial CRs or PRs, no participant had an event of progressive disease or death; 13 (92.9%) participants were ongoing at the PCD data-cut.

- Median IC-DoR was not reached.
- The range of IC-DoR was 2.9 to 22.6 months.
- The probability of being event-free at 12 months was 1.00.

Based on the investigator assessment of PPINV Analysis Set, of the 13 participants with confirmed intracranial CRs or PRs, 1 (7.7%) participant had progressive disease; 11 (84.6%) participants were ongoing at the PCD data-cut.

- Median IC-DoR was not reached.
- The range of IC-DoR was 2.8 to 22.1 months.
- The probability of being event-free at 12 months was 0.923 (95%CI: 0.566, 0.989).

Time to Tumor Progression (TTP) per ICR and Investigator Assessment

Based on the ICR assessment in the ITT Analysis Set (N=71), 30 (42.3%) participants had progressive disease and 25 (35.2%) participants were ongoing without progressive disease.

- Kaplan-Meier estimate of the median TTP was 18.0 (95% CI: 9.7, NE) months.
- The probability of being event-free at 12 months was 0.585 (95%CI: 0.448, 0.699).
- Of the 60 participants who received prior ALK-TKI of alectinib, 29 (48.3%) had progressive disease, with Kaplan-Meier estimate of a median TTP of 12.2 (95%CI: 6.9, NE) months. Of the 11 participants who received prior ALK-TKI of ceritinib, 1 (9.1%) had progressive disease and the median TTP was not reached.

Based on the investigator assessment in the ITT Analysis Set (N=71), 34 (47.9%) participants had progressive disease and 22 (31.0%) participants were ongoing without progressive disease.

- Kaplan-Meier estimate of the median TTP was 12.2 (95%CI: 8.3, 24.8) months.
- The probability of being event-free at 12 months was 0.516 (95%CI: 0.379, 0.637).
- Of the 60 participants who received prior ALK-TKI of alectinib, 31 (51.7%) had progressive disease, with Kaplan-Meier estimate of a median TTP of 10.4 (95%CI: 7.1, 22.1) months. Of the 11 participants who received prior ALK-TKI of ceritinib, 3 (27.3%) had progressive disease and the median TTP was not reached.

Progression-Free Survival (PFS) per ICR and Investigator Assessment

Based on the ICR assessment in the ITT Analysis Set, of the 71 treated participants, 30 (42.3%) participants had progressive disease and 8 (11.3%) participants died; 25 (35.2%) participants were ongoing without an event at the PCD data-cut.

- Kaplan-Meier estimate of the median PFS was 12.2 (95%CI: 6.9, 22.1) months.

- The probability of being event-free at 12 months was 0.509 (95%CI: 0.381, 0.623).
- Of the 60 participants who received prior ALK-TKI of alectinib, 36 (60.0%) had progressed or died, with Kaplan-Meier estimate of a median PFS of 8.3 (95%CI: 5.5, 16.5) months. Of the 11 participants who received prior ALK-TKI of ceritinib, 2 (18.2%) had progressed or died and the median PFS was not reached.

Based on the investigator assessment in the ITT Analysis Set, of the 71 treated participants, 34 (47.9%) participants had progressive disease and 6 (8.5%) participants died; 22 (31.0%) participants were ongoing without an event at the PCD data-cut.

- Kaplan-Meier estimate of the median PFS was 9.7 (95%CI: 6.9, 18.4) months.
- The probability of being event-free at 12 months was 0.459 (95%CI: 0.332, 0.578).
- Of the 60 participants who received prior ALK-TKI of alectinib, 36 (60.0%) had progressed or died, with Kaplan-Meier estimate of a median PFS of 8.4 (95%CI: 6.1, 16.6) months. Of the 11 participants who received prior ALK-TKI of ceritinib, 4 (36.4%) had progressed or died and the median PFS was not reached.

Safety

Adverse events

An overview of all-causality and treatment-related TEAEs is presented in Table 6 and Table 7, respectively.

Table 6: Overview of TEAEs – Safety Analysis Set (Protocol B7461027)

Number (%) of Participants	Lorlatinib n (%)
Participants evaluable for adverse events	71
Number of adverse events	545
Participants with adverse events	69 (97.2)
Participants with serious adverse events	23 (32.4)
Participants with non-serious adverse events	69 (97.2)
Participants with Maximum Grade 3 or 4 adverse events	28 (39.4)
Participants with Maximum Grade 5 adverse events	10 (14.1)
Participants discontinued study drug due to AE[a]	9 (12.7)
Participants with dose reduced or temporary discontinuation due to adverse events	27 (38.0)

TEAEs are all causality unless otherwise specified.
Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn
MedDRA v27.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adae Table Generation: 12JUL2024 (10:43)
(Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/adae s020
Table 14.3.1.1.1 PF-06463922 is for Pfizer internal use.

Table 7: Overview of Treatment-Related TEAEs – Safety Analysis Set (Protocol B7461027)

Number (%) of Participants	Lorlatinib n (%)
Participants evaluable for adverse events	71
Number of adverse events	253
Participants with adverse events	64 (90.1)
Participants with serious adverse events	1 (1.4)
Participants with non-serious adverse events	64 (90.1)
Participants with Maximum Grade 3 or 4 adverse events	19 (26.8)
Participants with Maximum Grade 5 adverse events	0
Participants discontinued study drug due to AE[a]	0
Participants with dose reduced or temporary discontinuation due to adverse events	14 (19.7)

Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn
MedDRA v27.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adae Table Generation: 12JUL2024 (10:44)
(Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746_US/B7461027_CSR/adae_s021
Table 14.3.1.2.1 PF-06463922 is for Pfizer internal use.

Treatment-Emergent AEs

Frequencies of all-causality and treatment-related TEAEs occurring in ≥5% of participants at any grade are summarized by PT/Cluster Term in Table 8and Table 9, respectively.

Table 8: TEAEs (any Grade ≥ 5%) by PT/CLUSTER Term and Maximum CTCAE Grade – Safety Analysis Set (Protocol B7461027)

Number of Participants Evaluable for AEs	Lorlatinib (N=71)		
Number (%) of Participants: by CLUSTER or Preferred Term	Grade 1-2 n (%)	Grade 3-4 n (%)	Any Grade n (%)
With any adverse events	31 (43.7)	28 (39.4)	69 (97.2)
HYPERCHOLESTEROLEMIA	36 (50.7)	6 (8.5)	42 (59.2)
HYPERTRIGLYCERIDEMIA	31 (43.7)	9 (12.7)	40 (56.3)
EDEMA	30 (42.3)	3 (4.2)	33 (46.5)
FATIGUE	19 (26.8)	0	19 (26.8)
PERIPHERAL NEUROPATHY	14 (19.7)	1 (1.4)	15 (21.1)
Dyspnoea	10 (14.1)	4 (5.6)	14 (19.7)
Diarrhoea	12 (16.9)	1 (1.4)	13 (18.3)
Hyperlipidaemia	12 (16.9)	0	12 (16.9)
Pyrexia	12 (16.9)	0	12 (16.9)
Anaemia	8 (11.3)	1 (1.4)	9 (12.7)
Arthralgia	9 (12.7)	0	9 (12.7)
COVID-19	7 (9.9)	1 (1.4)	9 (12.7)
MOOD EFFECTS	9 (12.7)	0	9 (12.7)
Cough	8 (11.3)	0	8 (11.3)
Pain in extremity	7 (9.9)	1 (1.4)	8 (11.3)
Weight increased	7 (9.9)	0	7 (9.9)
COGNITIVE EFFECTS	5 (7.0)	1 (1.4)	6 (8.5)
Nausea	5 (7.0)	1 (1.4)	6 (8.5)
Rash	6 (8.5)	0	6 (8.5)
Vomiting	6 (8.5)	0	6 (8.5)
Blood creatinine increased	5 (7.0)	0	5 (7.0)
SARS-CoV-2 test positive	4 (5.6)	1 (1.4)	5 (7.0)
Alanine aminotransferase increased	2 (2.8)	2 (2.8)	4 (5.6)
Back pain	4 (5.6)	0	4 (5.6)
Blood glucose increased	4 (5.6)	0	4 (5.6)
Dizziness	3 (4.2)	1 (1.4)	4 (5.6)
Dyspnoea exertional	4 (5.6)	0	4 (5.6)
Headache	4 (5.6)	0	4 (5.6)
Hypertension	3 (4.2)	1 (1.4)	4 (5.6)
Hyperuricaemia	4 (5.6)	0	4 (5.6)
Pulmonary embolism	2 (2.8)	1 (1.4)	4 (5.6)
SPEECH EFFECTS	3 (4.2)	1 (1.4)	4 (5.6)
VISION DISORDER	4 (5.6)	0	4 (5.6)

TEAEs are all causality unless otherwise specified.
Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Decreasing order of frequency relative to Any Grade column.
MedDRA v27.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adae Table Generation: 09JUL2024 (13:00) (Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/adae s063 2 Table 14.3.1.1.5 PF-06463922 is for Pfizer internal use.

Table 9: Treatment-related TEAEs (any Grade ≥ 5%) by PT/CLUSTER Term and Maximum CTCAE Grade – Safety Analysis Set (Protocol B7461027)

Number of Participants Evaluable for AEs	Lorlatinib (N=71)		
Number (%) of Participants: by CLUSTER or Preferred Term	Grade 1-2 n (%)	Grade 3-4 n (%)	Any Grade n (%)
With any adverse events	45 (63.4)	19 (26.8)	64 (90.1)
HYPERCHOLESTEROLEMIA	34 (47.9)	5 (7.0)	39 (54.9)
HYPERTRIGLYCERIDEMIA	30 (42.3)	9 (12.7)	39 (54.9)
EDEMA	23 (32.4)	3 (4.2)	26 (36.6)
Hyperlipidaemia	11 (15.5)	0	11 (15.5)
PERIPHERAL NEUROPATHY	10 (14.1)	0	10 (14.1)
Diarrhoea	8 (11.3)	0	8 (11.3)
FATIGUE	8 (11.3)	0	8 (11.3)
COGNITIVE EFFECTS	5 (7.0)	1 (1.4)	6 (8.5)
MOOD EFFECTS	6 (8.5)	0	6 (8.5)
Weight increased	6 (8.5)	0	6 (8.5)
Pain in extremity	4 (5.6)	1 (1.4)	5 (7.0)
Nausea	3 (4.2)	1 (1.4)	4 (5.6)
Rash	4 (5.6)	0	4 (5.6)
SPEECH EFFECTS	3 (4.2)	1 (1.4)	4 (5.6)
Vomiting	4 (5.6)	0	4 (5.6)

Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Decreasing order of frequency relative to Any Grade column.
MedDRA v27.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adae Table Generation: 09JUL2024 (13:00)
(Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746_US/B7461027_CSR/adae_s071_2
Table 14.3.1.2.5 PF-06463922 is for Pfizer internal use.

Serious adverse event/deaths/other significant events

Treatment-Emergent SAEs

Frequency of all-causality treatment-emergent SAEs occurring in ≥2% of participants at any grade is summarized by PT/Cluster Term in Table 10.

Table 10: Treatment-Emergent SAEs (any Grade ≥ 2%) by PT/CLUSTER Term and Maximum CTCAE Grade – Safety Analysis Set (Protocol B7461027)

Number of Participants Evaluable for AEs	Lorlatinib (N=71)					
Number (%) of Participants: by CLUSTER or Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
With any adverse events	0	1 (1.4)	11 (15.5)	1 (1.4)	10 (14.1)	23 (32.4)
Dyspnoea	0	0	3 (4.2)	0	0	3 (4.2)
Pulmonary embolism	0	1 (1.4)	1 (1.4)	0	1 (1.4)	3 (4.2)
Cerebrovascular accident	0	0	1 (1.4)	0	1 (1.4)	2 (2.8)
Pneumonia	0	0	1 (1.4)	0	1 (1.4)	2 (2.8)

TEAEs are all causality unless otherwise specified.
Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Decreasing order of frequency relative to Total column.
MedDRA v27.0 coding dictionary applied.
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./B746_US/B7461027_CSR/adae_s063_3b
Table 14.3.1.1.6 PF-06463922 is for Pfizer internal use.

There was 1 treatment-related treatment-emergent SAE of Pneumonia reported in this study, and this SAE was CTCAE Grade 3 and resulted in study intervention interruption.

Deaths

Table 11: Summary of Deaths – Safety Analysis Set (Protocol (B7461027)

	Lorlatinib (N=71) n (%)
Deaths	20 (28.2)
Cause of Death	
DISEASE UNDER STUDY	15 (21.1)
CARCINOMA LUNG WITH BRAIN METASTASIS WITH CEREBROVASCULAR ACCIDENT.	1 (1.4)
CEREBRAL STROKE	1 (1.4)
LEFT BRONCHUS HEMORRHAGE	1 (1.4)
SUDDEN DEATH	1 (1.4)
UNKNOWN	1 (1.4)
Deaths within 28 days after last dose of study treatment	11 (15.5)
Cause of Death	
DISEASE UNDER STUDY	7 (9.9)
CARCINOMA LUNG WITH BRAIN METASTASIS WITH CEREBROVASCULAR ACCIDENT.	1 (1.4)
CEREBRAL STROKE	1 (1.4)
LEFT BRONCHUS HEMORRHAGE	1 (1.4)
SUDDEN DEATH	1 (1.4)
Deaths within 30 days after first dose of study treatment	3 (4.2)
Cause of Death	
DISEASE UNDER STUDY	2 (2.8)
SUDDEN DEATH	1 (1.4)

The denominator to calculate percentages is N, the number of participants in the safety analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: addd Table Generation: 16JUL2024 (15:00) (Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/addd s001 Table 14.3.2.1 PF-06463922 is for Pfizer internal use.

Table 12: TEAEs Leading to Death (Grade 5) by MedDRA SOC/PT – Safety Analysis Set (Protocol B7461027)

Number of Participants Evaluable for AEs	Lorlatinib (N=71)		
	All	Treatment-Related	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)
With any adverse events	10 (14.1)	0	10 (14.1)
NERVOUS SYSTEM DISORDERS	3 (4.2)	0	3 (4.2)
Cerebrovascular accident	1 (1.4)	0	1 (1.4)
Intracranial pressure increased	1 (1.4)	0	1 (1.4)
Syncope	1 (1.4)	0	1 (1.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.8)	0	2 (2.8)
Bronchial haemorrhage	1 (1.4)	0	1 (1.4)
Pulmonary embolism	1 (1.4)	0	1 (1.4)
CARDIAC DISORDERS	1 (1.4)	0	1 (1.4)
Right ventricular dysfunction	1 (1.4)	0	1 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.4)	0	1 (1.4)
Disease progression	1 (1.4)	0	1 (1.4)
INFECTIONS AND INFESTATIONS	1 (1.4)	0	1 (1.4)
Pneumonia	1 (1.4)	0	1 (1.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (1.4)	0	1 (1.4)
Neoplasm progression	1 (1.4)	0	1 (1.4)
RENAL AND URINARY DISORDERS	1 (1.4)	0	1 (1.4)
Hydronephrosis	1 (1.4)	0	1 (1.4)

TEAEs are all causality unless otherwise specified.
Includes data up to 28 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier.
Decreasing order of frequency relative to All column.
MedDRA v27.0 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 05JUL2024 (18:31) Source Data: adae Table Generation: 09JUL2024 (13:00)
(Data cutoff date : 29May2024 Database snapshot date : 03Jul2024) Output File: ./B746 US/B7461027 CSR/adae s207
Table 14.3.2.2 PF-06463922 is for Pfizer internal use.

Dose Modification and Discontinuations of Study Intervention Due to Adverse Events

Permanent Discontinuations of Study Intervention Due to TEAEs

- 9 (12.7%) participants experienced TEAEs leading to permanent discontinuation of study intervention.

  o 7 (9.9%) participants experienced Grade 5 TEAEs leading to permanent discontinuation of study intervention. Grade 5 TEAEs were Bronchial haemorrhage, Hydronephrosis, Neoplasm progression, Pneumonia, Pulmonary embolism, Right ventricular dysfunction and Disease progression. For the participant with Grade 5 Disease progression, there was a Grade 1 SAE of Acute kidney injury reported that led to permanent discontinuation of study intervention ahead of the Grade 5 Disease progression.

  o 1 (1.4%) participant experienced a Grade 3 TEAE of General physical health deterioration leading to permanent discontinuation of study intervention.

  o 1 (1.4%) participant experienced a Grade 2 TEAE of Anaemia leading to permanent discontinuation of study intervention.

- None of the TEAEs leading to permanent discontinuation of study intervention was related to the study intervention as assessed by the investigator.

Dose Interruptions of Study Intervention Due to TEAEs

- 22 (31.0%) participants experienced all-causality TEAEs leading to dose interruptions of study intervention.

- Of the all-causality TEAEs leading to dose interruptions, Blood creatinine increased, Dyspnoea, EDEMA (Oedema peripheral) and FATIGUE (Asthenia) were reported in 3 (4.2%) participants each, and Anaemia was reported in 2 (2.8%) participants; all other Cluster Term or PT of TEAEs leading to dose interruptions were reported in single participants.
- 10 (14.1%) participants experienced treatment-related TEAEs leading to dose interruptions of study intervention.
- Of the treatment-related TEAEs leading to dose interruptions, all Cluster Terms or PTs were reported in single participants except for EDEMA (Oedema peripheral, reported in 3 [4.2%] participants) and FATIGUE (Asthenia, reported in 2 [2.8%] participants).

Dose Reductions of Study Intervention Due to TEAEs

- 10 (14.1%) participants experienced all-causality TEAEs leading to dose reductions of study intervention.
- Of the all-causality TEAEs leading to dose reductions, all Cluster Terms or PTs were reported in single participants except for EDEMA (Oedema peripheral, reported in 3 [4.2%] participants) and SPEECH EFFECTS (reported in 3 [4.2%] participants: 2 with Speech disorder and 1 with Dysarthria).
- 6 (8.5%) participants experienced treatment-related TEAEs leading to dose reductions of study intervention.
- The treatment-related TEAEs leading to dose reductions were EDEMA (Oedema peripheral, reported in 3 [4.2%] participants), SPEECH EFFECTS (reported in 3 [4.2%] participants: 2 with Speech disorder and 1 with Dysarthria), COGNITIVE EFFECTS (Confusional state, reported in 1 [1.4%] participant) and Dizziness (reported in 1 [1.4%] participant).

Adverse reactions

No new adverse reactions were identified from study B7461027. However, frequencies of ADR were adjusted in order to reflect the updated safety data set including the 71 patients from study B7461027.

Table 13. Adverse reactions (full safety data set, 547 adults)

System organ class and adverse reaction	Frequency category	All Grades %	Grades 3-4 %
Blood and lymphatic system disorders			
Anaemia	Very common	19.6	4.4
Metabolism and nutrition disorders			
Hypercholesterolaemia[a]	Very common	79.0	19.2
Hypertriglyceridaemia[b]	Very common	67.5	20.3
Hyperglycaemia	Common	9.7	3.7
Psychiatric disorders			
Mood effects[c]	Very common	21.4	1.3
Psychotic effects[d]	Common	6.9	0.9
Mental status changes	Common	1.1	0.9
Nervous system disorders			
Cognitive effects[e]	Very common	27.4	3.5
Peripheral neuropathy[f]	Very common	44.2	2.6
Headache	Very common	18.6	0.7
Speech effects[g]	Common	8.2	0.7
Eye disorders			
Vision disorder[h]	Very common	16.1	0.2
Vascular disorders			
Hypertension	Very common	14.8	6.0

Respiratory, thoracic and mediastinal disorders			
Pneumonitis[i]	Common	2.4	0.7
Gastrointestinal disorders			
Diarrhoea	Very common	22.7	1.8
Nausea	Very common	17.6	0.9
Constipation	Very common	16.8	0.2
Skin and subcutaneous tissue disorders			
Rash[j]	Very common	14.6	0.2
Renal and urinary disorders			
Proteinuria	Common	3.7	0.4
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common	27.8	0.7
Myalgia[k]	Very common	15.0	0
General disorders and administration site conditions			
Oedema[l]	Very common	55.4	2.9
Fatigue[m]	Very common	30.7	1.1
Investigations			
Weight increased	Very common	29.8	11
Lipase increased	Very common	12.8	6.8
Amylase increased	Very common	11.3	2.7
Electrocardiogram PR prolongation	Uncommon	0.7	0

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

[a] Hypercholesterolaemia (including blood cholesterol increased, hypercholesterolaemia).
[b] Hypertriglyceridaemia (including blood triglycerides increased, hypertriglyceridaemia).
[c] Mood effects (including affective disorder, affect lability, aggression, agitation, anger, anxiety, bipolar I disorder, depressed mood, depression, depressive symptom, euphoric mood, irritability, mania, mood altered, mood swings, panic attack, personality change, stress).
[d] Psychotic effects (including auditory hallucination, hallucination, visual hallucination).
[e] Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder). Within these effects, terms from SOC Nervous system disorders were more frequently reported than terms from SOC Psychiatric disorder.
[f] Peripheral neuropathy (including burning sensation, dysaesthesia, formication, gait disturbance, hypoaesthesia, motor dysfunction, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, sensory disturbance).
[g] Speech effects (dysarthria, slow speech, speech disorder).
[h] Vision disorder (including diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).
[i] Pneumonitis (including interstitial lung disease, lung opacity, pneumonitis).
[j] Rash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash).
[k] Myalgia (including musculoskeletal pain, myalgia).
[l] Oedema (including generalised oedema, oedema, oedema peripheral, peripheral swelling, swelling).
[m] Fatigue (including asthenia, fatigue).

Discussion

Efficacy

The MAH has submitted the final CSR from the requested single-arm study B7461027, which was a SOB for the CMA of lorlatinib. This is a non-comparative study of use of lorlatinib in patients with advanced ALK-positive NSCLC, who had disease progression after one prior second-generation ALK-TKI (alectinib or ceritinib as first line of treatment) for metastatic disease. The study was designed to fulfill the goal to substantiate the clinical efficacy in this particular population with a larger sample size (N=71) compared to pivotal Study 1001 (EXP-3B cohort; N=28).

A total of 71 participants were treated with lorlatinib at 23 centres in 7 countries. The first participant was enrolled on 29 September 2020 and enrollment was completed on 13 June 2023. The primary

completion date (PCD) was 29 May 2024. All treated patients had at least 1 prior anti-cancer drug therapy, 16.9% received prior chemotherapies, 84.5% received alectinib as prior ALK inhibitor and 15.5% received ceritinib as prior ALK inhibitor. Moreover, 47.9% had at least 1 prior anti-cancer radiotherapy and 14.1% underwent at least 1 prior anti-cancer surgery. The median duration of study intervention was 9.69 months.

The primary efficacy endpoint was ORR by independent review (ICR) and the ITT analysis showed that 4 (5.6%) patients had a confirmed CR and 36.6% had a confirmed PR, resulting in an ORR of 42.3% (95%CI: 30.6%, 54.6%). The study met its primary endpoint as the lower limit of the 95%CI around the estimated ORR exceeded 30%. Of note, the ORR was a bit higher in patients who had received prior ceritinib (45.5%) versus those who had prior alectinib, however, no firm conclusions can be made due to the small sample size of patients who had prior ceritinib. Overall, the ORR of 42.3% is in line with what has previously been reported (42.9%), and therefore the efficacy in the second-line setting after a second-generation ALK-TKI is considered to be confirmed with a reasonable sample size (N=99).

Safety

No new safety signals were observed in the study so no new safety concerns are raised. Frequencies of adverse reactions were updated in sections 4.8 and 4.4 to reflect the updated safety data set including the additional 71 patients from study B7461027. They remain largely in line with existing frequencies.

In conclusion, the CHMP is of the opinion that the remaining Specific Obligation has been fulfilled and therefore recommends its deletion from the Annex II.

5.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding the remaining SOB has emerged. The new data emerged are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

During the period covered by this annual renewal, new data regarding the following SOB have emerged. The SOB is considered fulfilled:

002: Study B7461027: Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Whose Ongoing Disease Progressed After One Prior Second Generation ALK Tyrosine Kinase Inhibitor (TKI) This is a Phase 4 open-label, multicenter, multi-national, non-randomized, prospective, single-arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease.

6. Additional scientific data provided relevant for the assessment of the benefit/risk balance

6.1. Clinical efficacy

With this submission the MAH provided a short updated based on the request from procedure EMEA/H/C/0004646/II/15 for approval of the indication for the first-line treatment for ALK-positive advanced lung cancer based on the results of the pivotal Phase 3 CROWN trial. The CHMP requested that, in the absence of a mature OS analysis and with the aim to clarify the benefit deriving from treatment of patients with ALK positive advanced NSCLC previously not treated with an ALK inhibitor,

the MAH should provide PFS2 data updates for the CROWN (B7461006) study in the context of the annual renewals.

In annex to the updated overview the MAH provided some results. PFS2, a pre-specified secondary endpoint, was defined as the time from randomization to the date of disease progression on first subsequent systemic anticancer therapy or death. As of 31 October 2023, 48 PFS2 events (32%) and 78 PFS2 events (53%) have occurred in the lorlatinib and crizotinib arm, respectively. With a median duration of follow-up for PFS2 of 61.4 months (95%CI: 59.2-62.5) in the lorlatinib arm and 58.4 months (95%CI: 56.8-61.9) in the crizotinib arm, PFS2 was longer in patients from the lorlatinib compared to crizotinib arm (HR, 0.43; 95%CI: 0.30-0.62). Median PFS2 was NR (95%CI: NR-NR) with lorlatinib and 37.9 months (95%CI, 27.4-50.1) with crizotinib and the 60-month PFS2 rate was 67% in the lorlatinib arm and 37% in the crizotinib arm.

6.2. Clinical safety

Cumulatively, there have been 899 clinical trial cases (1056 SAEs) reported. During the reporting interval, there have been 35 clinical trial cases (38 SAEs) reported, which is fewer than in the previous interval (41 cases with 47 SAEs). In addition, there have been 9095 post-marketing cases (20,742 AEs/ADRs) reported cumulatively and 2477 post-marketing cases (5721 AEs/ADRs) reported during this reporting interval.

Completed Clinical Trials: There were no completed safety trials during the reporting period of the Addendum to the Clinical Overview (ACO). During the reporting period of the latest PBRER (DLP March 2024), there was 1 completed clinical trial from the lorlatinib development program that was not considered to be a safety trial:

- Study B7461001: A 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.

The MAH reports that lorlatinib was generally tolerable, as AEs were primarily mild to moderate in severity, and manageable as rates of permanent discontinuations due to AEs were low and could be managed by dosing interruption, dose reduction, and/or standard supportive medical therapy.

Ongoing Clinical Trials: During the reporting period, there were 6 ongoing clinical trials, that were not considered to be safety trials, from the lorlatinib development program: B7461006, B7461024, B7461027, B7461039, B7461040, and B7461042 (Cstone Study CS3011-201). No new clinically important information has emerged from above mentioned studies during the reporting period.

The Clinical Study Report (CSR) for EU Post-Authorisation Efficacy Study (PAES) B7461027 [A single-arm study of lorlatinib in participants with Anaplastic Lymphoma Kinase (ALK)-positive Non-Small Cell Lung Cancer (NSCLC) whose disease progressed after one prior second generation ALK Tyrosine Kinase Inhibitor (TKI)] was submitted on 09 September 2024. The MAH reports that 69 of 71 participants (97.2%) experienced treatment emergent adverse events (TEAEs), of whom 64 had treatment-related TEAEs.

- The most frequently reported (≥20% of participants) all-causality TEAEs were Hypercholesterolemia (59.2%), Hypertriglyceridemia (56.3%), Edema (46.5%), Fatigue (26.8%) and Peripheral Neuropathy (21.1%).
- 23 (32.4%) participants experienced serious adverse events (SAEs), of whom 1 participant had a treatment-related SAE. The all-causality treatment-emergent SAEs occurring in ≥2% of participants were Dyspnoea (4.2%), Pulmonary embolism (4.2%), Cerebrovascular accident (2.8%) and Pneumonia (2.8%). There was 1 treatment-related treatment-emergent SAE of Pneumonia reported in this study, and this SAE was CTCAE (Common Terminology Criteria for

Adverse Events) Grade 3 and resulted in study intervention interruption.
- 10 (14.1%) participants experienced Grade 5 TEAEs leading to deaths, with none of them related to the study intervention as assessed by the investigator.
- 9 (12.7%) participants experienced TEAEs leading to permanent discontinuation of study intervention. None of the TEAEs leading to permanent discontinuation of study intervention was related to the study intervention as assessed by the investigator.

In summary, lorlatinib treatment was generally tolerable, and when appropriate, AEs were manageable through temporary discontinuation, dose reduction, and/or standard supportive medical therapy. Safety data from this study were generally consistent with the known safety profile of lorlatinib with no new safety signals identified. Overall, the lorlatinib risk/benefit ratio remained favourable.

Lorlatinib is also being studied in 2 ongoing clinical trials from other Pfizer clinical development programs. The first (Study B9991046) is an open-label study for participants continuing from Pfizer-sponsored avelumab clinical studies. The second (Study C4481001) is: a phase 1, open-label, multi-center, dose escalation and dose expansion study to evaluate the safety, tolerability, PK, and preliminary evidence of anti-tumor activity of PF-07284892 (a SHP2 inhibitor) as a single agent and in combination therapy in participants with advanced solid tumors.

There are 14 ongoing Investigator Sponsored Research (ISR) Studies and Clinical Research Collaboration (CRC) Studies. No clinically relevant information has emerged from these studies.

Non-Interventional Studies: There were no completed or ongoing PASS.

Other studies where the primary aim of the trial was to identify, characterise or quantify a safety hazard or confirm the safety profile of the medicinal product include the ongoing non-interventional study B7461018. There were no completed safety studies.

- Study B7461018 - Special investigation for Lorbrena tablets: Lorbrena ALK NSCLC ROS1 PMS Japan. No clinically important information has emerged from this safety study.

There were 3 completed non-interventional studies that were not safety studies.

- Study B7461032 Therapeutic effectiveness of lorlatinib after alectinib in ALK-positive NSCLC patients in Japan
- Study B7461044 Profile and Treatment Patterns of Patients with locally advanced/metastatic ALK+ or EGFR + NSCLC in Mexico: A cross-sectional database study
- Study B7461046 Treatment patterns and clinical outcomes in patients with metastatic non-small cell lung cancer in Colombia.

There are 2 ongoing non-interventional studies

- Study B7461034 A prospective, single-arm, open-label, non-interventional, multicentre, Post Marketing Surveillance (PMS) study of Lorviqua (registered)
- Study B7461041 Drug treatment patterns and Effects for metastatic non-small cell Lung cancer patients In NORway (DELINOR)

No clinically important information has emerged from completed and ongoing non-interventional studies during the reporting period.

Medication Errors: During this reporting interval, there were no serious CT cases contained in the MAH's safety database that reported medication errors and no medication errors involving lorlatinib were identified from medical literature sources. Review of the post-marketing cases received during this reporting interval revealed no patterns of medication errors involving lorlatinib. There were 65 cases (2.6% of the total interval dataset as compared to 3.3% in the previous 1-year ACO) reporting 70 events potentially indicative of a medication error. In 7 cases, the error was a misuse of the product by the

patient (i.e. taking it incorrectly as personal preference). All of the medication error events were considered non-serious. The most frequently co-reported AEs were coded to the PTs: Off label use (8), Neoplasm progression (6), Abdominal discomfort (5), Asthenia, Haemoglobin decreased, and Oedema (4 each).

Literature: A search of the Medline and Embase databases identified 1 article for lorlatinib.

- LI, Huqun, Wang Chongshu, Guo, Cuilian, Post-marketing safety of lorlatinib: a real-world study based on the FDA adverse event reporting system. Front. Pharmacol. 15:1385036. doi: 10.3389/ fphar.2024.1385036

A total of 2,941 AE reports were found to be associated with lorlatinib among the 8,818,870 AE reports obtained from the FAERS database. 167 lorlatinib-related AE signals were identified. The frequently reported AEs including hypercholesterolemia, oedema, and cognitive disorder were in line with those observed in clinical trials and drug instruction. However, AEs such as interstitial lung disease and AV block indicated in the drug label require further evaluation. More attention should be paid to the new potential unexpected AEs including pulmonary arterial hypertension and radiation necrosis. The authors state that majority of AEs occurred within the first 2 months after lorlatinib initiation with a median onset time of 51 days.

The MAH comments that Radiation necrosis and Thromboembolic migrans are not labelled events for lorlatinib, and although the review of the available information from post marketing, clinical trials and literature does not support a causal association with lorlatinib at this time, this article is deemed to be relevant to be included in the ACO. Based on the data provided in the article, the MAH's conclusion could be endorsed. Nevertheless, this article is also presented in the PSUR that is currently under assessment (PSUSA/00010760/202409), in which a more detailed assessment will be performed. In addition, Interstitial lung disease, AV block and Pulmonary arterial hypertension are safety concerns in the PSUR and are being assessed in PSUSA procedures, including the ongoing PSUSA/00010760/202409 procedure.

Signal overview: During the reporting period, the signals of Proteinuria, Vision disorders and Respiratory disorders in combination with immunotherapy were evaluated and are presented below. These signals were refuted. There are no newly identified signals for lorlatinib between the DLP of the latest PSUR and the DLP of the ACO.

Table 14: Overview of signals

Overview of Signals Closed from the Beginning of the Reporting Period of the renewal period through the DLP of the last PSUR submitted 21 September 2023 through 20 March 2024.			
Signal	**Signal Type**	**Source**	**Category**
Proteinuria	Reopened and Closed	HA request	Refuted[a]
Vision disorders	New and Closed	Routine Pharmacovigilance	Refuted
Respiratory Disorders in combination with immunotherapy	New and closed	Clinical Research Collaboration	Refuted
Proteinuria is considered covered by the important potential risk Nephrotic syndrome.			

All reported signals were addressed through relevant PSUSA procedures (PSUSA/00010760/202309 and PSUSA/00010760/202403).

Summary of safety concerns: The important risks and missing information for lorlatinib through the DLP of the most recently submitted PSUR in the EU (21 September 2023 through 20 March 2024) are summarised in the table below. No changes were made to the safety concerns during the reporting

interval.

Important identified risks	Central nervous system effects[a]
	Interstitial lung disease/pneumonitis[b]
	QT interval prolonged[c]
Important potential risks	Atrioventricular block[d]
	Embryo-foetal toxicity
	Hepatic function disorder[e]
	Pancreatitis
	Nephrotic syndrome[f]
	Pulmonary arterial hypertension[g]
	Safety associated with combination use with CYP3A inducers[e]
Missing information	Patients with moderate or severe hepatic impairment[h]

a. Important identified risk in Japan: Central nervous system disorders/psychotic effects.
b. Important identified risk in Japan: Interstitial lung disease.
c. Important identified risk in Japan only.
d. Important potential risk in EU, but not considered an important risk in Japan
e. Important potential risk in Japan only.
f. Based on the PRAC FAR for PSUR #4 (reporting period 21 March 2020 through 20 September 2020), the signal *Nephrotic Syndrome* was determined to be an important potential risk, only in the PSUR not in the EU or Japan RMP.
g. Based on the PRAC FAR for PSUR #7 (reporting period 21 September 2021 through 20 March 2022), *Pulmonary arterial hypertension* was determined to be an important potential risk, only in the PSUR not in the EU or Japan RMP.
h. Missing information in Japan: Use in patients with hepatic function disorder

No new safety data has emerged which could influence the risk-benefit balance. The lorlatinib PSUR submission is per the EURD schedule, with the next data lock point through 20/09/2024. The PSUR is undergoing assessment and any relevant safety issue will be discussed in the upcoming PSUR assessment.

6.3. Pharmacovigilance inspections

The MAH has provided an overview of pharmacovigilance system inspections carried out during the reporting interval. None of the 10 conducted PhV inspections had impact on the benefit/risk of the medicinal product.

6.4. Discussion

The submitted PFS2 data with 32% and 53% events in the lorlatinib vs the crizotinib arm, respectively, shows a reassuring and promising HR of 0.43 (95%CI: 0.30-0.62). Median PFS2 was not reached with lorlatinib and 37.9 months (95%CI: 27.4-50.1) with crizotinib. Therefore, the risk of any detriment on OS seems unlikely and no further PFS2 data are requested.

The only outstanding request is the recommendation to submit final OS data from the phase 3 CROWN study (**B7461006)** by December 2027. The submission date is suggested to be postponed as it is an event-driven analysis and the OS event occurrence over the last 2 years have been slowing down. This is acceptable.

7. Risk management plan

The MAH has submitted an updated RMP (v5.2) within the annual renewal procedure.

Rationale for submitting an updated RMP: The purpose of this RMP update is to reflect the latest safety information on lorlatinib and to remove the specific obligation to submit the B7461027 CSR. B7461027

is a post-authorisation efficacy study designed to confirm the efficacy of lorlatinib in patients whose disease progressed after treatment with one prior second generation ALK-TKIs, alectinib or ceritinib. The submission of the B7461027 study report fulfils the specific obligation and thereby supports the conversion from conditional approval to standard marketing authorisation. Additionally, the proposed due date for submitting the CSR for the B7461006 study is updated.

Safety concerns

Table 15: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Central Nervous System (CNS) effects Interstitial lung disease (ILD)/pneumonitis
Important potential risks	Atrioventricular (AV) block Pancreatitis Embryo-foetal toxicity
Missing information	Patients with moderate or severe hepatic impairment

Considering the data in the safety specification, the safety concerns listed by the MAH are appropriate.

The MAH updated Part I Product Overview to remove information on additional monitoring for lorlatinib in the EU. The MAH also updated the following Part II modules:

SI Epidemiology of the Indication(s) and Target Population(s) - Epidemiological data has been updated with the most recent data available.

SIII Clinical Trial Exposure - The exposure data was updated with a new data lock point. The data for the B7461001 and B7461027 studies were based on the final CSRs, and the data lock point for B7461006 is 29 May 2024, with three datasets pooled together.

SIV Populations Not Studied in Clinical Trials - Relevant data has been updated.

SV Post Authorisation Experience - Post-marketing experience data has been updated up to the data lock point of 30 June 2024.

SVII Identified and Potential Risks - Updated safety data based on final B7461001 and B7461027 CSRs, data lock point for B7461006 study is 29 May 2024, and post marketing data till 30 June 2024.

According to the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2), Section SVII.1 "*Identification of safety concerns in the initial RMP submission*" is expected to be "locked" and not change after the approval of the initial RMP. Therefore, no change to this section can be endorsed (see assessment of the MAH responses). All other changes in Part I and Part II are endorsed.

Pharmacovigilance plan

Table 16: On-going and planned studies in the post-authorisation pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
Lorlatinib hepatic impairment study (**B7461040**) (Category 3)	The primary objective is to evaluate the effect of moderate and severe hepatic impairment on the 100 mg single dose plasma PK of lorlatinib. The secondary objective is to evaluate the safety and tolerability of a single 100 mg oral dose of lorlatinib in participants with normal hepatic function and participants with moderate or severe hepatic impairment.	Missing information on patients with moderate or severe hepatic impairment	Final Protocol Submission: Study/Trial Completion: Final Report Submission:	05 May 2022 31 December 2024 30 September 2025

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures).

No changes were made to RMP Part III Pharmacovigilance Plan. Lorlatinib hepatic impairment study (B7461040) is a required additional PhV activity that is currently ongoing.

Regarding Part IV Plans for Post-authorisation Efficacy Studies, the MAH removed the completed post-authorisation efficacy study B7461027 and updated the Milestone for the study B7461006 (01 Dec 2027), which is endorsed.

Risk minimisation measures

The MAH reported editorial changes to Part V.1 Routine Risk Minimisation Measures and consequently to Part V.3. Summary of Risk Minimisation Measures.

Table 17: Summary table of Risk Minimisation Measures

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: None
ILD/pneumonitis	Routine risk minimisation measures: SmPC sections **4.2**, 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risks		
AV block	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Pancreatitis	Routine risk minimisation measures: SmPC section 4.4, 4.8, **5.3** 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 (B7461040)

Elements for a public summary of the RMP

The elements for a public summary of the RMP require revision following the conclusion of the procedure:

Part VI has been updated according to the changes mentioned above (i.e. to Part IV and Part V). Study B7461027 is removed from studies which are conditions of the marketing authorisation, Milestone for the study B7461006 is updated, and editorial changes are made.

Annexes

The RMP annexes have been updated appropriately:

Annex 5: The completed post authorisation efficacy study B7461027 was removed.

Annex 8: The summary of changes made within RMP v5.2 was added.

In addition, the MAH took the opportunity to update Central Nervous System/ Psychiatric Events -

Specific Adverse Drug Reaction Follow-up form in Annex 4. The MAH removed questions from the FUQ that are part of every individual case safety report (e.g. start date and end date, outcome of the adverse event, action taken with lorlatinib, etc.), which could be endorsed. Updated FUQ now only contains questions for obtaining information that is not collected through standard reporting forms.

7.1. Overall conclusion on the RMP

The RMP version 5.3 is acceptable

8. Changes to the Product Information

Changes to the Product Information (PI), based on the submitted data within the scope of this procedure, are introduced during the assessment of this renewal (see attached PI with comments).

The MAH is amending the product information with the following changes:

- Removal of the specific obligation to submit B7461027 clinical study report and that the product has been authorised under "conditional approval" scheme
- Removal of inverted black triangle
- Changes to section 4.4, 4.8 and 5.1 were introduced to reflect data from study B7461027 (updated safety and efficacy data largely in line with existing safety and efficacy profile)
- Update of the due date for submitting the CSR including overall survival data of the B7461006 study
- Implementation of the QRD template v10.4 by removing the United Kingdom (Northern Ireland) local representative
- Update of the date of latest renewal
- Introduction of minor administrative change in the package leaflet (change in the name of the local representative for Ireland)

Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Lorviqua (Lorlatinib) is removed from the additional monitoring list as the condition(s) to the marketing authorisation have been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

9. Draft Request for Supplementary Information - RfSI

9.1. Major objections

None.

9.2. Other concerns

SmPC

1. The MAH should update the Tables 4+5 in section 5.1 of the SmPC, column 1 (One prior ALK-TKI with or without prior chemotherapy) with the newly submitted data. ORR by ICR should be used. The text below the Tables 4+5 should also be updated with the new results where relevant.

Risk Management Plan

2. The MAH is requested to follow the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2) regarding Section SVII.1 *Identification of safety concerns in the initial RMP submission*, including subsection SVII.1.2. *Risks considered important for inclusion in the list of safety concerns in the RMP*. According to the aforementioned guideline, this section is expected to be "locked" and not change after the approval of the initial RMP. Thus, changes implemented in section SVII.1.2. are not acceptable and should be removed.

10. Assessment of the MAH responses to the RfSI

10.1. Other concerns

Clinical aspects/SmPC

Question 1

The MAH should update the Tables 4+5 in section 5.1 of the SmPC, column 1 (One prior ALK-TKI with or without prior chemotherapy) with the newly submitted data. ORR by ICR should be used. The text below the Tables 4+5 should also be updated with the new results where relevant.

Summary of the MAH's response

Sections 4.4, 4.8 and 5.1 of the SmPC have been revised with the newly submitted data.

Assessment of the MAH's response

The SmPC is adequately addressed.

Conclusion

Issue resolved.

Risk Management Plan

Question 2.

The MAH is requested to follow the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) (EMA/838713/2011 Rev 2) regarding Section SVII.1 *Identification of safety concerns in the initial RMP submission*, including subsection SVII.1.2. *Risks considered important for inclusion in the list of safety concerns in the RMP*. According to the aforementioned guideline, this section is expected to be "locked" and not change after the approval of the initial RMP. Thus, changes implemented in section SVII.1.2. are not acceptable and should be removed.

Summary of the MAH's response

The MAH has submitted an updated RMP (v5.3) as a response to the above-mentioned request.

The changes implemented in section SVII.1.2. "Risks considered important for inclusion in the list of safety concerns in the RMP" within RMP version 5.2 submitted in support of the annual conditional marketing authorisation renewal have been removed, and the section content reverted to the currently EMA approved version of the RMP. In addition, the sentences "*Pancreatitis Grade 3 and Grade 2 were reported event in 1 and 2 cases, respectively. Otherwise, all other reported AEs involved asymptomatic elevations of blood lipase and amylase*" initially added within SVII.1.2 have been carried over in section SVII.3. No other change has been made. In addition, Annex 8 is updated accordingly:

5.3	Details of the currently approved RMP: Version number: 5.1 Approved with procedure: EMEA/H/C/004646/R/0031 Date of approval (opinion date): 5 April 2024 Other RMP versions under evaluation: None	Following the receipt of the CHMP and PRAC Rapporteurs Joint Assessment Report regarding RMP v 5.2 submitted on 31 October 2024 within procedure number EMEA/H/C/004646/R/0040, this RMP update removes the changes made in SVII.1.2. *Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP*. • Part II – SVII - Editorial changes made in SVII.1.2 and SVII.3. • Part VII – Annex 8 – Updated to reflect new changes

Assessment of the MAH's response

In the submitted RMP version 5.3 the MAH has removed the changes implemented in section SVII.1.2. "Risks considered important for inclusion in the list of safety concerns in the RMP" within the previous RMP version. Thus, the issue is considered resolved.

Conclusion

The submitted RMP (version 5.3) is considered acceptable.

11. Attachment

1. Product Information (changes highlighted)