# LORLATINIB (PF-06463922) RISK MANAGEMENT PLAN

**RMP version to be assessed as part of this application:**
RMP Version number: 5.3
Data lock point for Clinical exposure and Important risks data: the data for the B7461001 and B7461027 studies were based on the final CSRs (31 October 2023 and 9 September 2024, respectively), and the data lock point for B7461006 study is 29 May 2024.
Data lock point for Post-marketing exposure and Important risks data: 30 June 2024
Date of final sign off: 28 January 2025

**Rationale for submitting an updated RMP (v 5.3):** 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 certinib. The submission of the B7461027 study report fulfils the specific obligation and thereby supports the conversion from conditional approval to standard marketing authorisation. Additionally, to update the new proposed due date for submitting the CSR for the B7461006 study. 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*.

**Summary of significant changes in this RMP:**

| Part/Module | RMP Version 5.3<br>Changes |
|---|---|
| **Part I Product Overview** | Removal of additional monitoring for lorlatinib in the EU |
| **Part II Safety Specification** | |
| *SI Epidemiology of the Indication(s) and Target Population(s)* | Epidemiological data has been updated with the most recent data available |
| *SII Non-Clinical Part of the Safety Specification* | No changes made |
| *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 |
| *SVI Additional EU Requirements for the Safety Specification* | No changes made |
| *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. Editorial changes made in SVII.1.2 and SVII.3 based on the CHMP and PRAC Rapporteurs Joint Assessment Report. |
| *SVIII Summary of the Safety Concerns* | No changes made |

| Part/Module | RMP Version 5.3<br>Changes |
|---|---|
| **Part III Pharmacovigilance Plan (including Post-Authorisation Safety Studies [PASS])** | |
| III.1 Routine Pharmacovigilance activities | No changes made |
| III.2 Additional Pharmacovigilance activities | |
| III.3 Summary Table of Additional Pharmacovigilance Activities | |
| **Part IV Plans for Post-authorisation Efficacy Studies** | Removed the completed post-authorisation efficacy study, B7461027 and Milestone for the study B7461006 updated |
| **Part V Risk Minimisation Measures (RMM) (Including Evaluation of the Effectiveness of Risk Minimisation Activities)** | |
| V.1 Routine Risk Minimisation Measures | Editorial changes made |
| V.2 Additional Risk Minimisation Measures | No changes made |
| V.3. Summary of Risk Minimisation Measures | Editiorial changes made |
| **PART VI Summary of the Risk Management Plan** | Removal of B7461027 from studies which are conditions of the marketing authorisation and editorial updates and Milestone for the study B7461006 updated |
| **PART VII Annexes to the Risk Management Plan** | Annex 4: Central Nervous System/ Psychiatric Events - Specific Adverse Drug Reaction Follow-up form has been updated<br>Annex 5: Removed the completed post-authorisation efficacy study, B7461027<br>Annex 8: Added summary of changes made within RMP v5.3 |

**Other RMP versions under evaluation:** None

**Details of the currently approved RMP:**
Version number: 5.1
Approved with procedure: EMEA/H/C/004646/R/0031
Date of approval (opinion date): 05 April 2024

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s applicant´s QPPV. The electronic signature is available on file.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| 1L | First line |
| AE | Adverse Event |
| ALK | Anaplastic Lymphoma Kinase |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| ATP | Adenosine Triphosphate |
| AUC | Area Under the Curve |
| AV | Atrioventricular |
| BICR | Blinded Independent Central Review |
| BID | Bis in die (twice daily) |
| BMI | Body Mass Index |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CNS | Central Nervous System |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease |
| CrCl | Creatinine Clearance |
| CRM | Continual Reassessment Method |
| CSR | Clinical Study Report |
| CT | Clinical trial |
| DLP | Data-Lock Point |
| DLT | Dose-limiting toxicity |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| EEA | European Economic Area |
| eGFR | estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Reports |
| ERK5 | Extracellular signal-Regulated Kinase 5 |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| FDA | Food and Drug Administration |
| GGT | Gamma-glutamyl transferase |
| GLDH | Glutamate dehydrogenase |
| HCPs | Health Care Professionals |
| HCV | Hepatitis C virus |
| hERG | The Human Ether-a-go-go-Related Gene |
| HIV | Human Immunodeficiency Virus |
| HLGT | High-Level Group Terms |
| HLT | High Level Term |
| ICD | The International Classification of Diseases |
| ICR | Independent Central Review |
| ILD | Interstitial Lung Disease |
| INN | International Nonproprietary Names |
| JAK | Janus Kinase |
| LBBB | Left Bundle Branch Block |
| LFT | Liver Function Test |
| LIC | Lead in Cohort |
| LLT | Lowest Level Term |

| | |
|---|---|
| LOAEL | Lowest-Observed-Adverse-Effect Level |
| MAH | Marketing Authorisation Holder |
| MAPK | Mitogen-activated Protein Kinase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEK | Mitogen Activated Protein Kinase |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| N/A | Not Applicable |
| NEC | Not Elsewhere Classified |
| NOAEL | No Observed Adverse Effect Level |
| NSCLC | Non-small cell lung cancer |
| OS | Overall Survival |
| ORR | Objective Response Rate |
| PASS | Post-authorisation Safety Studies |
| PCD | Primary Completion Date |
| PD | Pharmacodynamics |
| PFS | Progression-Free Survival |
| P-gp | P-glycoprotein |
| PI3K-AKT | Phosphoinositide 3-Kinase-Protein Kinase B |
| PK | Pharmacokinetics |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PT | Preferred Term |
| QD | Quaque die (daily) |
| RMM | Risk Minimisation Measures |
| RMP | Risk Management Plan |
| ROS1 | c-ROS oncogene 1 |
| RP2D | Recommended Phase 2 dose |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| TKI | Tyrosine Kinase Inhibitor |
| TrK-b | Tyrosine Kinase B |
| UGT | UDP-glucuronosyltransferases |
| UK | United Kingdom |
| ULN | Upper Limit of Normal |
| US | United States |

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## PART I. PRODUCT OVERVIEW

| | |
|---|---|
| Active substance (INN or common name) | lorlatinib |
| Pharmacotherapeutic group (ATC Code) | Protein kinase inhibitor (L01ED05) |
| Marketing Authorisation Applicant: | Pfizer Europe MA EEIG |
| Medicinal product to which this RMP refers | Lorlatinib (PF-06463922) |
| Invented name in the European Economic Area (EEA) | Lorviqua |
| Marketing authorisation procedure | centralised |
| Brief description of the product | Chemical class: Protein kinase inhibitor |
| | Summary of mode of action: an oral, macrocyclic, Adenosine triphosphate (ATP) competitive small molecule inhibitor of ALK and c-Ros Oncogene 1 (ROS1) receptor tyrosine kinases. |
| | Important information about its composition: None |
| Hyperlink to the Product Information | Module 1.3.1 |
| Indication in the EEA | Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.<br><br>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:<br>• alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or<br>• crizotinib and at least one other ALK TKI |
| Dosage in the EEA | Current: 100 mg taken orally once daily continuously, with or without food |
| | Proposed: N/A |
| Pharmaceutical forms and strengths | Current: Oral film-coated tablets: 25 mg and 100 mg |
| | Proposed: N/A |

| | |
|---|---|
| Is the product subject to additional monitoring in the EU? | No |

## PART II. SAFETY SPECIFICATION

### Module SI Epidemiology of the Indication(s) and Target Population(s)

Lorlatinib is a selective, ATP competitive, brain-penetrant, small molecule inhibitor of ALK and ROS1 tyrosine kinases that addresses mechanisms of resistance following previous treatment with ALK inhibitor therapy.

**Indication:**

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

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

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

**Incidence:**

Global or European estimates of the incidence of ALK-positive NSCLC are not available, however, the incidence of all lung cancers has been estimated in the European Union and the United Kingdom (UK) for 2022. In the EU, the age-standardised incidence rate of all lung cancers is 28.8 per 100,000 and the cumulative lifetime incidence of lung cancer was 3.6%.[1] As the leading cause of cancer incidence[2], lung cancers were estimated to represent 12.1% of all new cancer cases in the EU-28. [3]

Per ESMO (European Society for Medical Oncology), NSCLC represents 85-90% of all lung cancer cases in Europe[4] and the ALK rearrangement is typically found in 2-7% of all NSCLC cases [5,6,7,8,9,10]. Assuming these proportions of NSCLC and ALK-positivity apply to European populations, the incidence of ALK-positive NSCLC in Europe would be projected to be between 0.49 per 100,000 and 1.81 per 100,000 and the cumulative lifetime incidence would be between 0.06% and 0.23%.[a]

To allow for comparisons across populations, lung cancer incidence rates have been standardised to a global age structure. Per Globocan 2022[1], the age-standardised lung cancer incidence rate in North America (31.9 per 100,000) exceeded the incidence rate in Europe (28.8 per 100,000), while the incidence rates in Asia (25.2 per 100,000), Africa (6.3 per 100,000), and Latin America and the Caribbean (12.1 per 100,000) were lower than the age-standardised incidence in the EU.[1]

[a] Calculations made by author. 28.8 per 100,000 x 0.85 x 0.02 = 0.49 per 100,000; 28.8 per 100,000 x 0.9 x 0.07 = 1.81 per 100,000; 3.6% x 0.85 x 0.02 = 0.06%; 3.6% x 0.9 x 0.07 = 0.23%

**Prevalence:**

The prevalence of ALK-positive NSCLC has not been described on a global or regional level. However, the 1-year period prevalence of all lung cancer was estimated to be 32.9 per 100,000 in Europe. [1,11]

The prevalence of ALK-positive lung cancer can be projected by assuming that between 85% and 90% of all lung cancers are NSCLC[4] and between 2% and 7% of all NSCLC have the ALK rearrangement.[5,6,7,8,9,10,12,13] Given these assumptions, the 1-year period prevalence of ALK-positive NSCLC in Europe would be between 0.56 per 100,000 and 2.07 per 100,000.[b]

The 1-year period prevalence for all lung cancer in North America (35.1 per 100,000) was higher than in Europe (32.9 per 100,000), and the 1-year period prevalence for all lung cancer in Asia (17.5 per 100,000), Africa (1.9 per 100,000), and Latin America and the Caribbean (8.1 per 100,000) was lower than in Europe.[1]

**Demographics of the population with ALK-positive advanced non-small cell lung cancer (NSCLC)**

Patients with ALK-positive NSCLC are younger and more likely to be female than those with other types of lung cancer. [14,15,16] In particular, compared with ALK-negative patients, ALK-positive patients are significantly younger, predominantly female and non-smokers.[10,17] Unlike other forms of lung cancer which are largely caused by tobacco smoking, ALK-positive NSCLC often occurs in patients with little or no history of smoking.[7,14,15,16,18,19,20] An observational study with smoking history data on 310 French ALK-positive NSCLC patients found that 55.8% (n = 173) of the patients had no history of smoking. By comparison, 10.9% (762/7008) of French NSCLC patients with and without the ALK rearrangement reported never having smoked.[21]

In terms of ethnicity, much of the early research on the ALK rearrangement focused on Asian populations,[15,22] but there remains no clear association between ALK-positive NSCLC and any ethnic or geographic population.[23] Nevertheless, regarding lung adenocarcinoma, a US-based study reported a higher proportion of ALK rearrangement among Asians compared to Whites and Blacks; 4.7%, 3.1%, and 1.8% respectively.[24]

**The Main Existing Treatment Options**

Alectinib,[25] ceritinib,[26] and brigatinib[27] are second-generation ALK-TKIs that prolong PFS and have CNS anti-tumor effects. These therapies are recommended for treating patients with previously untreated advanced ALK-positive NSCLC, with alectinib being the preferred treatment option.[28,29]

Most patients with ALK-positive NSCLC derive clinical benefit from first-line treatment with second-generation ALK TKIs. However, emergence of resistance mechanisms,

[b] 32.9 per 100,000 x 0.85 x 0.02 = 0.56 per 100,000; 32.9 per 100,000 x 0.9 x 0.07 = 2.07 per 100,000

including ALK mutations continues to be a treatment challenge even with the availability of second-generation ALK TKIs. Therefore, there is an urgent need for additional ALK TKIs with broader mutational coverage and CNS penetration.[30]

Lorlatinib is a third-generation, selective, ATP-competitive, brain-penetrant, small molecule inhibitor of the ALK tyrosine kinase that was designed to overcome or prevent major mechanisms of resistance that develop following previous ALK-inhibitor treatment. It was also designed to penetrate the blood-brain-barrier. In addition, lorlatinib's ability to overcome most known resistance mutations might delay ALK-dependent mechanisms of resistance.[30]

**Natural history of ALK-positive NSCLC, including mortality and morbidity**

NSCLC originates in the lung and can cause severe morbidity including persistent cough, haemoptysis, chest pain, shortness of breath, weight loss, weakness, fatigue and lung infections such as pneumonia. NSCLC grows locally and may spread to the lymph nodes and to distant sites such as the liver, bone and central nervous system (CNS). Lung cancer is the most common cause of cancer mortality, accounting for almost one-fifth of all cancer deaths.[3,31]

ALK is a transmembrane receptor tyrosine kinase that can activate multiple signaling cascades such as the PI3K-AKT, Crkl-C3G, MAP kinase kinase kinase 2/3-mitogenactivated protein kinase kinase (MEK)5-ERK5, Janus kinase (JAK)-STAT, and MAPK pathways that can lead to cell proliferation and de-differentiation.[9,32] ALK rearrangements is mainly found in adenocarcinomas (91-97%), while squamous cell carcinomas comprise only 3-8%.[9,33]

While 5-year relative survival rates for patients with metastatic NSCLC remain extremely low (about 6%), recent advances in the development of targeted therapies have extended survival outcomes in NSCLC, especially in ALK-positive patients.[34] Among the tyrosine kinase inhibitors (TKIs), ALK inhibitors have showed the longest survival times in patients undergoing systemic treatment for advanced lung cancer with the median overall survival (OS) exceeding 80 months for ALK-positive lung cancer patients.[32,34] Indeed, survival of ALK-rearranged NSCLC patients has dramatically improved by the use of multiple ALK-tyrosine kinase inhibitors (ALK-TKI).[33]

In a European-based study from 6 centers in Switzerland and Italy that included 121 stage IV ALK-rearranged NSCLC patients (median age: 52 years old, gender: 53.7% female), a significant difference in OS was observed in favour of patients treated with more than one treatment line of ALK-TKIs as compared to those treated only with one line of ALK-TKI (median OS of 85.7 vs 34.8 months, respectively, $p = 0.016$) and whose ALK-TKIs included alectinib or lorlatinib (median OS of 85.7 vs 37.3 months, respectively). The study concluded that targeted treatment for ALK-positive NSCLC patients leads to prolonged OS.[33] These results are consistent with a US-based study (N = 110 patients with ALK-positive NSCLC, median age: 53 years old, gender: 50% female) reporting a median OS time from diagnosis of stage IV disease of 81 months (6.8 years).[35]

**Important co-morbidities Present in the Target Population**

A number of comorbidities commonly co-occur with ALK-positive NSCLC, including cardiovascular disease,[36] pulmonary disease,[37] hypertension or diabetes mellitus.[17] A more exhaustive list of reported comorbidities includes:

- Anaemia[37]
- Bleeding[37]
- Cardiovascular disease[36]
- Chronic obstructive pulmonary disease (COPD)[37]
- Diabetes mellitus[37]
- Fluid and electrolyte disorders[37]
- Hypertension[37]
- Liver disease[36]
- Metabolic disease[36]
- Neurological/psychiatric disease[36]
- Peripheral vascular disease[37]
- Pneumonia[38]
- Renal disease[36]

**Module SII Non-Clinical Part of the Safety Specification**

The non-clinical safety profile of lorlatinib was evaluated in vitro and in vivo in rats and dogs. 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 most major metabolism pathways observed in humans. Consistent with the intended clinical route of administration, the toxicity studies were conducted using the oral administration route. Repeat-dose toxicity studies up to 13 weeks of daily dosing were conducted and were considered relevant to the recommended daily dosing regimen in the clinic. In addition, safety pharmacology, genetic, toxicity, and embryo-foetal development studies were conducted.

Based on the non-clinical safety studies conducted with lorlatinib, the potentially important toxicities included changes associated with inflammation across multiple tissues, and changes in the pancreas, hepatobiliary system, male reproductive system, cardiovascular system, gastrointestinal tract, and hyperlipidaemia in rats and dogs. Additional potentially important findings were observed in peripheral nerves, cognitive and neurological functions,

and the kidney of rats. Lorlatinib was also associated with the potential for embryo-foetal toxicity. In genetic toxicity tests, lorlatinib was identified as an aneugen.

Table 1 describes the non-clinical key safety findings and relevance to human usage.

**Table 1. Key Safety Findings and Relevance to Human Usage**

| Key Safety findings from Non-clinical Studies | Relevance to Human Usage |
|---|---|
| **Inflammation**<br>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 was also associated with an inflammatory leukogram, increases in acute phase proteins, an increased myeloid-to-erythroid ratio in the bone marrow, and lymphoid cellularity in the spleen. 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. The no observable adverse effect levels for the inflammatory changes in the 13-week studies in rats and dogs provide margins of 3.3x and 1.6x, respectively, the unbound human steady state AUC exposure for the 100 mg QD recommended human dose. | While lorlatinib has the potential to cause inflammation, a general inflammatory response does not appear to negatively impact the risk-benefit profile of lorlatinib.<br><br>Lorlatinib has the potential to cause interstitial lung disease (ILD)/pneumonitis in humans. For further information see SVII.3.1.2. Important Identified Risk – ILD/pneumonitis |
| **Pancreas**<br>Effects on the pancreas that were observed in an acute rat study and in both rats and dogs in repeat-dose studies ≤13 weeks in duration included degeneration and/or atrophy of pancreatic islet cells and associated higher amylase and lipase. Partial to full reversibility of the pancreatic microscopic findings and amylase and lipase changes was demonstrated following a 4-week non-dosing period in the 4-week and/or 13-week repeat-dose studies in both rats and dogs. The no observable adverse effect levels for the pancreatic findings in the 13-week studies in rats and dogs provide margins of 3.3x and 4.6x, respectively, the unbound human steady state AUC exposure. | Lorlatinib has the potential to cause pancreatitis in humans. For further information see SVII.3.1.4. Important Potential Risk – Pancreatitis. |
| **Hepatobiliary**<br>Effects on hepatobiliary system (liver, bile duct and gall bladder) were observed in rats and dogs in repeat-dose studies ≥2 weeks or ≥4 weeks in duration, respectively. Bile duct hyperplasia, fibrosis and mixed inflammatory cells associated with macroscopic bile duct dilation and/or icterus were observed in rats and/or dogs. Increases in sinusoidal Kuppfer cell pigmentation and haemorrhage in the gallbladder were also observed in dogs. Non-adverse hepatocellular hypertrophy and associated increased liver weight were considered an adaptive response to metabolic activation. | While elevations in liver tests results have been observed with lorlatinib, such elevations do not appear to negatively impact the risk-benefit profile of lorlatinib. Moreover, there is no evidence from clinical studies that lorlatinib may be associated with cholestasis. |

## Table 1. Key Safety Findings and Relevance to Human Usage

| Key Safety findings from Non-clinical Studies | Relevance to Human Usage |
|---|---|
| Hepatobiliary changes were associated with elevations in liver enzymes (ALT, AST, ALP, GLDH and/or GGT) and increases in total bilirubin at in rats and/or dogs. Following a 4-week non-dosing period after 4 and/or 13 weeks of dosing to rats and dogs, liver enzyme elevations, changes in liver weight and microscopic findings in the hepatobiliary system were partially or fully reversed with the exception of hepatic bile duct hyperplasia after 13 weeks of lorlatinib administration to rats. The NOAEL following 13 weeks of lorlatinib administration in rats and dogs provide margins of 3.3x and 1.6x, respectively, the unbound human steady-state AUC exposure. | |
| **Cardiovascular**<br>Lorlatinib was identified as a weak inhibitor of the hERG potassium channel and L-type calcium channels, and also increased late sodium currents. Lorlatinib increased QRS and PR intervals ex vivo and/or in vivo, and induced changes in blood pressure and heart rate in vivo in rats and/or dogs. Non-adverse increases in heart weight and/or cellularity of Anichkov cells were also observed after administration of lorlatinib for ≥4 weeks to rats. Reversibility of the effects on blood pressure, heart rate, and electrocardiogram intervals was demonstrated following a 5-day non-dosing period in dogs after 5 days of lorlatinib administration. Increases in heart weight and/or cellularity of Anichkov cells were reversible in rats following a 4-week non-dosing period after 4 or 13 weeks of lorlatinib administration. A NOAEL for cardiovascular effects (blood pressure and heart rate) was not determined in the rat; the margin associated with the LOAEL was 2.2x the unbound human steady-state Cmax exposure. The NOAEL for cardiovascular effects (blood pressure, heart rate, and ECG changes) in the dog provided a margin of 0.3x the unbound human steady-state Cmax. The NOAEL for heart weight and histology findings in the rat provided a margin of 3.3x in rats. | Lorlatinib has the potential to cause AV block in humans. See SVII.3.1.3. Important Potential Risk – Atrioventricular (AV) block.<br><br>Blood pressure and heart rate effects of lorlatinib in animals are not considered to have significant effects in humans. |
| **Reproductive and Developmental Toxicity**<br><br><u>Male Reproductive</u><br>Effects on male reproductive organs (testis, 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 | Male reproductive effects of lorlatinib in animals are not considered to have significant effects in humans.<br><br>Lorlatinib has the potential to cause embryo-foetal abnormalities in humans. For further information see SVII.3.1.5. Important Potential Risk – Embryo-foetal toxicity. |

**Table 1. Key Safety Findings and Relevance to Human Usage**

| Key Safety findings from Non-clinical Studies | Relevance to Human Usage |
|---|---|
| prostate weights in dogs. The changes in the male reproductive system were not considered adverse based on limited severity and persistence of spermatogenic activity. 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. The NOAEL in rats and dogs provide margins of 13x and 4.6x, respectively, the unbound human steady-state AUC.<br><br><u>Embryo-foetal toxicity</u><br>In embryo-foetal development studies in rats and rabbits total litter loss and abortion, reduced embryo-foetal viability, demonstrated by higher numbers of early and late resorptions, higher post-implantation losses and lower numbers of live foetuses, was observed after lorlatinib administration. In rats, lower foetal body weights and a low incidence of lorlatinib - related external and visceral malformations (a single foetus with multiple malformations consisting of rotated hind limbs, a supernumerary digit on the left forepaw, and gastroschisis, and single foetus with a small kidney or an interrupted aortic arch) were observed. There were no lorlatinib-related effects on foetal body weights in rabbits, however, a higher incidence of foetal malformations including a single foetus with multiple foetal malformations (domed head with corresponding severe dilation of the lateral and third ventricles of the brain, medially malrotated forelimbs, and hyperextended forepaws), and two other foetuses with visceral malformations (malpositioned and misshapened kidneys, one of which was also noted with a retroesophageal subclavian artery). A developmental no effect level was established in rats. The LOAEL in the rat and the NOAEL in the rabbit provide margins of 1.1x and 0.1x, respectively, the unbound human steady-state AUC exposure. | |
| **Gastrointestinal**<br>Emesis in dogs and abnormal feces in rats and dogs were observed acutely and following multiple doses. In the stomach, erosion/ulceration and/or oedema were noted in rats and/or dogs following 2 weeks of lorlatinib administration.<br><br>Additional gastrointestinal changes included single cell necrosis (gastric glands), mucosal atrophy (stomach), and/or erosion/ulceration and/or villous atrophy, crypt hyperplasia, epithelial degeneration and/or subacute inflammation in the small and/or large intestines after 2 and/or 13 weeks of dosing. However, these findings | While lorlatinib has the potential to cause gastrointestinal abnormalities in humans, it does not appear to negatively impact the risk-benefit profile of lorlatinib. |

**Table 1. Key Safety Findings and Relevance to Human Usage**

| Key Safety findings from Non-clinical Studies | Relevance to Human Usage |
|---|---|
| were considered non adverse. Partial or complete reversibility of the gastrointestinal effects in rats and dogs was demonstrated following a 4-week non-dosing recovery period after 4 or 13 weeks of lorlatinib administration. The NOAEL in rats and dogs provide margins of 11x and 4.6x, respectively, the unbound human steady-state AUC exposure. | |
| **Nervous System**<br><br>Peripheral Nerves<br>Axonal degeneration in peripheral nerves was identified in rats after ≥4 weeks of lorlatinib administration. Axon degeneration was not present after a 4-week non-dosing period, after 4 or 13 weeks of lorlatinib administration. The NOAEL in the rat provide a margin of 3.3x the unbound human steady-state AUC exposure.<br><br>Cognitive and Neurologic Function<br>Lorlatinib caused a reduction in amplitude of long-term potentiation in hippocampal brain slices and in a contextual renewal model, lower memory recall scores were observed following a single dose of lorlatinib. Functional observational battery effects after 14 days of lorlatinib administration to rats included abnormal behavior (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). 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 NOAEL in rats provide a margin of 7.1x the unbound human steady-state AUC exposure. | While lorlatinib has the potential to cause peripheral neurological abnormalities in humans, it does not appear to negatively impact the risk-benefit profile of lorlatinib.<br><br>Lorlatinib has the potential to cause cognitive effects in humans. See SVII.3.1.1. Important Identified Risk – CNS Effects. |
| **Kidney**<br>Renal changes in rats observed in repeat-dose toxicity studies ≥4 weeks in duration included glomerulopathy, tubular hyaline casts and/or arterial degeneration/necrosis, and increased incidence and/or severity of tubular basophilia and tubular pigmentation Renal changes correlated with urinalysis findings of higher urine volume, lower specific gravity and pH, and dark urine color with higher amount of bilirubin. Following 4 weeks of lorlatinib administration to rats, higher blood urea nitrogen, creatinine, and lower urine pH, were observed with no microscopic correlates in the kidney. The renal changes in rats were partially or completely reversible following a 4-week non-dosing | While lorlatinib has the potential to cause renal abnormalities in humans, it does not appear to negatively impact the risk-benefit profile of lorlatinib. |

**Table 1. Key Safety Findings and Relevance to Human Usage**

| Key Safety findings from Non-clinical Studies | Relevance to Human Usage |
|---|---|
| period after 4 or 13 weeks of lorlatinib administration. The NOAEL for renal changes provided a margin of 3.3x the unbound human steady-state AUC exposure. | |
| **Hyperlipidaemia**<br>Non-adverse higher cholesterol and /or triglycerides were observed in rats and dogs after ≥2 weeks of lorlatinib administration. The alterations in lipid profiles in both rats and dogs were without histologic correlates, and partially or completely reversed at the end of a 4-week non-dosing period after 4 or 13 weeks lorlatinib administration. The NOAEL in the rat provided a margin of 7.1x the unbound human steady-state AUC exposure. | While lorlatinib has the potential to cause hyperlipidaemia in humans, it does not appear to negatively impact the risk-benefit profile of lorlatinib. |
| **Mutagenicity, Clastogenicity, and Carcinogenicity**<br>Lorlatinib was identified as an aneugen, but not a mutagen or clastogen. Micronucleus formation was detected in vitro with or without metabolic activation and in vivo 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. The no effect level for in vivo micronucleus formation in the rat provided a margin of 9.2x the unbound human steady-state AUC exposure.<br><br>Animal carcinogenicity studies have not been conducted with lorlatinib. | Lorlatinib was identified as an aneugen however, not in a clinically relevant dose range. |

## Module SIII Clinical Trial Exposure

### SIII.1. Brief Overview of Development

Study B7461001 (hereafter referred to as Study 1001, but may use full protocol number in tables) "A phase 1/2, open-label, multicentre, multiple-dose, dose-escalation, safety, pharmacokinetics (PK), Pharmacodynamics (PD) and antitumour efficacy exploration study of lorlatinib as a single agent in patients with advanced ALK-positive or advanced ROS1-positive NSCLC" was completed on 24 May 2023 (Last Patient Last Visit) and CSR for this trial was completed on 31 October 2023. In this trial, 54 patients received study drug in Phase 1 and 275 patients received study drug in Phase 2, in addition, 3 Japanese patients from Lead in Cohort (LIC) also received study drug. In the Phase 1 part of Study 1001, patients were assigned to receive lorlatinib doses ranging from 10 to 200 mg daily (QD) or twice daily (BID) as part of a dose escalation study design. Phase 1 established lorlatinib 100 mg QD as the recommended Phase 2 dose (RP2D), which was the dose that was used in the Phase 2 portion of Study 1001. Study 1001 also comprised a drug-drug-interaction substudy to explore lorlatinib PK, safety and efficacy with single doses of four different drugs that are metabolized or transported via pathways that include CYP2B6, CYP2C9, P-gp, and select UGT isoforms. Thirty-two (32) patients participated and have been evaluated. These 32 patients are part of the total patients (N=327) presented below.

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

Study B7461006 (hereafter referred to as Study 1006, but may use full protocol number in tables) is an ongoing Phase 3, multinational, multicenter, randomized, open label, parallel 2 arm study in which 296 previously untreated participants with advanced ALK positive NSCLC were randomized using a 1:1 ratio to receive lorlatinib 100 mg QD monotherapy or crizotinib 250 mg BID monotherapy according to the study design. Participants were stratified according to:

- Presence of brain metastases (Yes vs. No);
- Ethnic origin (Asian vs. non-Asian).

Study treatment continued until confirmed disease progression assessed by BICR, participant refusal, participant lost to follow up, or unacceptable toxicity, whichever came first. Participants who developed radiological disease progression confirmed by BICR assessment but were otherwise continuing to derive clinical benefit from study treatment were eligible to continue with the treatment they were assigned to, provided that the treating physician determined that the benefit/risk for doing so was favorable. Crossover between treatment arms was not permitted.

Study B7461027 (also referred to as Study 1027, but may use full protocol number in tables) was a Phase 4 post-authorisation efficacy study entitled “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)”. The final CSR for this study was completed on 09 September 2024. In this study, participants took lorlatinib at the approved dose of 100 mg once daily (QD). Participants were treated until disease progression, participant refusal/lost to follow-up, or unacceptable toxicity.

The study met its primary endpoint as the lower limit of the 95% CI for ORR exceeded 30%, the historical ORR for platinum-based doublet chemotherapy. In 71 participants whose disease had progressed on alectinib or ceritinib as the first ALK TKI therapy, the confirmed ORR with lorlatinib was 42.3% (95% CI: 30.6%, 54.6%) per ICR assessment. The median DoR was not reached with over 50% of responders remaining in response at the time of PCD.

In summary, lorlatinib continued to show clinically meaningful benefit in participants with previously treated advanced ALK-positive NSCLC. 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.

**SIII.2. Clinical Trial Exposure**

The Clinical Trial Exposure is presented based on 2 pools:

- Pool A: Pool of patients with advanced ALK/ROS1-positive NSCLC from clinical study 1001 (n=327), advanced ALK-positive NSCLC from clinical study 1006 (n=149), and participants with advanced ALK-positive NSCLC whose disease had progressed on alectinib or ceritinib as the first ALK TKI therapy from clinical study 1027 (n=71) who received lorlatinib 100 mg QD (total n=547). This includes patients who were treatment naive and patients who received prior treatment with one, two, or more ALK TKIs with or without chemotherapy (referred hereafter as “any lines”)

- Pool B: Remaining patients from the Phase 1 portion of study 1001 who received doses other than 100 mg QD (n=37)

The clinical trial exposure tables for the pivotal Studies 1001 and 1006 and post-authorisation efficacy study 1027 are displayed in Table 2 through Table 5 below. Please note that the stratification by indication/dose in the following tables is based on the initial dosing group that the patients were randomised to; however, the Phase 1 portion allowed intra-patient dose escalations.

In the Phase 1 portion of Study 1001, lorlatinib was to be evaluated at escalating doses of 10, 25, 50, 75, 100, 150, 200, 250, 300, and 400 mg/once daily (QD), depending on toxicities observed.

Starting at the 25 mg dose level, a Continual Reassessment Method (CRM) was employed to assign patients to dose levels in order to estimate the Maximum Tolerated Dose (MTD) and select the Recommended Phase 2 Dose (RP2D). For each dose level, patients were to be enrolled in cohorts of a minimum of 3 patients with dose-limiting toxicities (DLTs) evaluated during the first cycle. The goal of the Phase 1 portion was to determine the dose of lorlatinib that was the closest to but no higher than a 33% probability of a DLT (i.e. a target DLT rate of 0.33). Each dose cohort was to initially include at least 3 patients evaluable for toxicity within the first cycle. The first 3 patients (i.e. the first cohort) were to be treated at 10 mg QD, and the following dose level explored was to be 25 mg QD. Dose escalation process progressed and although the MTD was not formally identified, 100 mg QD was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

**Table 2. Duration of Exposure**

| Duration of exposure | Persons | Person time (person-years) |
|---|---|---|
| **Pool A** | | |
| <3 months | 97 | 13.2 |
| 3 to <6 months | 45 | 16.7 |
| 6 to <9 months | 48 | 29.5 |
| 9 to <12 months | 35 | 30.8 |
| 12 to <15 months | 30 | 33.5 |
| 15 to <18 months | 25 | 34.7 |
| 18 to <21 months | 20 | 31.9 |
| 21 to <24 months | 12 | 22.3 |
| ≥24 months | 235 | 1179.6 |
| **Total person time (≥ 1 dose)** | 547 | 1392.2 |
| **Pool B[b]** | | |
| <3 months | 10 | 1.2 |
| 3 to <6 months | 4 | 1.5 |
| 6 to <9 months | 3 | 2.0 |
| 9 to <12 months | 3 | 2.4 |
| 12 to <15 months | 1 | 1.2 |
| 15 to <18 months | 1 | 1.4 |
| 18 to <21 months | 1 | 1.7 |
| 21 to <24 months | 2 | 3.7 |
| ≥24 months | 12 | 65.8 |
| **Total person time (≥ 1 dose)** | 37 | 81.0 |

Duration of exposure (months) = (last dose date - Cycle 1 Day 1 date + 1)/30.4375
For patients receiving only lead-in dose, the duration of exposure is defined as 1 day.
Source Data: adex Output File: ./B746_IB2024/B746_pool_IB2024/adex_expo1a Date of Generation: 08OCT2024 (05:29)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Output File: ./B746_IB2024/B7461001/adex_expo1b Date of Generation: 01 SEP 2024 (22:30) B7461001 was based on final CSR data.

a. All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
b. All patients who received lorlatinib doses other than 100 mg.

## Table 3. Exposure by Age Group and Gender

| Age Group | Persons | | Person time (person-years) | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| **Pool A[a]** | | | | |
| <18 years | 0 | 0 | 0 | 0 |
| 18-<45 years | 59 | 61 | 161.9 | 158.3 |
| 45-<65 years | 130 | 153 | 314.6 | 445.3 |
| ≥65 years | 59 | 85 | 123.3 | 188.9 |
| Total | 248 | 299 | 599.8 | 792.5 |
| **Pool B[b]** | | | | |
| <18 years | 0 | 0 | 0 | 0 |
| 18-<45 years | 3 | 7 | 11.6 | 19.1 |
| 45-<65 years | 8 | 11 | 14.6 | 28.1 |
| ≥65 years | 5 | 3 | 3.2 | 4.4 |
| Total | 16 | 21 | 29.3 | 51.6 |

Duration of exposure (months) = (last dose date - Cycle 1 Day 1 date + 1)/30.4375
For patients receiving only lead-in dose, the duration of exposure is defined as 1 day.
For B7461006 and B7461027, Age at Screening (years)=(date of informed consent given-date of birth +1)/365.25. For B7461001, Age at Screening (years)=(date of collection-date of birth + 1)/365.25.
Source Data: adex Output File: ./B746_IB2024/B746_pool_IB2024/adex_expo2a Date of Generation: 10OCT2024 (02:15)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Output File: ./B746_IB2024/B7461001/adex_expo2b Date of Generation: 31 AUG 2024 (07:51) B7461001 was based on final CSR data.
a. All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
b. All patients who received lorlatinib doses other than 100 mg.

## Table 4. Exposure by Dose

| Dose of exposure | Persons | Person time (person-years) |
|---|---|---|
| **Pool A[a]** | 547 | 1392.2 |
| **Pool B[b]** | 37 | 81.0 |

Source Data: adex Output File: ./B746_IB2024/B746_pool_IB2024/adex_expo1a Date of Generation: 08OCT2024 (05:29)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Output File: ./B746_IB2024/B7461001/adex_expo1b Date of Generation: 01 SEP 2024 (22:30) B7461001 was based on final CSR data.
a. All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
b. All patients who received lorlatinib doses other than 100 mg.

## Table 5. Exposure by Ethnic or Racial Origin

| Ethnic/Racial Origin | Persons | | Person Time (person-years) | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| **Pool A[a]** | | | | |
| White | 129 | 163 | 268.1 | 429.2 |
| Black or African Americans | 2 | 1 | 0.9 | 0.6 |
| Asian | 91 | 108 | 245.2 | 280.6 |

**Table 5. Exposure by Ethnic or Racial Origin**

| Ethnic/Racial Origin | Persons | | Person Time (person-years) | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| Other | 6 | 8 | 14.2 | 20.1 |
| Not Reported | 20 | 19 | 71.3 | 62.0 |
| Total | 248 | 299 | 599.8 | 792.5 |
| **Pool B[b]** | | | | |
| White | 11 | 13 | 16.1 | 21.5 |
| Black or African American | 1 | 2 | 0.02 | 2.5 |
| Asian | 2 | 3 | 10.5 | 13.9 |
| Other | 0 | 0 | 0 | 0 |
| Not Reported | 2 | 3 | 2.6 | 13.8 |
| Total | 16 | 21 | 29.3 | 51.6 |

Duration of exposure (months) = (last dose date - Cycle 1 Day 1 date + 1)/30.4375
For patients receiving only lead-in dose, the duration of exposure is defined as 1 day.
Source Data: adex Output File: ./B746 IB2024/B746 pool IB2024/adex expo3a Date of Generation: 08OCT2024 (22:00) B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Output File: ./B746 IB2024/B7461001/adex expo3b Date of Generation: 31AUG2024 (07:49) B7461001 was based on final CSR data.

a. All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
b. All patients who received lorlatinib doses other than 100 mg.

## Module SIV Populations Not Studied in Clinical Trials

### SIV.1. Important Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

There has been limited exposure of special populations to lorlatinib and no epidemiologic studies have been conducted in pregnant/lactating women, paediatric patients (<age 18), and specific subpopulations that were excluded from the CT development programme.

Following are the important exclusion criteria in the pivotal clinical studies across the development programme:

**Patients using concomitant strong CYP3A4/5 inducers**

Reason for exclusion: Early non-clinical data had indicated that CYP3A4/5 is involved in lorlatinib metabolism. Based on this, in the First in Human (Study 1001) protocol, use of strong CYP3A4/5 inducers was an exclusion criterion based on anticipated lowering of lorlatinib plasma concentrations. Subsequently a formal drug interaction study (B7461011) was conducted in healthy volunteers, in which increases in AST and ALT were noted when lorlatinib was given in combination with rifampin, a strong CYP3A4/5 inducer. Based on the safety results from this study, the subsequent use of strong CYP3A4/5 was contraindicated with lorlatinib.

Co-administration with multiple doses of rifampin (a strong CYP3A4/5 inducer) has been associated with reversible, severe increase of LFT values (AST and ALT) in healthy subjects; there were no concurrent increases in total bilirubin or alkaline phosphatase. The etiology of this is not entirely clear.

Is it considered to be included as missing information? No

Rationale: Strong CYP3A4/5 inducers will remain as a contraindication and not as missing information because the data is already available to define this as an important exclusion and no further characterisation therefore is planned.

### SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions (ARs) such as uncommon or rare ARs, ARs with a long latency, and ARs caused by prolonged exposure.

### SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 6 lists the patient populations that have been under-represented in CTs in the lorlatinib clinical development programme.

**Table 6. Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| Pregnant Women | Pregnant women were not included in the lorlatinib clinical development programme. |
| Breastfeeding Women | Breastfeeding women were not included in the lorlatinib clinical development programme. |
| Patients with relevant comorbidities | |
| • Patients with Hepatic Impairment | 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 x ULN, or if there were liver metastases involvement, >5.0 x ULN or with total bilirubin >1.5 x ULN. Population PK analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=53). No dose adjustments are recommended for patients with mild hepatic impairment. No information is currently available for patients with moderate or severe hepatic impairment.<br><br>A clinical trial (B7461040) to evaluate the effect of moderate and severe hepatic impairment on the 100 mg single dose plasma PK of lorlatinib is ongoing. 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. |

**Table 6. Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| • Patients with Renal Impairment | It has been observed that less than 1% of the administered dose is detected as unchanged lorlatinib in urine. Clinical studies excluded patients with serum creatinine >1.5 x ULN or estimated creatinine clearance < 60 mL/min. Population pharmacokinetic analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild (n=103; CrCl 60-89 mL/min) or moderate (n=41; CrCl 30-59 mL/min) renal impairment. Lorlatinib use in patients with severe renal impairment (CrCl <30 mL/min) is limited (n=1). No dose adjustments are recommended for patients with mild or moderate renal impairment. A reduced dose of lorlatinib is recommended in patients with severe renal impairment, e.g., a once daily oral starting dose of 75 mg. No information is available for patients on renal dialysis. |
| • Patients with other relevant co-morbidities | No relevant exposure |
| • Patients with a disease severity different from inclusion criteria in clinical trials | Patients with disease severity different from the inclusion criteria were not included in the lorlatinib clinical development programme. |
| • Immuno-compromised patients | No relevant exposure |
| Population with relevant different ethnic origin (Non-Caucasian non-Asian patients) | Non-Caucasian non-Asian patients accounted for 3.1% (17/547) of patients with advanced ALK/ROS1-positive NSCLC from clinical studies 1001, 1006, and 1027 who received lorlatinib 100 mg QD (n=547) |
| Subpopulations carrying known and relevant genetic polymorphisms | Subpopulations carrying relevant genetic polymorphisms were not included in the lorlatinib clinical development programme. Based on a population PK analysis using pooled data from 7 lorlatinib clinical studies, CYP2C9, CYP2C19 and CYP3A5 phenotypes that were tested as covariates did not have a statistically significant effect on lorlatinib PK.[39] |
| Other | |
| • Elderly Patients | Elderly patients (age 65 years or older) accounted for 26.3% (144/547) of patients with advanced ALK/ROS1-positive NSCLC from clinical studies 1001, 1006, and 1027 who received lorlatinib 100 mg QD (n=547). |
| • Paediatric Patients | Paediatric patients were not included in the lorlatinib clinical development programme. |
| • Patients using concomitant strong CYP3A4/5 inducers | The use of strong CYP3A4/5 inducers was not allowed in lorlatinib patient studies. In a drug interaction study in healthy subjects, coadministration of multiple doses of rifampin (a |

**Table 6. Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| | strong CYP3A4/5 inducer) decreased lorlatinib $AUC_{inf}$ by 85% and decreased the $C_{max}$ by 76% relative to a single lorlatinib 100 mg dose given alone. Co-administration with multiple doses of rifampin in this study also led to reversible, severe increase of LFT values (AST and ALT) in all subjects; there were no concurrent increases in total bilirubin or alkaline phosphatase. Based on this, the use of strong CYP3A4/5 inducers with lorlatinib is contraindicated. |
| • Patients using concomitant strong CYP3A4/5 inhibitors | The use of strong CYP3A4/5 inhibitors was not allowed in lorlatinib patient studies. In a healthy subject drug interaction study coadministration of multiple doses of itraconazole (a strong CYP3A4/5 inhibitor) with a single 100 mg of lorlatinib increased lorlatinib $AUC_{inf}$ by 42% and $C_{max}$ by 24%. Based on this, it is recommended that use of strong CYP3A4/5 inhibitors should be avoided. If they cannot be avoided, then the lorlatinib dose should be reduced to 75 mg QD when given in combination with a strong CYP3A4/5 inhibitor. |

## Module SV Post-Authorisation Experience

### SV.1. Post-authorisation exposure

### SV.1.1. Method Used to Calculate Exposure

The estimated cumulative patient exposure is based on worldwide sales in kilograms (kg) provided by IQVIA sold through the 1st quarter of 2024 and extrapolated through 30 June 2024. The sales of lorlatinib from 01 April 2024 to 30 June 2024 were extrapolated by taking the average of sales of the previous 4 quarters. Patient days were calculated by assuming a dose of 100 mg tablet daily, per the recommended dose schedule in the current SmPC. Patient days (days of therapy) were further divided by 365.25 (days in a year) to obtain patient-years.

### SV.1.2. Exposure

The cumulative exposure to lorlatinib from marketing experience since product approval through 30 June 2024 is estimated to be 17,832 patient-years. The cumulative patient exposure is based on worldwide sales of 651 kg (651,309,521 mg) and is presented in Table 7.

**Table 7. Cumulative Estimated Exposure for Lorlatinib (through 30 June 2024)**

| Region | Total (kg) | Patient Days | Patient Years[a] |
|---|---|---|---|
| United States | 120 | 1,203,397 | 3,295 |
| European Union | 211 | 2,112,915 | 5,785 |
| Japan | 92 | 916,327 | 2,509 |
| Rest of World | 228 | 2,280,455 | 6,244 |
| Total | 651 | 6,513,095 | 17,832 |

a. Patient years have been rounded-off to the closest whole number and therefore the total may reflect this slight variance.

## Module SVI Additional EU Requirements for the Safety Specification

### SVI.1. Potential for Misuse for Illegal Purposes

Lorlatinib does not have characteristics that make it attractive for use for illegal purposes therefore there is a low potential for lorlatinib misuse for illegal purposes.

## Module SVII Identified and Potential Risks

### SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initial RMP are listed below:

**Table 8. 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 |
| | Patients with severe renal impaiment |

### SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in this RMP include:

- Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
    - Vision disorders
- Known risks that do not require further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):
    - Hypercholesterolaemia
    - Hypertriglyceridaemia
    - Oedema
    - Peripheral neuropathy
    - Hypertension
    - Hyperglycemia
- Known risks that do not impact the risk-benefit profile:
    - Fatigue
    - Diarrhoea
    - Constipation
    - Arthralgia
- Other reasons for considering the risks not important:
    - The use of strong CYP3A4/5 inducers is contraindicated and no plan for further characterisation is considered.

### SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Important Identified Risk: CNS Effects**

The frequency of all-causality adverse events (AEs) indicative of CNS effects (including cognitive, mood, speech, and psychotic effects) with lorlatinib treatment is 44.96% (214/476) (95% CI: 40.4, 49.6) in all patients who received lorlatinib 100 mg QD for advanced NSCLC in Studies 1001 and 1006. Although no potential mechanism of CNS effects associated with lorlatinib treatment has been identified in humans, potential inhibition of Trk-b may be considered.

Risk-benefit impact:

Severe CNS effects considered related to drug, may have the potential to affect the risk-benefit profile of lorlatinib.

**Important Identified Risk: ILD/pneumonitis**

The frequency of all causality adverse events (AEs) of ILD/pneumonitis with lorlatinib treatment is 1.89% (9/476) (95% CI: 0.9, 3.6) in all patients who received lorlatinib 100 mg QD for advanced NSCLC in Studies 1001 and 1006. ILD/pneumonitis is a known class-effect risk associated with other ALK inhibitors.

Risk-benefit impact: Life threatening and/or fatal cases of ILD/pneumonitis, if established as related to drug, may have the potential to affect the risk-benefit profile of lorlatinib.

**Important Potential Risk: AV block**

The frequency of all causality AEs of AV block with lorlatinib treatment is 1.89% (9/476) (95% CI: 0.9, 3.6) in all patients who received lorlatinib 100 mg QD for advanced NSCLC in Studies 1001 and 1006, although the relationship between lorlatinib treatment and AV block has not been demonstrated. Further characterisation of the potential risk of AV block may help to determine if there is a causal association with lorlatinib.

The exposure response for PR prolongation versus lorlatinib plasma concentrations was modeled using data from 8 lorlatinib clinical studies (PMAR-684). The probability of experiencing a PR interval ≥ 200 msec at a baseline PR of 180 msec was 0.268 for the lorlatinib 100 mg QD dose. Given that 90% of the observed baseline PR interval values were below 180 msec, the risk of experiencing a first-degree AV blockage was considered low.[40]

Risk-benefit impact: Currently there is no known impact of AV block on the overall risk-benefit balance of lorlatinib because the relationship to lorlatinib has not been determined.

Life threatening and/or fatal cases of AV block, if established as related to drug, may have the potential to affect the risk-benefit profile of lorlatinib.

**Important Potential Risk: Pancreatitis**

The frequency of cases reporting all causality AEs potentially indicative of pancreatitis with lorlatinib treatment is 18.70% (89/476) (95% CI: 15.3, 22.5) in all patients who received lorlatinib 100 mg QD for advanced NSCLC in Studies 1001 and 1006. With the exception of one reported event of pancreatitis, all other reported AEs were of asymptomatic elevation of blood lipase and amylase.

Risk-benefit impact: Asymptomatic increase in blood lipase or amylase may not impact the risk-benefit profile of lorlatinib. If pancreatitis is Grade 1 or 2, the impact on an individual patient may be limited. Pancreatitis Grade 3 or 4 can require medical intervention, be a life-threatening event or can have a fatal outcome.

**Important Potential Risk: Embryo-foetal toxicity**

No AEs suggestive of embryo-foetal toxicity were reported with lorlatinib treatment. Further characterisation of the potential risk of embryo-foetal toxicity may help to determine if there is a causal association with lorlatinib.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance is not known because the relationship of embryo-foetal toxicity to lorlatinib treatment has not been identified.

If embryo-foetal toxicity is established as related to drug, it may have the potential to affect the risk-benefit profile of lorlatinib.

## SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

## SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

The identified and potential risks for lorlatinib are characterised based on a pool of patients (see Pool A, Part II, Module SIII. Clinical trial exposure) with advanced ALK/ROS1-positive NSCLC from clinical study 1001 (n=327), advanced ALK-positive NSCLC from clinical study 1006 (n=149), and with advanced ALK-positive NSCLC whose disease had progressed on alectinib or ceritinib as the first ALK TKI therapy from clinical study 1027 (n=71) who received lorlatinib 100 mg QD (total n=547). This includes patients who were treatment naive and patients who received prior treatment with one, two, or more ALK TKIs with or without chemotherapy (referred hereafter as “any lines”).

#### SVII.3.1.1. Important Identified Risk – CNS Effects

The important identified risk of CNS effects was sub-divided into 4 categories including cognitive, mood, speech, and psychotic effects.

### SVII.3.1.1.1. Potential Mechanisms

Currently, no established mechanism of CNS effects associated with lorlatinib treatment has been identified in humans. However, potential inhibition of Trk-b may be considered. Cognitive effects have been seen in animals treated with lorlatinib.

### SVII.3.1.1.2. Evidence Source and Strength of Evidence

Evidence Source: Lorlatinib non-clinical and clinical studies.

Strength of Evidence: The relationship between lorlatinib administration and CNS effects has been demonstrated in non-clinical and clinical studies. Temporary discontinuation and dose reduction have been successful in the management of CNS effects.

### SVII.3.1.1.3. Characterisation of the Risk

### Frequency with 95% CI

All-causality AEs indicative of CNS Effects (including cognitive, mood, speech, and psychotic effects) occurred with a frequency of 44.97% (246/547) (95% CI: 40.7, 49.3) in all patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).

### Seriousness/outcomes

**Table 9. All-Causality Adverse Events of Cognitive Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 150 patients)**

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Amnesia | 58 (17.63) | 0 | 40 (68.97) | 18 (31.03) | 0 | 0 |
| Attention deficit hyperactivity disorder | 2 (0.61) | 0 | 1 (50.00) | 1 (50.00) | 0 | 0 |
| Cognitive disorder | 42 (12.77) | 3 (7.14) | 26 (61.90) | 16 (38.10) | 0 | 0 |
| Confusional state | 33 (10.03) | 7 (21.21) | 25 (75.76) | 8 (24.24) | 0 | 0 |
| Delirium | 13 (3.95) | 6 (46.15) | 13 (100.00) | 0 | 0 | 0 |
| Dementia | 1 (0.30) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Disorientation | 8 (2.43) | 0 | 8 (100.00) | 0 | 0 | 0 |
| Disturbance in attention | 51 (15.50) | 0 | 40 (78.43) | 11 (21.57) | 0 | 0 |
| Memory impairment | 113 (34.35) | 0 | 77 (68.14) | 35 (30.97) | 0 | 1 (0.88) |
| Mental impairment | 7 (2.13) | 0 | 5 (71.43) | 2 (28.57) | 0 | 0 |
| Reading disorder | 1 (0.30) | 0 | 1 (100.00) | 0 | 0 | 0 |
| **Total Events** | **329** | **16 (4.86)** | **236 (71.73)** | **92 (27.96)** | **0** | **1 (0.30)** |

## Table 9. All-Causality Adverse Events of Cognitive Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 150 patients)

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLGTs (all paths): Mental impairment disorders, Cognitive and attention disorders and disturbances, Deliria (including confusion)



## Table 10. All-Causality Adverse Events of Mood Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 117 patients)

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Affect lability | 15 (7.35) | 0 | 13 (86.67) | 2 (13.33) | 0 | 0 |
| Affective disorder | 12 (5.88) | 0 | 10 (83.33) | 2 (16.67) | 0 | 0 |
| Aggression | 2 (0.98) | 0 | 2 (100.00) | 0 | 0 | 0 |
| Agitation | 9 (4.41) | 0 | 6 (66.67) | 3 (33.33) | 0 | 0 |
| Anger | 3 (1.47) | 0 | 3 (100.00) | 0 | 0 | 0 |
| Anxiety | 45 (22.06) | 0 | 29 (64.44) | 16 (35.56) | 0 | 0 |
| Apathy | 1 (0.49) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Bipolar I disorder | 2 (0.98) | 0 | 2 (100.00) | 0 | 0 | 0 |
| Claustrophobia | 1 (0.49) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Depressed mood | 10 (4.90) | 0 | 8 (80.00) | 1 (10.00) | 0 | 1 (10.00) |
| Depression | 37 (18.14) | 0 | 27 (72.97) | 10 (27.03) | 0 | 0 |
| Depressive symptom | 2 (0.98) | 0 | 2 (100.00) | 0 | 0 | 0 |
| Emotional disorder | 1 (0.49) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Euphoric mood | 3 (1.47) | 0 | 3 (100.00) | 0 | 0 | 0 |
| Irritability | 31 (15.20) | 0 | 27 (87.10) | 4 (12.90) | 0 | 0 |
| Mania | 4 (1.96) | 0 | 4 (100.00) | 0 | 0 | 0 |
| Mood altered | 10 (4.90) | 0 | 8 (80.00) | 2 (20.00) | 0 | 0 |
| Mood swings | 5 (2.45) | 0 | 3 (60.00) | 2 (40.00) | 0 | 0 |

## Table 10. All-Causality Adverse Events of Mood Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 117 patients)

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Panic attack | 2 (0.98) | 0 | 2 (100.00) | 0 | 0 | 0 |
| Personality change | 6 (2.94) | 0 | 5 (83.33) | 1 (16.67) | 0 | 0 |
| Psychomotor retardation | 1 (0.49) | 0 | 1 (100.00) | 0 | 0 | 0 |
| Stress | 2 (0.98) | 0 | 1 (50.00) | 1 (50.00) | 0 | 0 |
| **Total Events** | **204** | **0** | **156 (76.47)** | **47 (23.04)** | **0** | **1 (0.49)** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLGTs (all paths): Mood disorders and disturbances NEC, Anxiety disorders and symptoms, Depressed mood disorders and disturbances, Personality disorders and disturbances in behavior, Manic and bipolar mood disorders and disturbances

## Table 11. All-Causality Adverse Events of Speech Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 45 patients)

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Dysarthria | 53 (60.92) | 1 (1.89) | 48 (90.57) | 3 (5.66) | 0 | 2 (3.77) |
| Incoherent | 1 (1.15) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Slow speech | 18 (20.69) | 0 | 11 (61.11) | 7 (38.89) | 0 | 0 |
| Speech disorder | 15 (17.24) | 1 (6.67) | 14 (93.33) | 1 (6.67) | 0 | 0 |
| **Total Events** | **87** | **2 (2.30)** | **73 (83.91)** | **12 (13.79)** | **0** | **2 (2.30)** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_5a Date of Generation: 08OCT2024 (05:33)

**Table 11. All-Causality Adverse Events of Speech Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 45 patients)**

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |

B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLTs (all paths): Speech and language abnormalities

**Table 12. All-Causality Adverse Events of Psychotic Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 38 patients)**

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **N (%=n/N1)** |
| Acute psychosis | 1 (1.89) | 1 (100.00) | 1 (100.00) | 0 | 0 | 0 |
| Delusion | 4 (7.55) | 1 (25.00) | 4 (100.00) | 0 | 0 | 0 |
| Hallucination | 20 (37.74) | 0 | 18 (90.00) | 2 (10.00) | 0 | 0 |
| Hallucination, auditory | 15 (28.30) | 0 | 11 (73.33) | 4 (26.67) | 0 | 0 |
| Hallucination, visual | 11 (20.75) | 0 | 8 (72.73) | 3 (27.27) | 0 | 0 |
| Illusion | 1 (1.89) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Schizophreniform disorder | 1 (1.89) | 1 (100.00) | 1 (100.00) | 0 | 0 | 0 |
| **Total Events** | **53** | **3 (5.66)** | **43 (81.13)** | **10 (18.87)** | **0** | **0** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - SMQ: Psychosis and Psychotic disorders (narrow)
PT: Psychotic symptom

## Severity and nature of risk

### Table 13. All-Causality Adverse Events of Cognitive Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 150 patients)

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Amnesia | 28 (18.67) | 10 (6.67) | 0 | 0 | 0 | 38 (25.33) |
| Attention deficit hyperactivity disorder | 2 (1.33) | 0 | 0 | 0 | 0 | 2 (1.33) |
| Cognitive disorder | 18 (12.00) | 9 (6.00) | 4 (2.67) | 0 | 0 | 31 (20.67) |
| Confusional state | 10 (6.67) | 9 (6.00) | 9 (6.00) | 0 | 0 | 28 (18.67) |
| Delirium | 2 (1.33) | 2 (1.33) | 4 (2.67) | 0 | 0 | 8 (5.33) |
| Dementia | 1 (0.67) | 0 | 0 | 0 | 0 | 1 (0.67) |
| Disorientation | 0 | 1 (0.67) | 1 (0.67) | 0 | 0 | 2 (1.33) |
| Disturbance in attention | 24 (16.00) | 4 (2.67) | 0 | 0 | 0 | 28 (18.67) |
| Memory impairment | 46 (30.67) | 12 (8.00) | 1 (0.67) | 0 | 0 | 59 (39.33) |
| Mental impairment | 5 (3.33) | 1 (0.67) | 0 | 0 | 0 | 6 (4.00) |
| Reading disorder | 1 (0.67) | 0 | 0 | 0 | 0 | 1 (0.67) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLGTs (all paths): Mental impairment disorders, Cognitive and attention disorders and disturbances, Deliria (including confusion)

### Table 14. All-Causality Adverse Events of Mood Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 117 patients)

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Affect lability | 9 (7.69) | 2 (1.71) | 0 | 0 | 0 | 11 (9.40) |
| Affective disorder | 6 (5.13) | 2 (1.71) | 0 | 0 | 0 | 8 (6.84) |
| Aggression | 2 (1.71) | 0 | 0 | 0 | 0 | 2 (1.71) |
| Agitation | 6 (5.13) | 1 (0.85) | 1 (0.85) | 0 | 0 | 8 (6.84) |
| Anger | 1 (0.85) | 1 (0.85) | 0 | 0 | 0 | 2 (1.71) |
| Anxiety | 29 (24.79) | 10 (8.55) | 1 (0.85) | 0 | 0 | 40 (34.19) |
| Apathy | 0 | 1 (0.85) | 0 | 0 | 0 | 1 (0.85) |

## Table 14. All-Causality Adverse Events of Mood Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 117 patients)

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Bipolar I disorder | 0 | 0 | 1 (0.85) | 0 | 0 | 1 (0.85) |
| Claustrophobia | 0 | 1 (0.85) | 0 | 0 | 0 | 1 (0.85) |
| Depressed mood | 7 (5.98) | 2 (1.71) | 0 | 0 | 0 | 9 (7.69) |
| Depression | 10 (8.55) | 14 (11.97) | 2 (1.71) | 0 | 0 | 26 (22.22) |
| Depressive symptom | 0 | 1 (0.85) | 0 | 0 | 0 | 1 (0.85) |
| Emotional disorder | 1 (0.85) | 0 | 0 | 0 | 0 | 1 (0.85) |
| Euphoric mood | 3 (2.56) | 0 | 0 | 0 | 0 | 3 (2.56) |
| Irritability | 18 (15.38) | 2 (1.71) | 4 (3.42) | 0 | 0 | 24 (20.51) |
| Mania | 1 (0.85) | 2 (1.71) | 0 | 0 | 0 | 3 (2.56) |
| Mood altered | 6 (5.13) | 1 (0.85) | 0 | 0 | 0 | 7 (5.98) |
| Mood swings | 4 (3.42) | 1 (0.85) | 0 | 0 | 0 | 5 (4.27) |
| Panic attack | 2 (1.71) | 0 | 0 | 0 | 0 | 2 (1.71) |
| Personality change | 5 (4.27) | 0 | 0 | 0 | 0 | 5 (4.27) |
| Psychomotor retardation | 1 (0.85) | 0 | 0 | 0 | 0 | 1 (0.85) |
| Stress | 1 (0.85) | 1 (0.85) | 0 | 0 | 0 | 2 (1.71) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLGTs (all paths): Mood disorders and disturbances NEC, Anxiety disorders and symptoms, Depressed mood disorders and disturbances, Personality disorders and disturbances in behavior, Manic and bipolar mood disorders and disturbances

## Table 15. All-Causality Adverse Events of Speech Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 45 patients)

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Dysarthria | 13 (28.89) | 6 (13.33) | 2 (4.44) | 0 | 0 | 21 (46.67) |
| Incoherent | 1 (2.22) | 0 | 0 | 0 | 0 | 1 (2.22) |
| Slow speech | 11 (24.44) | 1 (2.22) | 1 (2.22) | 0 | 0 | 13 (28.89) |
| Speech disorder | 8 (17.78) | 2 (4.44) | 1 (2.22) | 0 | 0 | 11 (24.44) |

**Table 15. All-Causality Adverse Events of Speech Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 45 patients)**

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria – HLTs (all paths): Speech and language abnormalities

**Table 16. All-Causality Adverse Events of Psychotic Effects in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 38 patients)**

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Acute psychosis | 0 | 0 | 1 (2.63) | 0 | 0 | 1 (2.63) |
| Delusion | 1 (2.63) | 1 (2.63) | 0 | 1 (2.63) | 0 | 3 (7.89) |
| Hallucination | 14 (36.84) | 1 (2.63) | 0 | 0 | 0 | 15 (39.47) |
| Hallucination, auditory | 7 (18.42) | 3 (7.89) | 1 (2.63) | 0 | 0 | 11 (28.95) |
| Hallucination, visual | 6 (15.79) | 4 (10.53) | 1 (2.63) | 0 | 0 | 11 (28.95) |
| Illusion | 1 (2.63) | 0 | 0 | 0 | 0 | 1 (2.63) |
| Schizophreniform disorder | 0 | 0 | 0 | 1 (2.63) | 0 | 1 (2.63) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRAv27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_5a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - SMQ: Psychosis and Psychotic disorders (narrow)
PT: Psychotic symptom

## Post-Marketing

The safety database was searched cumulatively through 30 June 2024 for cases reporting adverse events consistent with CNS effects (including cognitive, mood, speech, and psychotic effects) in the post-marketing setting. The search identified 1629 cases reporting 2593 relevant events which represents 18.6% of the overall dataset (n=8752).

## Table 17. Post-Marketing Data in MAH Safety Database – CNS Effects

| | | | | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| **PT** | **No. of Events (% of Total PTs)** | **No. of Serious Events (% of PT)** | **No. of Events with Criterion of Hospitalization (% of PT)** | **Fatal** | **Resolved / Resolving** | **Resolved with Sequelae** | **Not Resolved** | **Unknown / No Data** |
| **All PTs** | **2593 (100)** | **825 (31.8)** | **246 (9.5)** | **3 (0.1)** | **817 (31.5)** | **4 (0.2)** | **289 (11.1)** | **1482 (57.2)** |
| Cognitive disorder | 284 (11) | 42 (14.8) | 20 (7) | 1 (0.4) | 86 (30.3) | 2 (0.7) | 30 (10.6) | 166 (58.5) |
| Hallucination | 228 (8.8) | 209 (91.7) | 24 (10.5) | 1 (0.4) | 83 (36.4) | 1 (0.4) | 25 (11) | 118 (51.8) |
| Memory impairment | 181 (7) | 11 (6.1) | 7 (3.9) | 0 | 38 (21) | 1 (0.6) | 27 (14.9) | 115 (63.5) |
| Asthenia | 121 (4.7) | 26 (21.5) | 17 (14) | 0 | 21 (17.4) | 0 | 17 (14) | 83 (68.6) |
| Confusional state | 116 (4.5) | 32 (27.6) | 17 (14.7) | 0 | 39 (33.6) | 0 | 19 (16.4) | 58 (50) |
| Anxiety | 111 (4.3) | 11 (9.9) | 5 (4.5) | 0 | 30 (27) | 0 | 9 (8.1) | 72 (64.9) |
| Speech disorder | 99 (3.8) | 13 (13.1) | 6 (6.1) | 0 | 29 (29.3) | 0 | 14 (14.1) | 56 (56.6) |
| Depression | 85 (3.3) | 6 (7.1) | 0 | 0 | 17 (20) | 0 | 9 (10.6) | 59 (69.4) |
| Delirium | 80 (3.1) | 80 (100) | 20 (25) | 0 | 45 (56.3) | 0 | 5 (6.3) | 30 (37.5) |
| Amnesia | 74 (2.9) | 8 (10.8) | 1 (1.4) | 0 | 20 (27) | 0 | 13 (17.6) | 41 (55.4) |
| Hallucination, auditory | 70 (2.7) | 69 (98.6) | 5 (7.1) | 0 | 30 (42.9) | 0 | 8 (11.4) | 33 (47.1) |
| Hallucination, visual | 69 (2.7) | 66 (95.7) | 5 (7.2) | 0 | 43 (62.3) | 0 | 3 (4.3) | 23 (33.3) |
| Dysarthria | 65 (2.5) | 9 (13.8) | 7 (10.8) | 0 | 22 (33.8) | 0 | 2 (3.1) | 41 (63.1) |
| Irritability | 59 (2.3) | 6 (10.2) | 3 (5.1) | 0 | 16 (27.1) | 0 | 4 (6.8) | 39 (66.1) |
| Psychotic disorder | 59 (2.3) | 27 (45.8) | 13 (22) | 1 (1.7) | 21 (35.6) | 0 | 8 (13.6) | 29 (49.2) |
| Affective disorder | 51 (2) | 6 (11.8) | 4 (7.8) | 0 | 17 (33.3) | 0 | 1 (2) | 33 (64.7) |
| Mood altered | 48 (1.9) | 4 (8.3) | 1 (2.1) | 0 | 15 (31.3) | 0 | 5 (10.4) | 28 (58.3) |
| Disturbance in attention | 46 (1.8) | 2 (4.3) | 0 | 0 | 16 (34.8) | 0 | 8 (17.4) | 22 (47.8) |
| Aggression | 45 (1.7) | 13 (28.9) | 9 (20) | 0 | 17 (37.8) | 0 | 2 (4.4) | 26 (57.8) |
| Anger | 38 (1.5) | 2 (5.3) | 0 | 0 | 9 (23.7) | 0 | 5 (13.2) | 24 (63.2) |
| Disorientation | 37 (1.4) | 12 (32.4) | 6 (16.2) | 0 | 19 (51.4) | 0 | 3 (8.1) | 15 (40.5) |
| Personality change | 33 (1.3) | 6 (18.2) | 2 (6.1) | 0 | 13 (39.4) | 0 | 1 (3) | 19 (57.6) |
| Agitation | 32 (1.2) | 7 (21.9) | 7 (21.9) | 0 | 12 (37.5) | 0 | 3 (9.4) | 17 (53.1) |
| Aphasia | 32 (1.2) | 5 (15.6) | 5 (15.6) | 0 | 13 (40.6) | 0 | 3 (9.4) | 16 (50) |

## Table 17. Post-Marketing Data in MAH Safety Database – CNS Effects

| | | | | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| **PT** | **No. of Events (% of Total PTs)** | **No. of Serious Events (% of PT)** | **No. of Events with Criterion of Hospitalization (% of PT)** | **Fatal** | **Resolved / Resolving** | **Resolved with Sequelae** | **Not Resolved** | **Unknown / No Data** |
| Mood swings | 29 (1.1) | 2 (6.9) | 0 | 0 | 5 (17.2) | 0 | 5 (17.2) | 19 (65.5) |
| Depressed mood | 28 (1.1) | 2 (7.1) | 1 (3.6) | 0 | 8 (28.6) | 0 | 4 (14.3) | 16 (57.1) |
| Language disorder | 27 (1) | 3 (11.1) | 1 (3.7) | 0 | 11 (40.7) | 0 | 4 (14.8) | 12 (44.4) |
| Dysphonia | 24 (0.9) | 2 (8.3) | 1 (4.2) | 0 | 3 (12.5) | 0 | 4 (16.7) | 17 (70.8) |
| Dementia | 21 (0.8) | 21 (100) | 2 (9.5) | 0 | 7 (33.3) | 0 | 5 (23.8) | 9 (42.9) |
| Brain fog | 18 (0.7) | 2 (11.1) | 1 (5.6) | 0 | 3 (16.7) | 0 | 2 (11.1) | 13 (72.2) |
| Mania | 18 (0.7) | 8 (44.4) | 3 (16.7) | 0 | 6 (33.3) | 0 | 2 (11.1) | 10 (55.6) |
| Stress | 17 (0.7) | 0 | 0 | 0 | 0 | 0 | 2 (11.8) | 15 (88.2) |
| Delusion | 16 (0.6) | 5 (31.3) | 4 (25) | 0 | 6 (37.5) | 0 | 0 | 10 (62.5) |
| Mental impairment | 16 (0.6) | 16 (100) | 2 (12.5) | 0 | 2 (12.5) | 0 | 1 (6.3) | 13 (81.3) |
| Emotional disorder | 14 (0.5) | 0 | 0 | 0 | 1 (7.1) | 0 | 1 (7.1) | 12 (85.7) |
| Euphoric mood | 13 (0.5) | 3 (23.1) | 1 (7.7) | 0 | 4 (30.8) | 0 | 1 (7.7) | 8 (61.5) |
| Slow speech | 13 (0.5) | 2 (15.4) | 1 (7.7) | 0 | 4 (30.8) | 0 | 1 (7.7) | 8 (61.5) |
| Crying | 12 (0.5) | 0 | 0 | 0 | 4 (33.3) | 0 | 0 | 8 (66.7) |
| Hallucinations, mixed | 12 (0.5) | 11 (91.7) | 6 (50) | 0 | 9 (75) | 0 | 1 (8.3) | 2 (16.7) |
| Tension | 12 (0.5) | 0 | 0 | 0 | 0 | 0 | 0 | 12 (100) |
| Disorganised speech | 11 (0.4) | 3 (27.3) | 3 (27.3) | 0 | 4 (36.4) | 0 | 0 | 7 (63.6) |
| Nervousness | 11 (0.4) | 1 (9.1) | 1 (9.1) | 0 | 0 | 0 | 2 (18.2) | 9 (81.8) |
| Depressive symptom | 8 (0.3) | 2 (25) | 2 (25) | 0 | 5 (62.5) | 0 | 1 (12.5) | 2 (25) |
| Fear | 8 (0.3) | 1 (12.5) | 0 | 0 | 0 | 0 | 2 (25) | 6 (75) |
| Mutism | 8 (0.3) | 2 (25) | 2 (25) | 0 | 1 (12.5) | 0 | 0 | 7 (87.5) |
| Affect lability | 7 (0.3) | 2 (28.6) | 2 (28.6) | 0 | 2 (28.6) | 0 | 0 | 5 (71.4) |
| Paranoia | 7 (0.3) | 0 | 0 | 0 | 2 (28.6) | 0 | 1 (14.3) | 4 (57.1) |
| Psychotic symptom | 7 (0.3) | 7 (100) | 2 (28.6) | 0 | 4 (57.1) | 0 | 0 | 3 (42.9) |
| Screaming | 7 (0.3) | 2 (28.6) | 2 (28.6) | 0 | 1 (14.3) | 0 | 1 (14.3) | 5 (71.4) |
| Acute psychosis | 6 (0.2) | 6 (100) | 2 (33.3) | 0 | 4 (66.7) | 0 | 0 | 2 (33.3) |
| Anxiety disorder | 6 (0.2) | 0 | 0 | 0 | 4 (66.7) | 0 | 0 | 2 (33.3) |
| Apathy | 6 (0.2) | 1 (16.7) | 1 (16.7) | 0 | 1 (16.7) | 0 | 0 | 5 (83.3) |

## Table 17. Post-Marketing Data in MAH Safety Database – CNS Effects

| | | | | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| **PT** | **No. of Events (% of Total PTs)** | **No. of Serious Events (% of PT)** | **No. of Events with Criterion of Hospitalization (% of PT)** | **Fatal** | **Resolved / Resolving** | **Resolved with Sequelae** | **Not Resolved** | **Unknown / No Data** |
| Aphonia | 6 (0.2) | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 5 (83.3) |
| Hallucination, olfactory | 6 (0.2) | 6 (100) | 0 | 0 | 2 (33.3) | 0 | 2 (33.3) | 2 (33.3) |
| Panic attack | 6 (0.2) | 2 (33.3) | 1 (16.7) | 0 | 3 (50) | 0 | 1 (16.7) | 2 (33.3) |
| Dysphoria | 5 (0.2) | 2 (40) | 1 (20) | 0 | 1 (20) | 0 | 1 (20) | 3 (60) |
| Persecutory delusion | 5 (0.2) | 3 (60) | 3 (60) | 0 | 1 (20) | 0 | 1 (20) | 3 (60) |
| Reading disorder | 5 (0.2) | 0 | 0 | 0 | 2 (40) | 0 | 0 | 3 (60) |
| Bipolar I disorder | 4 (0.2) | 4 (100) | 1 (25) | 0 | 0 | 0 | 2 (50) | 2 (50) |
| Bradyphrenia | 4 (0.2) | 0 | 0 | 0 | 0 | 0 | 2 (50) | 2 (50) |
| Dyslalia | 4 (0.2) | 0 | 0 | 0 | 1 (25) | 0 | 0 | 3 (75) |
| Frustration tolerance decreased | 4 (0.2) | 1 (25) | 0 | 0 | 1 (25) | 0 | 1 (25) | 2 (50) |
| Illusion | 4 (0.2) | 1 (25) | 1 (25) | 0 | 3 (75) | 0 | 0 | 1 (25) |
| Lethargy | 4 (0.2) | 0 | 0 | 0 | 0 | 0 | 1 (25) | 3 (75) |
| Logorrhoea | 4 (0.2) | 1 (25) | 1 (25) | 0 | 0 | 0 | 3 (75) | 1 (25) |
| Major depression | 4 (0.2) | 4 (100) | 2 (50) | 0 | 2 (50) | 0 | 0 | 2 (50) |
| Soliloquy | 4 (0.2) | 0 | 0 | 0 | 1 (25) | 0 | 0 | 3 (75) |
| Substance-induced psychotic disorder | 4 (0.2) | 4 (100) | 4 (100) | 0 | 3 (75) | 0 | 0 | 1 (25) |
| Emotional distress | 3 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (33.3) | 2 (66.7) |
| Feeling of despair | 3 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (100) |
| Panic reaction | 3 (0.1) | 0 | 0 | 0 | 1 (33.3) | 0 | 0 | 2 (66.7) |
| Personality disorder | 3 (0.1) | 1 (33.3) | 1 (33.3) | 0 | 3 (100) | 0 | 0 | 0 |
| Apraxia | 2 (0.1) | 1 (50) | 0 | 0 | 0 | 0 | 2 (100) | 0 |
| Delusional disorder, persecutory type | 2 (0.1) | 1 (50) | 1 (50) | 0 | 1 (50) | 0 | 1 (50) | 0 |
| Delusional perception | 2 (0.1) | 0 | 0 | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Discouragement | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (100) |
| Dyscalculia | 2 (0.1) | 0 | 0 | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Dysphemia | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (100) |
| Incoherent | 2 (0.1) | 1 (50) | 0 | 0 | 1 (50) | 0 | 1 (50) | 0 |
| Judgement impaired | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (100) |

## Table 17. Post-Marketing Data in MAH Safety Database – CNS Effects

| | | | | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| **PT** | **No. of Events (% of Total PTs)** | **No. of Serious Events (% of PT)** | **No. of Events with Criterion of Hospitalization (% of PT)** | **Fatal** | **Resolved / Resolving** | **Resolved with Sequelae** | **Not Resolved** | **Unknown / No Data** |
| Laziness | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (50) | 1 (50) |
| Negative thoughts | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (50) | 1 (50) |
| Obsessive-compulsive disorder | 2 (0.1) | 0 | 0 | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Panic disorder | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (100) |
| Schizophrenia | 2 (0.1) | 2 (100) | 1 (50) | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Acrophobia | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Bipolar disorder | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Borderline personality disorder | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Claustrophobia | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Compulsive shopping | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Decreased interest | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Dementia Alzheimer's type | 1 (0) | 1 (100) | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Depression suicidal | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Disinhibition | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Distractibility | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Fear of death | 1 (0) | 1 (100) | 1 (100) | 0 | 1 (100) | 0 | 0 | 0 |
| Fear of disease | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Generalised anxiety disorder | 1 (0) | 1 (100) | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Grandiosity | 1 (0) | 1 (100) | 1 (100) | 0 | 1 (100) | 0 | 0 | 0 |
| Hallucination, tactile | 1 (0) | 1 (100) | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Hydrophobia | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Hypomania | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Impatience | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Inappropriate affect | 1 (0) | 0 | 0 | 0 | 0 | 0 | 1 (100) | 0 |
| Manic symptom | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Mental fatigue | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Mood disorder due to a general medical condition | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Paranoid personality disorder | 1 (0) | 1 (100) | 1 (100) | 0 | 1 (100) | 0 | 0 | 0 |

**Table 17. Post-Marketing Data in MAH Safety Database – CNS Effects**

| | | | | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| **PT** | **No. of Events (% of Total PTs)** | **No. of Serious Events (% of PT)** | **No. of Events with Criterion of Hospitalization (% of PT)** | **Fatal** | **Resolved / Resolving** | **Resolved with Sequelae** | **Not Resolved** | **Unknown / No Data** |
| Poverty of speech | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Psychomotor retardation | 1 (0) | 1 (100) | 1 (100) | 0 | 1 (100) | 0 | 0 | 0 |
| Psychopathic personality | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Psychotic behaviour | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Psychotic disorder due to a general medical condition | 1 (0) | 1 (100) | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Repetitive speech | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Self-consciousness | 1 (0) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Self-destructive behaviour | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Senile dementia | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 1 (100) | 0 |
| Shared psychotic disorder | 1 (0) | 1 (100) | 1 (100) | 0 | 0 | 0 | 0 | 1 (100) |
| Suspiciousness | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Tachyphrenia | 1 (0) | 0 | 0 | 0 | 0 | 0 | 1 (100) | 0 |
| Tearfulness | 1 (0) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Violence-related symptom | 1 (0) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |

Reporting Interval: Cumulative through 30 June 2024.
Search criteria – HLGTs (all paths): Mental impairment disorders, Cognitive and attention disorders and disturbances, Deliria (including confusion), Mood disorders and disturbances NEC, Anxiety disorders and symptoms, Depressed mood disorders and disturbances, Personality disorders and disturbances in behaviour, Manic and bipolar mood disorders and disturbances, HLTs (all paths): Speech and language abnormalities, SMQ: Psychosis and Psychotic disorders (narrow) PT: Psychotic symptom
* For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

### SVII.3.1.1.4. Risk Factors and Risk Groups

There are no known risk factors or risk groups for CNS effects following the administration of lorlatinib.

### SVII.3.1.1.5. Preventability

The risk of CNS effects with lorlatinib treatment cannot be predicted given lack of known risk factors. Thus, there are currently no known preventive measures.

#### SVII.3.1.1.6. Impact on the Risk-Benefit Balance of the Product

Depending upon the severity, this event may be managed with dose modification or dose reduction.

#### SVII.3.1.1.7. Public Health Impact

The impact of this event is mostly limited to the individual patient.

### SVII.3.1.2. Important Identified Risk – ILD/pneumonitis

#### SVII.3.1.2.1. Potential Mechanisms

Currently, no potential mechanism of ILD/pneumonitis associated with lorlatinib treatment has been identified in humans. Lung inflammation has been identified in animals treated with lorlatinib, although the relevance to humans has not been established.

#### SVII.3.1.2.2. Evidence Source and Strength of Evidence

Evidence Source: Lorlatinib non-clinical and clinical studies.

Strength of Evidence: ILD/pneumonitis is a known effect of other ALK/ROS1 inhibitors. ILD/pneumonitis can progress to pulmonary fibrosis and other life threatening pulmonary conditions.

#### SVII.3.1.2.3. Characterisation of the Risk

**Frequency with 95% CI**

All-causality AEs indicative of ILD/pneumonitis occurred with a frequency of 2.38% (13/547) (95% CI: 1.3, 4.0) in all patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).

**Seriousness/outcomes**

**Table 18. All-Causality Adverse Events of ILD/pneumonitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 13 patients)**

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Interstitial lung disease | 2 (11.76) | 1 (50.00) | 1 (50.00) | 1 (50.00) | 0 | 0 |
| Lung opacity | 1 (5.88) | 0 | 0 | 1 (100.00) | 0 | 0 |
| Pneumonitis | 14 (82.35) | 8 (57.14) | 12 (85.71) | 2 (14.29) | 0 | 0 |
| **Total Events** | **17** | **9 (52.94)** | **13 (76.47)** | **4 (23.53)** | **0** | **0** |

**Table 18. All-Causality Adverse Events of ILD/pneumonitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 13 patients)**

| Risk Terms (MedDRA Terms) | Total Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| Preferred Terms | N1 (%) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_1a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - Interstitial Lung Disease SMQ (narrow and broad)

## Severity and nature of risk

**Table 19. All-Causality Adverse Events of ILD/pneumonitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 13 patients)**

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| Risk Terms (MedDRA Terms) Preferred Terms | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) | Total n (%) |
| Interstitial lung disease | 0 | 1 (7.69) | 1 (7.69) | 0 | 0 | 2 (15.38) |
| Lung opacity | 1 (7.69) | 0 | 0 | 0 | 0 | 1 (7.69) |
| Pneumonitis | 0 | 7 (53.85) | 2 (15.38) | 1 (7.69) | 0 | 10 (76.92) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_1a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - Interstitial Lung Disease SMQ (narrow and broad)

## Post-Marketing

The safety database was searched cumulatively through 30 June 2024 for cases reporting adverse events consistent with ILD/pneumonitis in the post-marketing setting. The search identified 151 cases reporting 156 relevant events which represents 1.7% of the overall dataset (n=8752).

**Table 20. Post-Marketing Data in MAH Safety Database – ILD/pneumonitis**

| PT | No. of Events (% of Total PTs) | No. of Serious Events (% of PT) | No. of Events with Criterion of Hospitalization (% of PT) | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown / No Data |
| **All PTs** | **156 (100)** | **130 (83.3)** | **49 (31.4)** | **11 (7.1)** | **53 (34)** | **2 (1.3)** | **8 (5.1)** | **82 (52.6)** |
| Pneumonitis | 76 (48.7) | 60 (78.9) | 27 (35.5) | 7 (9.2) | 26 (34.2) | 1 (1.3) | 3 (3.9) | 39 (51.3) |
| Interstitial lung disease | 48 (30.8) | 48 (100) | 17 (35.4) | 1 (2.1) | 22 (45.8) | 1 (2.1) | 1 (2.1) | 23 (47.9) |
| Lung opacity | 8 (5.1) | 2 (25) | 1 (12.5) | 0 | 0 | 0 | 2 (25) | 6 (75) |
| Pulmonary toxicity | 6 (3.8) | 6 (100) | 1 (16.7) | 1 (16.7) | 2 (33.3) | 0 | 0 | 3 (50) |
| Acute respiratory distress syndrome | 2 (1.3) | 2 (100) | 0 | 1 (50) | 0 | 0 | 0 | 1 (50) |
| Organising pneumonia | 1 (0.6) | 1 (100) | 1 (100) | 0 | 1 (100) | 0 | 0 | 0 |
| Pulmonary fibrosis | 3 (1.9) | 3 (100) | 0 | 0 | 0 | 0 | 0 | 3 (100) |
| Hypersensitivity pneumonitis | 2 (1.3) | 2 (100) | 0 | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Lung infiltration | 2 (1.3) | 0 | 0 | 0 | 1 (50) | 0 | 0 | 1 (50) |
| Pulmonary alveolar haemorrhage | 2 (1.3) | 2 (100) | 0 | 0 | 0 | 0 | 0 | 2 (100) |
| Radiation pneumonitis | 2 (1.3) | 1 (50) | 0 | 0 | 0 | 0 | 0 | 2 (100) |
| Acute lung injury | 1 (0.6) | 1 (100) | 1 (100) | 1 (100) | 0 | 0 | 0 | 0 |
| Eosinophilic pneumonia acute | 1 (0.6) | 1 (100) | 1 (100) | 0 | 0 | 0 | 1 (100) | 0 |
| Pulmonary septal thickening | 1 (0.6) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Pulmonary vasculitis | 1 (0.6) | 1 (100) | 0 | 0 | 0 | 0 | 1 (100) | 0 |

Reporting Interval: Cumulative through 30 June 2024.
Search criteria - Interstitial Lung Disease SMQ (narrow and broad)
* For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

### SVII.3.1.2.4. Risk Factors and Risk Groups

Risk factors for ILD/pneumonitis include chemotherapy, antibiotics, anti-arrhythmics, and statins. Other contributing factors that may be associated with ILD/pneumonitis include

environmental exposures to inhaled asbestos and silicone, infections, and connective tissue disease.

**SVII.3.1.2.5. Preventability**

The risk of ILD/pneumonitis with lorlatinib treatment cannot be predicted given lack of known association of ILD/pneumonitis with lorlatinib treatment. Thus, there are currently no known preventive measures.

**SVII.3.1.2.6. Impact on the Risk-Benefit Balance of the Product**

Currently there is no known impact of ILD/pneumonitis to the overall risk-benefit balance of lorlatinib. Further characterisation of the potential risk of ILD/pneumonitis may help to determine if there is a causal association with lorlatinib.

**SVII.3.1.2.7. Public Health Impact**

The expected absolute risk of ILD/pneumonitis in the post-marketing setting due to lorlatinib is not known since the relationship between lorlatinib administration and ILD/pneumonitis has not been established. However, should it occur due to lorlatinib in post-marketing, the public health impact of lorlatinib-related ILD/pneumonitis is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from lorlatinib) and the frequency of hospitalisations, and life-threatening or fatal cases of ILD.

**SVII.3.1.3. Important Potential Risk – AV block**

**SVII.3.1.3.1. Potential Mechanisms**

Currently, no potential mechanism for PR interval prolongation associated with lorlatinib treatment in humans has been identified.

Lorlatinib increased PR interval in a dose-dependent manner in a guinea pig isolated Langendorff-perfused heart model.

**SVII.3.1.3.2. Evidence Source and Strength of Evidence**

Evidence Source: Lorlatinib non-clinical and clinical studies.

Strength of Evidence: The relationship between lorlatinib administration and AV block is not yet established. PR interval increase may become symptomatic AV block and in certain cases require placement of pacemaker. If untreated, complete AV block may lead to life threatening or fatal consequences.

**SVII.3.1.3.3. Characterisation of the Risk**

**Frequency with 95% CI**

All-causality AEs indicative of AV block occurred with a frequency of 2.56% (14/547) (95% CI: 1.4, 4.3) in all patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).

## Seriousness/outcomes

### Table 21. All-Causality Adverse Events of AV block in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 14 patients)

| Risk Terms (MedDRA Terms) | All Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Atrial conduction time prolongation | 2 (10.00) | 0 | 1 (50.00) | 1 (50.00) | 0 | 0 |
| Atrioventricular block | 2 (10.00) | 0 | 2 (100.00) | 0 | 0 | 0 |
| Atrioventricular block complete | 1 (5.00) | 1 (100.00) | 1 (100.00) | 0 | 0 | 0 |
| Atrioventricular block first degree | 10 (50.00) | 0 | 9 (90.00) | 1 (10.00) | 0 | 0 |
| Electrocardiogram PR prolongation | 5 (25.00) | 0 | 4 (80.00) | 1 (20.00) | 0 | 0 |
| **Total** | **20** | **1 (5.00)** | **17 (85.00)** | **3 (15.00)** | **0** | **0** |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_3a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - PTs: Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Paroxysmal atrioventricular block, Electrocardiogram PR prolongation

## Severity and nature of risk

### Table 22. All-Causality Adverse Events of AV block in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 14 patients)

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Atrial conduction time prolongation | 2 (14.29) | 0 | 0 | 0 | 0 | 2 (14.29) |
| Atrioventricular block | 2 (14.29) | 0 | 0 | 0 | 0 | 2 (14.29) |
| Atrioventricular block complete | 0 | 0 | 1 (7.14) | 0 | 0 | 1 (7.14) |
| Atrioventricular block first degree | 6 (42.86) | 0 | 0 | 0 | 0 | 6 (42.86) |

**Table 22. All-Causality Adverse Events of AV block in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 14 patients)**

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| **Risk Terms (MedDRA Terms) Preferred Terms** | **Grade 1 n (%)** | **Grade 2 n (%)** | **Grade 3 n (%)** | **Grade 4 n (%)** | **Grade 5 n (%)** | **Total n (%)** |
| Electrocardiogram PR prolongation | 4 (28.57) | 0 | 0 | 0 | 0 | 4 (28.57) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_3a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - PTs: Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Paroxysmal atrioventricular block, Electrocardiogram PR prolongation

## Post-Marketing

The safety database was searched cumulatively through 30 June 2024 for cases reporting adverse events consistent with AV block in the post-marketing setting. The search identified 15 cases reporting 16 relevant events which represents 0.2% of the overall dataset (n=8752).

**Table 23. Post-Marketing Data in MAH Safety Database – AV block**

| PT | No. of Events (% of Total PTs) | No. of Serious Events (% of PT) | No. of Events with Criterion of Hospitalization (% of PT) | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown / No Data |
| **All PTs** | **16 (100)** | **6 (37.5)** | **2 (12.5)** | **0** | **2 (12.5)** | **0** | **1 (6.3)** | **13 (81.3)** |
| Atrioventricular block | 6 (37.5) | 1 (16.7) | 1 (16.7) | 0 | 1 (16.7) | 0 | 0 | 5 (83.3) |
| Atrioventricular block second degree | 4 (25) | 1 (25) | 1 (25) | 0 | 1 (25) | 0 | 0 | 3 (75) |
| Electrocardiogram PR prolongation | 3 (18.8) | 2 (66.7) | 0 | 0 | 0 | 0 | 0 | 3 (100) |
| Atrioventricular block complete | 1 (6.3) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Atrioventricular block first degree | 2 (12.5) | 1 (50) | 0 | 0 | 0 | 0 | 1 (50) | 1 (50) |

Reporting Interval: Cumulative through 30 June 2024.
Search criteria - PTs: Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Paroxysmal atrioventricular block, Electrocardiogram PR prolongation

**Table 23. Post-Marketing Data in MAH Safety Database – AV block**

| PT | No. of Events (% of Total PTs) | No. of Serious Events (% of PT) | No. of Events with Criterion of Hospitalization (% of PT) | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown / No Data |

* For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

### SVII.3.1.3.4. Risk Factors and Risk Groups

Risk factors for AV block include idiopathic fibrosis and sclerosis of the conduction system, ischemic heart disease, drugs (e.g., beta-blockers, calcium channel blockers, digoxin, or amiodarone), increased vagal tone, valvulopathy, prior myocardial infarction, valvular abnormalities, cardiac surgery, advanced age, congenital heart or genetic disorder.

### SVII.3.1.3.5. Preventability

The risk of AV block with lorlatinib treatment cannot be predicted given lack of known association of AV block with lorlatinib treatment, however, ECG monitoring is recommended and pacemaker placement should be considered for patients who develop refractory symptomatic second-degree AV block or complete AV block.

### SVII.3.1.3.6. Impact on the Risk-Benefit Balance of the Product

Currently there is no known impact of AV block to the overall risk-benefit balance of lorlatinib. Further characterisation of the potential risk of AV block may help to determine if there is a causal association with lorlatinib.

### SVII.3.1.3.7. Public Health Impact

The expected absolute risk of AV block in the post-marketing setting due to lorlatinib is not known since the relationship between lorlatinib administration and AV block has not been established. The public health impact of lorlatinib-related AV block is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from lorlatinib) and the frequency of hospitalisations, and life-threatening or fatal cases of AV block.

## SVII.3.1.4. Important Potential Risk – Pancreatitis

### SVII.3.1.4.1. Potential Mechanisms

Lorlatinib may cause asymptomatic increase of pancreatic enzymes and pancreatitis due to a currently unknown intrinsic mechanism and/or drug-induced hypertriglyceridemia.

### SVII.3.1.4.2. Evidence Source and Strength of Evidence

Evidence Source: Lorlatinib non-clinical and clinical studies.

Strength of Evidence: Pancreatic enzymes elevation and pancreatitis are known effects of some ALK/ROS1 inhibitors. If untreated, pancreatitis may lead to life threatening or fatal consequences.

### SVII.3.1.4.3. Characterisation of the Risk

**Frequency with 95% CI**

Overall, the frequency of these events was 19.01% (104/547) (95% CI: 15.8, 22.6) in all patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines). Pancreatitis Grade 3 and Grade 2 were reported in 1 and 2 cases, respectively. Otherwise, all other reported AEs involved asymptomatic elevations of blood lipase and amylase.

**Seriousness/outcomes**

**Table 24. All-Causality Adverse Events of Pancreatitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 104 patients)**

| Risk Terms (MedDRA Terms) | All Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| **Preferred Terms** | **N1 (%)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** | **n (%=n/N1)** |
| Amylase increased | 210 (50.36) | 0 | 196 (93.33) | 12 (5.71) | 0 | 2 (0.95) |
| Blood bilirubin increased | 4 (0.96) | 0 | 3 (75.00) | 1 (25.00) | 0 | 0 |
| Hyperamylasaemia | 3 (0.72) | 0 | 2 (66.67) | 1 (33.33) | 0 | 0 |
| Hyperlipasaemia | 1 (0.24) | 0 | 1 (100.00) | 0 | 0 | 0 |
| Lipase increased | 195 (46.76) | 0 | 192 (98.46) | 2 (1.03) | 0 | 1 (0.51) |
| Pancreatic enzymes increased | 1 (0.24) | 0 | 1 (100.00) | 0 | 0 | 0 |
| Pancreatitis | 3 (0.72) | 2 (66.67) | 3 (100.00) | 0 | 0 | 0 |
| **Total Events** | **417** | **2 (0.48)** | **398 (95.44)** | **16 (3.84)** | **0** | **3 (0.72)** |

**Table 24. All-Causality Adverse Events of Pancreatitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Seriousness and Outcome (N = 104 patients)**

| Risk Terms (MedDRA Terms) | All Events | Serious Events | Resolved Events | Not Resolved Events | Fatal Events | Unknown |
|---|---|---|---|---|---|---|
| Preferred Terms | N1 (%) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) | n (%=n/N1) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= number of patients for each cluster with risk factor. N1= total number of events reported for preferred term. n= number of events for preferred term.
Percentages for Total Events column are based on Total Events. Percentages for Serious, Resolved, Not Resolved, Fatal, and Unknown Events are based on N1.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk7_2a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - Acute pancreatitis SMQ (narrow and broad B)

## Severity and nature of risk

**Table 25. All-Causality Adverse Events of Pancreatitis in 100 mg (ALK and ROS1 positive and any lines) Pool by Grade (N = 104 patients)**

| | Maximum Severity | | | | | |
|---|---|---|---|---|---|---|
| Risk Terms (MedDRA Terms) Preferred Terms | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) | Total n (%) |
| Amylase increased | 34 (32.69) | 13 (12.50) | 13 (12.50) | 2 (1.92) | 0 | 62 (59.62) |
| Blood bilirubin increased | 2 (1.92) | 0 | 1 (0.96) | 0 | 0 | 3 (2.88) |
| Hyperamylasaemia | 3 (2.88) | 0 | 0 | 0 | 0 | 3 (2.88) |
| Hyperlipasaemia | 1 (0.96) | 0 | 0 | 0 | 0 | 1 (0.96) |
| Lipase increased | 18 (17.31) | 15 (14.42) | 29 (27.88) | 8 (7.69) | 0 | 70 (67.31) |
| Pancreatic enzyme increased | 1 (0.96) | 0 | 0 | 0 | 0 | 1 (0.96) |
| Pancreatitis | 0 | 2 (1.92) | 1 (0.96) | 0 | 0 | 3 (2.88) |

Included data from the first dose of study treatment through end of study follow-up (infinite lag) or start of new anti-cancer therapy, whichever occurred first.
N= total number of patients for each cluster with risk factor; n= number of patients with preferred term. Percentages are based on N.
MedDRA v27.0 coding dictionary applied.
Pool A: All patients who received lorlatinib 100 mg (ALK and ROS1 positive and any lines).
Source Data: adae_rmp Output File: ./B746_IB2024/B746_pool_IB2024/adae_risk6_2a Date of Generation: 08OCT2024 (05:33)
B7461001, B7461027 were based on final CSR data. Cutoff date 29May2024 applied to study B7461006.
Search criteria - Acute pancreatitis SMQ (narrow and broad B)

**Post-Marketing**

The safety database was searched cumulatively through 30 June 2024 for cases reporting adverse events consistent with Pancreatitis in the post-marketing setting. The search identified 45 cases reporting 55 relevant events which represents 0.5% of the overall dataset (n=8752).

**Table 26. Post-Marketing Data in MAH Safety Database – Pancreatitis**

| PT | No. of Events (% of Total PTs) | No. of Serious Events (% of PT) | No. of Events with Criterion of Hospitalization (% of PT) | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown / No Data |
| **All PTs** | **55 (100)** | **28 (50.9)** | **5 (9.1)** | **0** | **11 (20)** | **0** | **8 (14.5)** | **36 (65.5)** |
| Amylase increased | 17 (30.9) | 8 (47.1) | 0 | 0 | 3 (17.6) | 0 | 3 (17.6) | 11 (64.7) |
| Lipase increased | 12 (21.8) | 3 (25) | 0 | 0 | 4 (33.3) | 0 | 2 (16.7) | 6 (50) |
| Pancreatitis | 10 (18.2) | 10 (100) | 4 (40) | 0 | 0 | 0 | 0 | 10 (100) |
| Blood bilirubin increased | 8 (14.5) | 2 (25) | 0 | 0 | 1 (12.5) | 0 | 2 (25) | 5 (62.5) |
| Hyperbilirubinaemia | 3 (5.5) | 3 (100) | 1 (33.3) | 0 | 2 (66.7) | 0 | 0 | 1 (33.3) |
| Pancreatitis acute | 1 (1.8) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Hyperamylasaemia | 1 (1.8) | 0 | 0 | 0 | 0 | 0 | 1 (100) | 0 |
| Hyperlipasaemia | 1 (1.8) | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 |
| Pancreatic enzymes increased | 1 (1.8) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| Pancreatitis necrotising | 1 (1.8) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |

Reporting Interval: Cumulative through 30 June 2024.
Search criteria - Acute pancreatitis SMQ (narrow and broad B)
* For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

## SVII.3.1.4.4. Risk Factors and Risk Groups

Risk factors for pancreatitis include hypertriglyceridaemia, gallstones, heavy alcohol abuse, direct trauma, variety of medications (e.g., steroids, HIV medications, diuretics, anticonvulsants, chemotherapy, antihyperglycemic agents, and atypical antipsychotics), infections such as mumps, smoking, and cystic fibrosis.

#### SVII.3.1.4.5. Preventability

The risk of pancreatitis with lorlatinib treatment can be reduced by monitoring hypertriglyceridemia.

#### SVII.3.1.4.6. Impact on the Risk-Benefit Balance of the Product

Currently there is no identified impact of pancreatitis to the overall risk-benefit balance of lorlatinib. Further characterisation of the potential risk of pancreatitis may help to determine if there is a causal association with lorlatinib.

#### SVII.3.1.4.7. Public Health Impact

The expected absolute risk of pancreatitis in the post-marketing setting due to lorlatinib is not known since the relationship between lorlatinib administration and pancreatitis has not been established. The potential public health impact of lorlatinib-related pancreatitis is predominantly determined by the frequency of required permanent dose discontinuations (precluding patients from benefiting from lorlatinib) and the frequency of hospitalisations, and life-threatening or fatal cases of pancreatitis.

### SVII.3.1.5. Important Potential Risk – Embryo-foetal toxicity

#### SVII.3.1.5.1. Potential Mechanisms

Embryo-foetal toxicity is a class effect for ALK inhibitors, including complete litter loss, increased resorptions and post-implantation loss, decreased foetal weight, and/or external and visceral malformations (crizotinib U.S. FDA, 2011; ceritinib U.S. FDA, 2014; alectinib U.S. FDA, 2015; brigatinib U.S. FDA, 2017) and there is some evidence ALK is important in nervous system embryological development (Palmer et al, 2009).

In lorlatinib embryo-foetal animal studies, total litter loss, abortion, and reduced embryo-foetal viability were the main findings observed. However, the relationship between lorlatinib use and embryo-foetal toxicity has not been established in humans.

#### SVII.3.1.5.2. Evidence Source and Strength of Evidence

Evidence source: Lorlatinib non-clinical and clinical studies.

Strength of Evidence: Studies in animals treated with lorlatinib and other drugs in class have shown embryo-foetal toxicity, however, the relationship between lorlatinib use and embryo-foetal toxicity has not been established in humans. Lorlatinib may cause foetal harm when administered to a pregnant woman.

#### SVII.3.1.5.3 Characterisation of the Risk

**Frequency with 95% CI**

Based on final CSR data of B7461001 and B7461027 studies and as of the cutoff date 29 May 2024 applied to study B7461006, among the 547 patients with advanced ALK/ROS1-positive NSCLC who received lorlatinib 100 mg QD, all patients were 18 years

of age or older and there were no patients that became pregnant, and therefore there were no relevant AEs suggestive of embryo-foetal toxicity.

**Seriousness/outcomes**

As of the final CSR data of B7461001 and B7461027 studies and as of the cutoff date 29 May 2024 applied to study B7461006, there were no relevant AEs suggestive of embryo-foetal toxicity.

**Severity and nature of risk**

As of the final CSR data of B7461001 and B7461027 studies and as of the cutoff date 29 May 2024 applied to study B7461006, there were no relevant AEs suggestive of embryo-foetal toxicity.

**Post-Marketing**

The safety database was searched cumulatively through 30 June 2024 for cases reporting events suggestive of embryo-foetal toxicity. The search identified 1 case reporting 1 relevant event which represents 0.01% of the overall dataset (n = 8752).

**Table 27. Post-Marketing Data in MAH Safety Database – Embryo-foetal toxicity**

| PT | No. of Events (% of Total PTs) | No. of Serious Events (% of PT) | No. of Events with Criterion of Hospitalization (% of PT) | Distribution of Event by Outcome* N (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Fatal | Resolved / Resolving | Resolved with Sequelae | Not Resolved | Unknown / No Data |
| **All PTs** | **1 (100)** | **1 (100)** | **0** | **0** | **0** | **0** | **0** | **1 (100)** |
| Abortion induced | 1 (100) | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 (100) |

Reporting Interval: Cumulative through 30 June 2024.
Search criteria – SMQs: Termination of pregnancy and risk of abortion (narrow) and Foetal disorders (narrow and broad)
* For the event count, the multiple Lowest Level Terms (LLTs) that code to the same MedDRA PTs within a case, or the PTs duplicated during migration from legacy databases for matching the original assessment are counted once. For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

### SVII.3.1.5.4. Risk Factors and Risk Groups

Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women.

### SVII.3.1.5.5. Preventability

Women of childbearing potential should be advised to avoid becoming pregnant while receiving lorlatinib. A highly effective method of contraception is required for patients or

partners of patients during treatment with lorlatinib, and for at least 3 months after discontinuing treatment.

### SVII.3.1.5.6. Impact on the Risk-Benefit Balance of the Product

Given the known preclinical data regarding embryo-foetal toxicity with lorlatinib and other drugs in class, lorlatinib is not recommended during pregnancy or for women of childbearing potential not using contraception.

### SVII.3.1.5.7. Public Health Impact

The expected absolute risk of embryo-foetal toxicity in the post-marketing setting due to lorlatinib is not known. Embryo-foetal toxicity may potentially be associated with a significant impact on public health should foetal or developmental abnormalities be encountered as a result of lorlatinib exposure.

## SVII.3.2. Presentation of the Missing Information

Missing information for lorlatinib consists of use of lorlatinib in patients with moderate or severe hepatic impairment.

### SVII.3.2.1. Missing Information: Patients with moderate or severe hepatic impairment

**Table 28. Missing Information: Patients with moderate or severe hepatic impairment**

| | |
|---|---|
| Evidence source and strength of evidence | Because a formal hepatic impairment study has not been conducted, it is not known if there is any difference in the safety profile of patients with normal hepatic function versus those who have moderate or severe impairment among the 547 ALK and ROS1-positive patients in the proposed indication.<br><br><u>Population in need of further characterisation:</u><br>Populations in need of further characterisation include ALK-positive patients in the proposed indication with moderate or severe hepatic impairment; this information is currently not available but is under current study.<br>Population PK analyses have shown that lorlatinib exposure was not clinically meaningfully altered in patients with mild hepatic impairment (n=53). |
| Anticipated risk/consequence of the missing information | ALK-positive patients with moderate or severe hepatic impairment treated with lorlatinib could have a different PK profile from patients without hepatic impairment. A clinical trial (B7461040) to evaluate the effect of moderate and severe hepatic impairment on the 100 mg single dose plasma PK of lorlatinib is ongoing. 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. |

## Module SVIII Summary of the Safety Concerns

### Table 29. Summary of Safety Concerns

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

## PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

### III.1. Routine Pharmacovigilance Activities

None

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

  Follow up questionnaire for CNS effects

- **Other forms of routine pharmacovigilance activities for safety concerns:**

  None proposed

### III.2. Additional Pharmacovigilance Activities

Study short name and title:
B7461040 – Lorlatinib hepatic impairment study

Rationale and study objectives:
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.

Study design:
This will be a Phase 1, open-label, parallel-group study with participants with normal hepatic function serving as the control. The study will be conducted in participants with moderate and severe hepatic impairment who are otherwise healthy.

Approximately 24 participants will be enrolled to study intervention. Participants will be assigned into the moderate hepatic impairment, severe hepatic impairment, or normal hepatic function cohort based on their modified Child-Pugh score. Each participant, regardless of study cohort, will be administered a single 100 mg dose of lorlatinib by mouth on Day 1.

Study population:
The study population will consist of participants whose eligibility criteria for participation in the study are considered appropriate.

Inclusion Criteria:

1. Participants must be male or female of nonchildbearing potential of 18 to 75 years of age, inclusive, at the time of signing the ICD.

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

3. BMI of 17.5 to 40 kg/$m^2$; and a total body weight >50 kg (110 lb).

4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICD and in the protocol.

Additional Inclusion Criteria for Participants with Normal Hepatic Function (Cohort 3)

1. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead ECG or clinical laboratory tests. Particularly, should confirm with no known or suspected hepatic impairment based on liver function tests (eg, alanine aminotransferase [ALT], AST, alkaline phosphatase [ALP], and bilirubin), albumin and prothrombin time defined as the following, with a single repeat permitted to assess eligibility, if needed:

    a. ALT and AST ≤upper limit of normal (ULN);

    b. Total bilirubin ≤ULN. Note that participants with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ULN plus ALT and AST are ≤ULN plus alkaline phosphatase, hemoglobin, and reticulocyte count are all ≤ULN;

    c. ALP ≤ULN;

    d. Albumin within the normal range (local laboratory ranges);

    e. Prothrombin time ≤ULN.

2. Participants must fit the demographic-matching criteria, including:

    - Body weight ±15 kg of the median of the combined moderate and severe hepatic impairment cohorts (Cohorts 1 and 2), as provided by the Sponsor.

    - Age ±10 years of the median of the combined moderate and severe hepatic impairment cohorts (Cohorts 1 and 2), as provided by the Sponsor.

    - Comparable male/female ratio to moderate and severe hepatic impairment cohorts (Cohorts 1 and 2).

Additional Inclusion Criteria for Participants with Moderately Impaired Hepatic Function (Cohort 1)

1. Meet the criteria for Class B (moderate hepatic impairment) of the Child Pugh classification.

2. A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or magnetic resonance imaging (MRI).

3. Stable hepatic impairment, defined as no clinically significant known change in disease status within the last 30 days, as documented by the participant's recent medical history (eg, no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%).

4. Stable drug regimen is defined as not starting a new drug or changing dosage within 7 days or 5 half lives (whichever is longer) prior to the dosing of lorlatinib.

5. History of alcohol abuse is permissible providing that the results of alcohol test are negative at Screening or on Day 1, and the participant is willing and able to abide by the lifestyle guidelines described in the protocol.

Additional Inclusion Criteria for Participants with Severely Impaired Hepatic Function (Cohort 2)

1. Meet the criteria for Class C (severe hepatic impairment) of the Child Pugh classification.

2. A diagnosis of hepatic dysfunction due to hepatocellular disease (and not secondary to any acute ongoing hepatocellular process) documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or magnetic resonance imaging (MRI).

3. Stable hepatic impairment, defined as no clinically significant known change in disease status within the last 30 days, as documented by the participant's recent medical history (eg, no worsening clinical signs of hepatic impairment, or no worsening of total bilirubin or prothrombin time by more than 50%).

4. Stable drug regimen is defined as not starting a new drug or changing dosage within 7 days or 5 half lives (whichever is longer) prior to the dosing of lorlatinib.

5. History of alcohol abuse is permissible providing that the results of alcohol test are negative on Day -1, and the participant is willing and able to abide by the lifestyle guidelines described in the protocol.

Exclusion Criteria:

**Medical Conditions:**

1. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

2. History of or current positive results for HIV infection.

3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg. Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

4. Participants with an eGFR) of ≤60 mL/min/1.73 $m^2$ based on the 2021 CKD-EPI equation with a single repeat permitted to assess eligibility, if needed.

**Prior/Concomitant Therapy:**

5. Concurrent use of any of the following prohibited concomitant medication(s) within 12 days prior to the first dose of lorlatinib:

    a. Known strong CYP3A inhibitors (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg. Seville oranges, pomelos]). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

    b. Known strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifabutin, rifampin, St. John's Wort).

    c. Known P-gp substrates with a narrow therapeutic index (eg, digoxin).

6. Concurrent use of CYP3A substrates with narrow therapeutic indices (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozide, quinidine, sirolimus, tacrolimus) within 12 days prior to the first dose of lorlatinib.

**Prior/Concurrent Clinical Study Experience:**

7. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

8. Known hypersensitivity to lorlatinib or its excipients.

**Diagnostic Assessments:**

9. A positive urine drug test. Participants with moderate or severe hepatic impairment (Cohorts 1 and 2) will be eligible to participate if their urine drug test is positive with a drug for a prescribed condition that is not expected to interfere with the PK of lorlatinib.

**Other Exclusions:**

10. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

11. History of sensitivity to heparin or heparin-induced thrombocytopenia.

12. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of the protocol.

13. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Additional Exclusion Criteria for Participants with Normal Hepatic Function (Cohort 3)

In addition, participants in the normal hepatic function cohort (Cohort 3) presenting with any of the following will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies deemed relevant for participation in this study, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.

3. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If initial supine BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

4. Baseline standard 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate age myocardial infarction, ST T interval changes suggestive of myocardial ischemia, second or third degree AV block, baseline PR interval >200, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is

>450 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

5. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half lives (whichever is longer) prior to the first dose of study medication. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case by case basis following approval by the Sponsor. Herbal supplements and hormone replacement therapy must have been discontinued at least 28 days prior to the dose of lorlatinib.

6. Participants with a history of or current positive results for hepatitis B or hepatitis C, including hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb).

Additional Exclusion Criteria for Participants with Moderate and Severe Hepatic Impairment (Cohorts 1 and 2)

1. Other clinically significant disease that contraindicates study drug or that may affect the PK of lorlatinib

2. Hepatic carcinoma and hepatorenal syndrome.

3. Undergone porta-caval shunt surgery.

4. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than 1 month prior to study entry.

5. Any clinically significant laboratory abnormality except for those parameters influenced by hepatic impairment.

6. Presence of clinically active Stage 2, 3 or 4 encephalopathy.

7. Severe uncontrolled ascites and/or pleural effusion.

8. Screening supine blood pressure ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), on a single measurement following at least 5 minutes of rest. If initial supine BP is ≥160 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the participant’s eligibility.

9. Screening supine 12-lead ECG demonstrating QTcF >470 msec. If initial QTcF exceeds 470 msec, the ECG should be repeated two more times and the average of the three QTcF values should be used to determine the participant's eligibility.

10. Second-degree or third-degree AV block (unless paced) or baseline PR interval >200 msec at any time prior to dosing of study treatment.

Milestones:
Final Protocol Submission: 05 May 2022
Study Completion: 31 December 2024
Final Report Submission: 30 September 2025

## III.3. Summary Table of Additional Pharmacovigilance Activities

### III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

**Table 30. Ongoing and Planned Additional Pharmacovigilance Activities**

| Study<br><br>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 study (B7461040) | The primary objective is to evaluate the effect of moderate and severe hepatic impairment on the 100 mg single dose plasma PK of lorlatinib.<br><br>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:<br><br>Study/Trial Completion:<br><br>Final Report Submission: | 05 May 2022<br><br>31 December 2024<br><br>30 September 2025 |

## PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

### Table 31. Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation

| Study<br><br>Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Efficacy studies which are conditions of the marketing authorisation** | | | | |
| A Phase 3, randomized, open label study of lorlatinib (PF-06463922) monotherapy versus crizotinib monotherapy in the first line treatment of patients with advanced ALK positive NSCLC (B7461006)<br><br>Ongoing | The Primary endpoint for efficacy: PFS based on Blinded Independent Central Review (BICR) assessment (RECIST v.1.1) Safety and tolerability of lorlatinib | To demonstrate that single agent lorlatinib is superior to single agent crizotinib in prolonging PFS in ALK-positive NSCLC patients who are treatment naïve. Additional data on OS will be available. | Clinical Study Report | 01 December 2027 |

## PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## RISK MINIMISATION PLAN

### V.1. Routine Risk Minimisation Measures

**Table 32. Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| **Important Identified Risks** | |
| CNS effects | Routine risk communication:<br>SmPC sections 4.2, 4.4, 4.7, 4.8<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| ILD/pneumonitis | Routine risk communication:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| **Important Potential Risks** | |
| AV block | Routine risk communication:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| Pancreatitis | Routine risk communication:<br>SmPC sections 4.4, 4.8, 5.3<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| Embryo-foetal toxicity | Routine risk communication:<br>SmPC sections 4.4, 4.6, 5.3<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk: |

**Table 32. Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| | None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |
| **Missing Information** | |
| Patients with moderate or severe hepatic impairment | Routine risk communication:<br>SmPC sections 4.2, 5.2<br><br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br><br>Other routine risk minimisation measures beyond the Product Information:<br>None |

## V.2. Additional Risk Minimisation Measures

There are no additional risk minimisation measures.

## V.3. Summary of Risk Minimisation Measures

**Table 33. 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:<br>SmPC sections 4.2, 4.4, 4.7, and 4.8<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>Follow up questionnaire<br><br>Additional pharmacovigilance activities:<br>None |
| ILD/pneumonitis | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>None |
| **Important Potential Risks** | | |
| AV block | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>None |

**Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Pancreatitis | Routine risk minimisation measures:<br>SmPC section 4.4, 4.8, 5.3<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>None |
| Embryo-foetal toxicity | Routine risk minimisation measures:<br>SmPC sections 4.4, 4.6, 5.3<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>None |
| **Missing Information** | | |
| Patients with moderate or severe hepatic impairment | Routine risk minimisation measures:<br>SmPC sections 4.2, 5.2<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>Lorlatinib Hepatic Impairment Trial (B7461040) |

## PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

### Summary of the risk management plan for Lorviqua (lorlatinib)

This is a summary of the Risk Management Plan (RMP) for Lorviqua. The RMP details important risks of Lorviqua, how these risks can be minimised, and how more information will be obtained about Lorviqua's risks and uncertainties (missing information).

Lorviqua's proposed Summary of Product Characteristics (SmPC) and its package leaflet give essential information to Healthcare Professionals (HCPs) and patients on how Lorviqua should be used.

This summary of the RMP for Lorviqua should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lorviqua's RMP.

### I. The Medicine and What it is Used for

Lorviqua is indicated for adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC) who have not previously been treated with an ALK inhibitor.

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

Lorviqua is administered orally once a day and is available as film-coated tablets of 25 mg and 100 mg.

Further information about the evaluation of Lorviqua's benefits can be found in Lorviqua's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/lorviqua).

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Lorviqua, together with measures to minimise such risks and the proposed studies for learning more about Lorviqua's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Lorviqua is not yet available, it is listed under 'missing information' below.

### II.A. List of Important Risks and Missing Information

Important risks of Lorviqua are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lorviqua. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

### Table 34. List of Important Risks and Missing Information

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

## II.B. Summary of Important Risks

### Table 35. Summary of Important Risks and Missing Information

| | |
|---|---|
| **Important Identified Risk: CNS Effects** | |
| Evidence for linking the risk to the medicine: | Lorviqua non-clinical and clinical studies<br><br>The relationship between Lorviqua administration and CNS effects has been demonstrated in non-clinical and clinical studies. Temporary discontinuation and dose reduction have been successful in the management of CNS effects. |
| Risk factors and risk groups: | There are no known risk factors or risk groups for CNS effects following the administration of Lorviqua |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.7, and 4.8<br><br>Additional risk minimisation measures:<br>None |
| **Important Identified Risk: ILD/pneumonitis** | |
| Evidence for linking the risk to the medicine: | Lorviqua non-clinical and clinical studies<br><br>ILD/pneumonitis is a known effect of other ALK/ROS1 inhibitors. However, the relationship between Lorviqua administration and ILD/pneumonitis is not yet established. ILD/pneumonitis can progress to pulmonary fibrosis and other life threatening pulmonary conditions |
| Risk factors and risk groups: | Risk factors for ILD/pneumonitis include chemotherapy, antibiotics, anti-arrhythmics, and statins. Other contributing factors that may be associated with ILD/pneumonitis include environmental exposures to inhaled asbestos and silicone, infections, and connective tissue disease. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>None |
| **Important Potential Risk: AV block** | |
| Evidence for linking the risk to the medicine: | Lorviqua non-clinical and clinical studies<br>The relationship between Lorviqua administration and AV block is not yet established. PR interval increase may become symptomatic AV block and in certain cases require placement of pacemaker. If untreated, complete AV block may lead to life threatening or fatal consequences. |
| Risk factors and risk groups: | Risk factors for AV block include idiopathic fibrosis and sclerosis of the conduction system, ischemic heart disease, drugs (e.g., beta-blockers, calcium channel blockers, digoxin, amiodarone), increased vagal tone, valvulopathy, prior myocardial infarction, |

## Table 35. Summary of Important Risks and Missing Information

| | |
|---|---|
| | valvular abnormalities, cardiac surgery, advanced age, congenital heart, genetic, or other disorder. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>None |
| **Important Potential Risk: Pancreatitis** | |
| Evidence for linking the risk to the medicine: | Lorviqua non-clinical and clinical studies<br>Pancreatic enzymes elevation and pancreatitis are known effects of some ALK/ROS1 inhibitors, however the relationship between Lorviqua administration and pancreatitis is not yet established. If untreated, pancreatitis may lead to life threatening or fatal consequences. |
| Risk factors and risk groups: | Risk factors for pancreatitis include hypertriglyceridaemia, gallstones, heavy alcohol abuse, direct trauma, variety of medications (e.g., steroids, HIV medications, diuretics, anticonvulsants, chemotherapy, antihyperglycemic agents, and atypical antipsychotics), infections such as mumps, smoking, and cystic fibrosis. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.4, 4.8, 5.3<br><br>Additional risk minimisation measures:<br>None |
| **Important Potential Risk: Embryo-foetal toxicity** | |
| Evidence for linking the risk to the medicine: | Lorviqua non-clinical and clinical studies<br><br>Studies in animals treated with Lorviqua and other drugs in class have shown embryo-foetal toxicity, however, the relationship between Lorviqua use and embryo-foetal toxicity has not been established in humans. Lorviqua may cause foetal harm when administered to a pregnant woman. |
| Risk factors and risk groups: | Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC Sections 4.4, 4.6, 5.3<br><br>Additional risk minimisation measures:<br>None |
| **Missing Information: Patients with moderate or severe hepatic impairment** | |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 5.2<br><br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activities: | Additional pharmacovigilance activities:<br>Lorviqua Hepatic Impairment Trial (B7461040) |

## II.C. Post-Authorisation Development Plan

### II.C.1. Studies Which are Conditions of the Marketing Authorisation

The following study is a condition of the marketing authorisation:

- Study B7461006: A Phase 3, randomized, open label study of lorlatinib (PF-06463922) monotherapy versus crizotinib monotherapy in the first line treatment of patients with advanced ALK positive non small cell lung cancer (B7461006) comparing lorlatinib versus crizotinib in the first line treatment for patients with advanced ALK positive NSCLC to further characterise the efficacy of lorlatinib.

  Purpose of the study:
  The ongoing study B7461006 will additionally characterize the efficacy of lorlatinib in the first line treatment of patients with ALK-positive NSCLC and submit overall survival data by 01 December 2027.

This study is a condition to the safe and effective use of lorlatinib drug product and a post-authorisation measure to be completed by the MAH within the stated timeframe.

### II.C.2. Other Studies in Post-Authorisation Development Plan

**Lorviqua Hepatic Impairment Trial (B7461040)**

Purpose of the study:

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.

## PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 1 – Eudravigilance Interface

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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## ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

### CNS – Psychiatric Adverse Event Questionnaire

The following questions are intended to better evaluate central nervous system / psychiatric events in patients treated with lorlatinib.

1. **Were any of the following imaging tests performed prior to start and/or during lorlatinib treatment?**

| Test | Date Performed | Results |
|---|---|---|
| CT scan of the brain | | |
| MRI of the brain | | |
| Other imaging test, please specify: | | |

2. **Were any other diagnostic tests performed related to central nervous system / psychiatric adverse event (e.g., cognitive test, mood test, EEG)? If yes, please provide the results.**

| Test | Date Performed | Results |
|---|---|---|
| | | |
| | | |

3. **Did the patient have any relevant medical history for the reported event(s) (e.g., central nervous system disorders, cardiovascular conditions)?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please specify:

4. **Was the patient taking any medications to treat any central nervous system / psychiatric disorders <u>within three months</u> prior to the onset of the adverse event?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please complete for each medication:

| Product Name | Reason for taking | Dose Unit and Frequency |
|---|---|---|
| | | |
| | | |

5. **Did the patient have brain metastases at the time of the adverse event?**

   ☐ Yes ☐ No ☐ Unknown

6. **Did the patient have an ongoing history of alcohol or recreational drug use (e.g., cocaine) at the time of the adverse event?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please specify:

7. **Did the patient have a family history of cognitive conditions or psychiatric symptoms/disorder?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please specify:

## ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not Applicable.