EU RISK MANAGEMENT PLAN (RMP)

for

ALUNBRIG (Brigatinib)

RMP Version Number: 7.0

Date: 20-November-2024

European Union (EU) Risk Management Plan (RMP) for ALUNBRIG (Brigatinib)

RMP version to be assessed as part of this application:

RMP version number: 7.0

Data lock point (DLP) for this RMP: 31-October-2024

Date of final sign-off: 20-November-2024

Rationale for submitting an updated RMP:

The RMP is being amended following completion of Brigatinib-5007 Post Authorisation Safety Study (PASS) and reflect fulfillment of the PASS study requirement by European Medicines Agency (EMA). Also, the additional risk minimisation measure (aRMM) of Patient Alert Card (PAC) is being removed and accordingly the list of safety concerns is updated as per Good Pharmacovigilance Practices (GVP) Module V Rev. 2 guidelines. Furthermore, the additional monitoring requirement for Brigatinib in EU is updated to 'No' post completion of five-year monitoring period.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Aligned 'summary of mode of action' and added 'composition', 'dosage' information per current summary of product characteristics (SmPC), dated July 2023. Updated additional monitoring of the product in EU to 'No'.
Part II Safety Specification	
• **Module SI Epidemiology of the Indication(s) and Target Population(s)**	Incorporated editorial changes and updated as per the DLP of the RMP.
• **Module SII Nonclinical Part of the Safety Specification**	Not applicable
• **Module SIII Clinical Trial Exposure**	Updated the Expanded Access Program exposure data as per the DLP of the RMP
• **Module SIV Populations Not Studied in Clinical Trials**	Not applicable
• **Module SV Post-authorisation Experience**	Post-authorisation exposure data was updated till 31-October-2024.
• **Module SVI Additional EU Requirements for the Safety Specification**	Not applicable
• **Module SVII Identified and Potential Risks**	Added justification for the removal of important identified risk of "Pulmonary toxicity (including early-onset pulmonary events [EOPE] and later-onset pneumonitis)"
• **Module SVIII Summary of the Safety Concerns**	Removed important identified risk of "Pulmonary toxicity (including EOPE and later-onset pneumonitis)".
Part III Pharmacovigilance Plan	PASS (Brigatinib-5007) was completed and therefore, removed as additional pharmacovigilance activity.

RMP Module:	Significant Changes:
Part IV Plans for Post-authorisation Efficacy Studies	Not applicable
Part V Risk Minimisation Measures	V.1: Upon removal of the important identified risk of pulmonary toxicity the 'Routine Risk Minimisation Measures' were deleted V.2: Removed PAC as the "Additional Risk Minimisation Measure" V.3: 'Summary of risk minimisation measures' was updated to 'Not applicable'
Part VI Summary of the RMP	Removed important identified risk of "Pulmonary toxicity (including EOPE and later-onset pneumonitis)" from Table II.A List of Important Risks and Missing Information and Table II.B: Summary of important risks II.C. Post authorisation Development Plan - updated Brigatinib PASS study status as completed.
Part VII Annexes	Annex 2: Updated Brigatinib-5007 study status from ongoing to completed. Annex 8: Updated to include summary of changes to the risk management plan version 7.0.

Other RMP versions under evaluation: None.

Details of the currently approved RMP:

Version number: 6.0

Approved with procedure: EMEA/H/C/004248/II/0037

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Qualified Person for Pharmacovigilance (QPPV) name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV, [redacted] on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW 8
PART II: SAFETY SPECIFICATION 10
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) 10
PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION 14
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE 21
PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS 24
SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program 24
SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs 24
SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs 25
PART II: MODULE SV – POST AUTHORISATION EXPERIENCE 26
SV.1. Post authorisation Exposure 26
SV.1.1. Method used to calculate exposure 26
SV.1.2. Exposure 26
PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION 27
PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS 28
SVII.1. Identification of Safety Concerns in the Initial RMP Submission 28
SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP 28
SVII.1.2. Risks Considered Important for Inclusion in the list of safety concerns in the Initial RMP 28
SVII.2. New Safety Concerns and Reclassification with Submission of an Updated RMP 31
SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 31
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks 31
SV VII.3.2. Presentation of the Missing Information 31
PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS 32
PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) 33
III.1. Routine Pharmacovigilance Activities 33
III.2. Additional Pharmacovigilance Activities 33
III.3. Summary Table of Additional Pharmacovigilance Activities 33
PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES 34
PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) 35
V.1. Routine Risk Minimisation Measures 35
V.2. Additional Risk Minimisation Measures 35
V.3. Summary of Risk Minimisation Measures 35
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 36
I. The Medicine and What It Is Used For 36
II. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks 36
II.A List of Important Risks and Missing Information 36
II.B Summary of Important Risks 37

II.C. Post-authorisation Development Plan 37
II.C.1. Studies Which Are Conditions of the MA 37
II.C.2. Other Studies in Post-authorisation Development Plan 37
PART VII: ANNEXES 38
Annex 4 Specific Adverse Drug Reaction Follow-Up Forms 42
Annex 6 Details of Proposed Additional Risk Minimisation Activities (If Applicable) 44

List of Abbreviations

Abbreviation	Definition/Description
ADD	Average Daily Dose
ADR	Adverse Drug Reaction
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALK+	Anaplastic Lymphoma Kinase Positive
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
aRMM	Additional Risk Minimisation Measure
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{∞}	Area Under the Concentration-Time Curve From Time 0 To Infinity
AUC_{120}	Area Under the Concentration-Time Curve From Time 0 To 120 Hours
BCRP	Breast Cancer Resistance Protein
BSEP	ATP Binding Cassette Protein
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum Observed Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CV	Cardiovascular
CYP	Cytochrome P-450
DDI	Drug-Drug Interaction
DLP	Data Lock Point
ECOG	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EML4	Echinoderm Microtubule-Associated Protein-Like 4
EOPE	Early-Onset Pulmonary Event(s)
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices

Abbreviation	Definition/Description
HCP	Healthcare Professional
HR	Hazard Ratio
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IRC	Independent Review Committee
MA	Marketing Authorisation
MATE	Multidrug And Toxin Extrusion Protein
mRNA	Messenger Ribonucleic Acid
NOAEL	No-Observed-Adverse-Effect Level
NSCLC	Non–Small-Cell Lung Cancer
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
ORR	Objective Response Rate
OS	Overall Survival
PAC	Patient Alert Card
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
P-gp	P-Glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Patient Years
ROS1	ROS Proto-Oncogene 1
RSI	Request For Supplementary Information
QD	Once Daily
QPPV	Qualified Person Responsible For Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SmPC	Summary Of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
US	United States

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN [International Nonproprietary Names] or common name)	Brigatinib
Pharmacotherapeutic group(s) (ATC code)	Antineoplastic agent, protein kinase inhibitors (L01ED04)
Marketing Authorisation (MA) Holder	Takeda Pharma A/S
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Alunbrig
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class Tyrosine kinase inhibitor (TKI)
	Summary of mode of action Brigatinib is a TKI that targets anaplastic lymphoma kinase (ALK), ROS1 (ROS Proto-Oncogene 1), and IGF-1R (insulin-like growth factor 1 receptor). Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling protein STAT3 in *in vitro* and *in vivo* assays. Brigatinib inhibited the *in vitro* proliferation of cell lines expressing echinoderm microtubule-associated protein-like 4 (EML4) ALK and NPM (nucleophosmin) ALK fusion proteins and demonstrated dose-dependent inhibition of EML4 anaplastic lymphoma kinase positive (ALK+) non-small-cell lung cancer (NSCLC) xenograft growth in mice. Brigatinib inhibited the *in vitro* and *in vivo* viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M.
	Important information about its composition Alunbrig 30 mg film coated tablets: Each film-coated tablet contains 30 mg of brigatinib and 56 mg of lactose monohydrate. Alunbrig 90 mg film coated tablets: Each film-coated tablet contains 90 mg of brigatinib and 168 mg of lactose monohydrate. Alunbrig 180 mg film coated tablets: Each film-coated tablet contains 180 mg of brigatinib and 336 mg of lactose monohydrate.
Hyperlink to the Product Information (PI)	Refer to electronic Common Technical Document (eCTD) Module 1.3.1 for approved PI.
Indication(s) in the EEA	Current:

	Alunbrig is indicated as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib. Alunbrig is indicated as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously not treated with an ALK inhibitor.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily. If Alunbrig is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time. Treatment should continue as long as clinical benefit is observed.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Alunbrig 180 mg film-coated tablets Alunbrig 90 mg film-coated tablets Alunbrig 30 mg film-coated tablets
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Abbreviation: ALK, anaplastic lymphoma kinase; ELM, echinoderm microtubule-associated protein; NSCLC, non-small cell lung cancer; TKI, Tyrosine kinase inhibitor.

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

ALK+ NSCLC	
Incidence:	Lung cancer is the most common cancers in the world and is the leading cause of cancer death worldwide. Globally, 2.4 million new lung cancer cases are estimated to have occurred in 2022, and lung cancer was responsible for 1.8 million deaths [redacted].In Europe, there were an estimated 480,000 cases of lung cancer diagnosed in 2020 across 40 countries, with more than 380,000 deaths[redacted].
Prevalence:	Lung cancer is the most common cancer and leading cause of cancer death globally, presenting 12.4% of all cancer diagnoses and 18.7% of total cancer deaths in the world. Globally, in 2022, there were more than 2 million new cases of lung cancer and 1.8 million lung cancer-related deaths [redacted]. In the US, an estimated 234,580 new cases of lung and bronchial cancer will be diagnosed in 2024, with an estimated 125,070 deaths due to disease (American Cancer Society) [redacted]. In Europe, Lung cancer comprised 11.8% of all new cancer diagnoses and almost 20% of all cancer deaths in 2020 [redacted]. Non–small-cell lung cancer (NSCLC) is the most prevalent histologic class of lung cancer, accounting for nearly 85% of all cases. Traditionally, NSCLC has been further divided into one of several histologic subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and bronchioloalveolar carcinoma[redacted]. Importantly, however, tumors that appear identical by histologic criteria are often driven by distinct oncogenes and, therefore, respond differently to therapeutic interventions because of their individual molecular profiles. In recognition of this observation, lung cancer is also routinely differentiated by underlying molecular alterations. The focus of the development program for brigatinib, an anaplastic lymphoma kinase (ALK) inhibitor, is to examine this agent as a treatment for a specific molecular subtype of NSCLC, namely NSCLCs that contain oncogenic rearrangements in the ALK gene (ie, ALK+ NSCLC). ALK is a tyrosine kinase encoded on chromosome 2 that performs a physiologic role in early brain development. While expression levels are low in adults [redacted], the ALK gene can become altered and activated in several malignancies, including NSCLC, where it functions as a key driver of tumorigenesis. Estimates of the frequency of ALK rearrangement in the overall population of patients with NSCLC range from 2% to 7% [redacted], which corresponds to approximately 4000 to 14,000 new cases of ALK+ NSCLC per year in the US and 8000 to 28,500 in Europe, according to the latest incidence rates for lung cancer overall reported above.
Demographics of the target population in the indication:	Shaw et al reported that a significantly greater percentage of men than women were positive for EML4-ALK (23% vs 9%) in 141 NSCLC tumors screened[redacted]. Similarly, Barlesi reported that among 388 patients with ALK rearrangement, 53% were males [redacted]. In contrast, Cabillic et al reported an imbalanced sex ratio with women exhibiting a 2.2-fold relative risk for an alteration in 3244 NSCLC cases [redacted]. Compared with epidermal growth factor receptor (EGFR) or WT/WT, patients with EML4-ALK are significantly younger. The difference in median age between patients with EML4-ALK and either EGFR or WT/WT exceeded 10 years. Among the 19 patients with EML4-ALK, 4 were younger than 40 years old [redacted]. One recent study of EML4-ALK in Asian patients with NSCLC noted a non-statistically significant trend toward younger age (mean age: 56 years, age range: 33-74 years). Median age in EML-4ALK was 59 years (51-61 years) versus 64 years (55-71 years) in EML 4-ALK negative[redacted]. Similarly, Chinese (Han) patients with

ALK+ NSCLC	
	EML4-ALK rearrangements were significantly younger at diagnosis than those without such rearrangements (median age, 45 vs 58 years; p<0.001) [redacted]. Likewise, Blackhall et al found that ALK+ status was associated with younger age: (ALK immunohistochemistry/fluorescence in situ hybridization [IHC/FISH] positive [n = 28] mean age was 58 years, median age 60.2 years, and age range 29.8-77.7 years; ALK IHC positive/FISH negative [n = 52] mean age was 64.3 years, median age 63.09 years, and age range 28.6-82.8 years; ALK IHC/FISH negative [n = 1201] mean age was 64.5 years, median age 65.4 years and age range 23 to 86.1 years) [redacted]. Sacher et al genotyped 2237 patients with NSCLC at the Dana-Farber Cancer Institute between 2002 and 2014 and found that ALK rearrangements were associated with an increased likelihood in patients diagnosed at a younger age [redacted]. Barlesi reported that among the 388 patients with ALK rearrangement the median age was 61.2 years; of the total of 17,664 patients with NSCLC, the median age was 64.5 years (range: 18-98 years) [redacted]. There is no strong evidence to suggest an ethnic difference of EML4-ALK translocation among patients with NSCLC. In summary, compared with the other NSCLCs, ALK+ NSCLC occurs in a somewhat younger population and may occur more frequently in women than men.
Risk factors for the disease:	Unlike the risk factors for lung cancers in general, which include cigarette smoking, secondhand or passive smoking, alcohol, air pollution, and occupational exposure to carcinogens, the risk of ALK+ NSCLC is not strongly associated with a smoking history [redacted].
The main existing treatment options:	While the standard treatment algorithm for unselected NSCLC patients has historically involved frontline treatment with chemotherapy, recent clinical studies have demonstrated that patients with locally advanced or metastatic ALK+ NSCLC fare better when treated with the ALK inhibitor crizotinib [redacted] than with chemotherapy. Docetaxel and pemetrexed have been used as second-line chemotherapy following platinum-based doublet chemotherapy [redacted]. In patients with ALK+ NSCLC receiving second-line therapy, a randomized study comparing platinum-based chemotherapy with crizotinib, demonstrated an ORR of 20% for the chemotherapy. In a randomized study comparing crizotinib to platinum-based pemetrexed combination chemotherapy for first-line treatment of advanced ALK+ NSCLC, the ORR in the chemotherapy arm was 45%[redacted]. Although crizotinib is an effective treatment for ALK+ NSCLC, 26% to 35% of patients fail to respond[redacted], and the majority of patients progress within 1 year, with multiple mechanisms of resistance having been identified. Two other ALK inhibitors—ceritinib (Zykadia) and alectinib (Alecensa)—have become available for patients with NSCLC with ALK rearrangements who have disease progression on or are intolerant to crizotinib. Ceritinib received accelerated approval from the US Food and Drug Administration (FDA) in April 2014, and was approved in the EU in May 2015 in patients previously treated with crizotinib [redacted]; full approval in front-line applications was granted in May 2017 in the US and in September 2017 in the EU, respectively. In a phase 2 study of ceritinib, patients who had progressed on crizotinib showed an objective response rate (ORR) of 38.6% and a median progression-free survival (PFS) of 5.7 months [redacted]. In patients with brain metastases, the ORR was 33% [redacted]. Gastrointestinal (GI) toxicity has been reported in a large percentage of

ALK+ NSCLC	
	patients treated with ceritinib. Dose reductions occurred in 59% of patients treated with the recommended phase 2 dose, the majority of which were due to GI toxicity[redacted]. In addition, lorlatinib was approved in EU in 2019 as a treatment for advanced ALK+ NSCLC whose disease had progressed after alectinib or ceritinib as the first ALK TKI therapy, or after crizotinib and at least one other ALK TKI. This approval was based on a single arm study, including 111 patients who had received 2 or more ALK TKIs, showing ORR 39.6% and median duration of response (DoR) at 9.9 months. Loratinib also has first line of indication now [ref: lorlatinib EU SmPC]. Alectinib was granted accelerated approval in the US in December 2015 for patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib and subsequently received a regular approval from FDA in front-line setting in November 2017[redacted]. In February 2017, alectinib was granted a conditional MA in the EU for patients with ALK+ NSCLC previously treated with crizotinib, which was converted into full approval in December 2017. A full approval for alectinib in patients with ALK+ NSCLC in the front-line setting was also granted in the EU in December 2017. In 2 clinical studies, alectinib has been shown to be well tolerated by patients. The ORR based on independent review committee (IRC) assessment was 38% and 44% in studies 1 and 2, respectively [redacted]. Median PFS was approximately 9 months [redacted]. In patients with intracranial central nervous system (CNS) metastases (N = 51), the ORR was 61%, with a median duration of CNS response of 9.1 months [redacted]. Alectinib is also being evaluated in 2 additional studies in advanced patients with ALK+ NSCLC who had not received prior ALK TKI therapy. The first is the J ALEX study, a randomized phase 3 study of alectinib versus crizotinib conducted in Japan [redacted], with the primary endpoint of PFS. This study demonstrated significantly prolonged PFS with alectinib compared with crizotinib (median PFS not reached for alectinib arm, 10.2 months in the crizotinib arm; hazard ratio [HR] = 0.34, stratified log-rank p<0.0001). The second study is the global randomized phase 3 ALEX study of alectinib versus crizotinib in patients with newly diagnosed advanced ALK+ NSCLC. This study demonstrated similar significantly prolonged PFS with alectinib (median PFS assessed by IRC: 25.7 months; HR = 0.50, stratified log-rank p<0.0001).
Natural history of the indicated condition in the population, including mortality and morbidity:	Five-year survival rates of lung cancer patients (regardless of stage of diagnosis or with/without actionable mutation) remain low: with 17.7% and 13% in the US and Europe, respectively [redacted]. From the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, the 5-year survival rate for people with stage IA NSCLC is about 49%. For people with stage IB NSCLC, the 5-year survival rate is about 45%. For stage IIA cancer, the 5-year survival rate is about 30%. For stage IIB cancer, the survival rate is about 31%. The 5-year survival rate for stage IIIA NSCLC is about 14%. For stage IIIB cancers the survival rate is about 5%. Metastatic, or stage IV, NSCLC has a 5-year survival rate of about 1% (cancer.org). Most lung cancer cases are diagnosed at advanced stages and about 78% of newly diagnosed patients have regional/distant disease [redacted]. Barlesi et al reported that in patients with ALK rearrangement, 12-month PFS was 54% with first-line treatment (95% CI: 46.8-61.3) and 12-month OS was 70% with second-line treatment (95% CI: 63.6-76.8). Kulig et al performed a literature review of retrospective studies, exclusive of those involving ALK inhibitor therapy, with the goal to evaluate

ALK+ NSCLC	
	historical survival outcomes and treatment outcomes from chemotherapy, EGFR TKI therapy, surgical therapy, and thoracic radiotherapy in ALK+ NSCLC. Overall, studies that controlled for potential confounding factors either by study design or in the analyses suggest worse or equivalent prognosis for ALK+ NSCLC cases. Only 1 analysis, studied by Wu et al, concluded that ALK rearrangement is a favorable predictive factor for OS in ALK+ NSCLC [redacted]. Approximately one-third of patients with newly diagnosed ALK+ NSCLC have brain metastases at baseline. Nearly two-thirds of patients who have progressed on crizotinib have brain metastases [redacted]. In an unselected NSCLC population, brain metastases resulted in reduced quality of life and limited survival [redacted]. Survival of patients with brain metastases has been considered very poor[redacted], with risk of death and significant impairments in quality of life being increased by a factor of 4 [42,43]. The median survival of unselected patients with NSCLC with untreated brain metastases is reported to be 1 to 3 months [redacted]. Emerging data from study PROFILE1014 showed ALK+ advanced NSCLC patients had encouraging long term survival, using crizotinib as first line therapy. With median follow-up of 46 months, median OS was not reached, and 4 year survival rate was 56.6%. [redacted]. More importantly, patients who continued on with a second ALK-TKI after progressing from crizotinib had the longest survival in this study. Based on current available medical evidence, the development and clinical usage of ALK-TKIs changed the natural history of ALK+ NSCLC and provides long term survival benefit for these patients. ALK TKI remains to be the foundation of treatment in these patients, despite the emergence of immune oncology medications.
Important comorbidities:	There is no specific information on comorbidities in patients with ALK+ NSCLC. However, patients with ALK+ NSCLC are approximately 10 years younger than unselected patients with NSCLC and thus there may potentially be a difference in comorbidity rates in the patients with ALK+ NSCLC compared with the unselected patients with NSCLC. The frequency of COPD (chronic obstructive pulmonary disease) coexistence in unselected patients with NSCLC was 52% in a study that assessed almost 5683 patients (unspecified lung cancer) [46]. Cardiovascular (CV) diseases are one of the most common comorbidities in lung cancer with prevalence from 12.9% to 43% according to different studies[redacted]. The occurrence of diabetes in lung cancer patients was 15.7%[redacted]. Data of 20,552 patients diagnosed with lung cancer in 2005 to 2011 from the Danish Lung Cancer Registry showed that the main comorbidities were chronic lung disease (13%), diabetes (6.2%), cerebrovascular disease (4.6%), and peripheral vascular disease (3.6%)[redacted].

Abbreviation: ALK, anaplastic lymphoma kinase; CNS, central nervous system; EGFR, epidermal growth factor receptor; ELM, echinoderm microtubule-associated protein; HR, hazard ratio; ORR, objective response rate; PD, programmed cell death; PFS, progression-free survival; NSCLC, non-small cell lung cancer; SEER, Surveillance Epidemiology and End Results; TKI, Tyrosine kinase inhibitor.

Part II: Module SII – Non-clinical Part of the Safety Specification

Key safety findings from nonclinical studies and relevance to human use:

Key Safety Findings	Relevance to Human Usage
Single-Dose Toxicity	No anticipated safety concerns in humans.
Repeat-Dose Toxicity The toxicity of repeated oral gavage doses of brigatinib has been assessed in rats and monkeys in studies of up to 6 months in duration. On the basis of brigatinib-related organ toxicity noted at all dose levels, a no-observed-adverse-event level (NOAEL) was not identified in the 6-month toxicity study in rats or monkeys. In addition to brigatinib-related lethality, the key target organs of toxicities identified in general toxicology studies in rats and/or monkeys were the lung, immune system, GI system, hematopoietic system, liver, kidney, bone, testis/epididymis, heart, pancreas, and eye. These organ toxicities were generally reversible except for effects noted in rats in the eye and testis/epididymis.	Multiorgan toxicities manifesting in animals at subtherapeutic exposures. Some of these toxicities manifest at clinically relevant exposures in patients receiving brigatinib and are discussed further in relevant sections below: cardiotoxicity, lung toxicity, pancreatic toxicity, and ocular toxicity.
Reproductive and Developmental Toxicity Brigatinib demonstrated potential for embryofetal toxicity as evidenced by decrease in litter mean fetal weights, as well as external, visceral and skeletal malformations such as anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding from herniated abdominal wall). The terminal systemic maternal area under the concentration-time curve (AUC) at the NOAEL for embryofetal toxicity was approximately 0.25 times the human AUC.	Embryotoxicity in rats was observed at maternal AUC comparable to the human AUC indicating potential risk for embryofetal and developmental toxicity at clinically relevant concentrations.
Effects on the Testes/Epididymes Macroscopic findings of reduced testicular and epidydimal size and weight were noted in both rats and monkeys. In rats, there were microscopic correlates of testicular seminiferous tubular degeneration. Findings of reduced sperm were noted in the lumen of the seminiferous tubules of the testes and in the epididymes in both rats and monkeys. The testicular and epidydimal effects were reversible in monkeys but not in rats. The testicular and epidydimal effects occurred in rats and monkeys at ≥0.9 and ≥0.2 times the human AUC, respectively.	According to the pivotal general toxicology studies in animals, irreversible testicular/epididymal toxicities were noted only in the rats and not in monkeys. There has been no overt evidence of testicular toxicity, as evidenced by testicular pain, in male patients treated with brigatinib. Testicular toxicity (reduced testicular weight, reduced sperm in the lumen, and/or degeneration of the seminiferous tubule) was noted in both rats and monkeys; it was not reversible in rats but was reversible in monkeys. No rat fertility studies have been conducted to assess if there is any functional significance of

Key Safety Findings	Relevance to Human Usage
	testicular degeneration in rats. There has been no overt evidence of testicular toxicity, as evidenced by testicular pain or significant decreases in circulating testosterone, in male patients treated with brigatinib to date. In addition, decreases in testosterone levels were minimal with low frequency in patients who had previously been treated with crizotinib. Overall, the risk for testicular toxicity and potential to reduce fertility in male patients is clearly outweighed by the therapeutic benefit for advanced lung cancer. The human relevance of testicular effects is not known.
Nephrotoxicity Clinical pathology changes such as increased serum urea and creatinine along with microscopic evidence of renal tubular degeneration were seen in both rats and monkeys at ≥0.9 and ≥0.2 times the human AUC, respectively. Renal toxicity was one of the causes of death in moribund rats at high doses. In a safety pharmacology study in rats, brigatinib had mild effects on the renal system (alterations in serum and urine chemistry) at clinically relevant doses.	Renal effects have been observed in lung cancer patients treated with brigatinib in the clinical studies. The majority of events were nonserious and lower grade in intensity. Clinical data does not support the causal relationship to brigatinib. Based on the totality of safety data available across the renal function range represented in the clinical development program for brigatinib, including the pivotal studies 201 and 301, it is concluded that there are no clinically meaningful effects of mild or moderate renal impairment on the safety of brigatinib.
Hepatotoxicity Increases in serum hepatic transaminases were observed in rats and monkeys at ≥0.9 and ≥0.2 times the human AUC; there was a microscopic correlate of hepatocellular necrosis in rats only.	While increases in serum hepatic transaminases have been observed in lung cancer patients treated with brigatinib in the clinical studies, there were no reports that met Hy's law. Serious adverse events (SAEs) were considered to be related to underlying disease rather than to brigatinib.
Cardiotoxicity Reversible, dose-related cardiomyocyte degeneration was noted microscopically in rats at exposures that were ≥0.9 times the human AUC. This change was considered to be one of the causes of early death of some animals. This change was characterized by loss of cross-striations and hyalinization of myocardial fibers with varying amounts of acute hemorrhage. This alteration was most severe in the left ventricular free wall, interventricular septum, and papillary muscle, but was observed in other regions of the heart as well. This alteration is distinguished from the background degeneration (early-stage cardiomyopathy) noted in	The reversible cardiomyocyte degeneration that was noted nonclinically was microscopically in concert with poor toleration and lethality in the 6-month rat toxicology study with brigatinib. It generally manifested at poorly tolerated doses and could potentially have been secondary to poor toleration. Currently, clinical data are available from 3 clinical studies in cancer patients. On the basis of the available clinical data, cardiac muscle toxicity and other cardiac diseases other

Key Safety Findings	Relevance to Human Usage
control rats by the severity and the presence of acute hemorrhage. It is unknown whether myocardial degeneration in rats may be related to changes in heart rate and blood pressure observed in the single-dose CV safety pharmacology assessment in monkeys. There were no brigatinib-related changes in CV functional parameters monitored in the 28-day and 6-month general toxicology studies in monkeys. It is not known whether there is any correlation of myocardial degeneration noted in rats with bradycardia and hypertension noted in brigatinib-treated patients.	than hypertension and bradycardia have not been observed as clear clinical signals in the 356 treated subjects.
Lung Toxicity Terminal microscopic changes in the lung comprising of reversible vacuolated [‘foamy’] alveolar macrophages were noted in monkeys (at ≥0.2 times the human AUC) but were not noted in rats. This finding has been reported as a background finding in naïve monkeys Although a transiently increased respiratory rate was noted in a safety pharmacology study in monkeys up to 42 hours after a single dose, there was no clinical evidence of respiratory distress in monkeys in repeat-dose- toxicology studies.	On the basis of the experience in clinical studies, brigatinib appears to be associated with certain pulmonary events that most commonly manifest in the first week of treatment (usually within 24-48 hours). Clinical evidence suggests that there may be a correlation between a lower starting dose and a lower risk of pulmonary events. These pulmonary events included, but were not limited to, dyspnea, hypoxia, cough, pneumonia, and pneumonitis, and in some cases including radiographic findings of linear or ground-glass opacities. These pulmonary events can be severe and fatal outcome has been observed.
Immune System Toxicity Depletion (hypocellularity) of immune-system–related organs such as spleen, gut-associated lymphoid tissue, thymus and lymph nodes were noted in rats and monkeys at ≥0.9 and ≥0.2 times the human AUC, and were considered to be primary effects of brigatinib and/or secondary to stress associated with poor toleration.	There have been no findings in clinical studies suggestive of depletion of the immune system, therefore currently there appears to be no human relevance of the observed nonclinical effects.
Hematopoietic System Toxicity Hypocellularity of the bone marrow was noted in rats and monkeys with accompanying clinical pathology changes such as reduced white blood cells, reduced red blood cells, hemoglobin, and hematocrit at ≥0.9 (rats) and ≥0.2 (monkeys) times the human AUC.	While reports of neutropenia have been reported in clinical studies, there have been no reports of febrile neutropenia. Decreases in hemoglobin and lymphocytes were mild.
Bone Toxicity Microscopic evidence of effects in the bone presented as osteoblast necrosis, thickening of the physeal cartilage (growth plate at the ends of long bones), and fibrosis of the periosteum in rats only, at 1.8 times the human AUC.	There have been no findings in the clinical studies suggestive of bone toxicity, therefore currently there appears to be no human relevance of the observed nonclinical effects.
GI Toxicity GI clinical signs such as loose stools, and emesis were noted in monkeys. Abdominal distention was noted in both rats and monkeys.	GI-related effects such as nausea, vomiting, abdominal pain and constipation have been noted in

Key Safety Findings	Relevance to Human Usage
Microscopic evidence of GI toxicity such as erosion, atrophy and/or necrosis was noted in rats and monkeys. These effects manifested in rats and monkeys at ≥1.1 and ≥0.4 times the human AUC, respectively, and were considered to be one of the causes of death in both species.	brigatinib-treated patients in clinical studies.
Pancreatic Toxicity Microscopic changes in the pancreas were noted in rats only, and comprised of acinar atrophy and fibroplasia of the islets. These changes were observed at exposures that were ≥0.9 times the human AUC.	Although chemical pancreatitis TEAEs occurred frequently, the incidence of clinical pancreatitis was low. Most patients with amylase and lipase elevations did not have abdominal symptoms. The data does not support a strong association between pancreatic enzyme elevation and clinical pancreatitis.
Ocular Toxicity Ocular toxicity manifested in rats as cataracts and retinal degeneration observed by ophthalmological examinations during the dosing phase. These changes were observed at exposures that were ≥0.9 times the human AUC. These effects were not reversible during the recovery phase. There were no ocular effects noted in monkeys in a 6-month toxicity study.	TEAEs associated with visual disturbances occurred commonly but were usually low grade.
Genotoxicity There were no genotoxic effects in the in vitro bacterial mutagenesis or chromosomal aberration assays. However, brigatinib demonstrated potential for chromosomal aberration based on evidence of micronucleus formation in the rat micronucleus study. The mechanism of micronucleus induction is assumed to be abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes, because the chromosomal aberration assay in human lymphocytes did not show any substantial increases in the incidence of chromatid or chromosome gaps under any experimental condition, but substantial increases in the incidence of polyploidy/endoreduplication/centromeric disruption were observed. At the maximum tolerated dose of 125 mg/kg/day, the induction of chromosomal damage was >2--fold compared with vehicle control. The projected exposure at this dose is approximately 5 times the human AUC.	No anticipated safety concerns in humans.
Carcinogenicity	Not applicable.
Phototoxicity There was no evidence of cutaneous phototoxicity or ocular toxicity in a single-dose phototoxicity study in pigmented rats. In a whole-body autoradiography study in rats, the eye lens and skin had some of the lowest concentrations of radioactivity in both pigmented and non-pigmented animals. Although tissue concentrations in the uvea of pigmented animals were higher than	Based on nonclinical data from other ALK inhibitors, a mechanism-based cause for phototoxicity cannot be ruled out. The incidence of photosensitivity reaction in patients treated with Brigatinib was low. And none of the reactions reported were Grade 4 or higher.

Key Safety Findings	Relevance to Human Usage
those in albino animals, concentrations in the pigmented eye uvea showed a slow but steady decline over time.	
General Safety Pharmacology Nonclinical safety pharmacology studies and assessments both in vitro (on the hERG [human ether-à-go-go–related gene] channels) and in vivo indicated that brigatinib-caused effects on the CV, respiratory, and renal systems, but had no effect on the CNS. Findings included altered respiration, blood pressure, and heart rates in monkeys, and alterations in serum and urine chemistry parameters in rats at clinically relevant doses.	In Study AP26113-11-101, the QT interval prolongation potential of brigatinib was assessed in 123 patients with advanced malignancies following QD brigatinib doses of 30 mg to 240 mg. The maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was less than 10 msec. An exposure-QT analysis suggested no concentration--dependent corrected QT interval prolongation. Additional effects on the CV, respiratory,- and renal systems have been observed in clinical studies. Findings included effects on respiratory function, elevations in blood pressure, decreases in heart rates and alterations in serum and urine chemistry parameters.
Mechanisms for Drug Interactions In vitro, cytochrome P-450 (CYP) CYP2C8 and CYP3A4 were the major isozymes responsible for brigatinib metabolism. Therefore, CYP3A4/5 and CYP2C8 inducers and/or inhibitors may affect circulating levels of brigatinib. Brigatinib caused a concentration-dependent increase in CYP3A4 messenger RNA (mRNA) levels with maximal induction of 6.54-fold (67% of positive control) at 2.5 µM, followed by decreased fold changes at higher concentrations, resulting in bell-shaped curves. Since activation of the PXR (pregnane X receptor) results in co-induction of CYP3A and CYP2C enzymes, brigatinib may have the potential for pharmacokinetic (PK) drug interactions with compounds for which CYP3A- and/or CYP2C-mediated metabolism constitutes the primary mechanism of clearance. In vitro, brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but not a substrate of organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OAT1, OAT3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion protein (MATE) 1, MATE2K, or ATP binding cassette protein (BSEP). Given that brigatinib exhibits high solubility and high permeability in vitro, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib. Brigatinib did not significantly inhibit transport activity for OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP, indicating a low likelihood of drug-drug interactions (DDIs) involving brigatinib and these transporters at clinically relevant concentrations.	**Effects of CYP3A Inhibitors on Brigatinib** In a crossover drug interaction study in healthy subjects (Study AP26113-15-105, N = 20), coadministration of multiple 200 mg twice-daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg brigatinib dose increased brigatinib- maximum observed concentration (C_{max}) by 21.2%, area under the concentration-time curve from time 0 to infinity (AUC_{∞}) by 101.2% (2-fold), and area under the concentration-time curve from time 0 to 120 hours (AUC_{120}) by 82.1% (<2-fold), relative to a single 90 mg brigatinib- dose given alone. The concomitant use of strong CYP3A inhibitors with brigatinib, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), mibefradil, and nefazodone, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided. Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) may increase the AUC of brigatinib by approximately

Key Safety Findings	Relevance to Human Usage
In vitro studies suggest that brigatinib and its metabolite AP26123 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant drug concentrations. Treatment of cultured human hepatocytes with brigatinib (concentration range: 0.25 to 20 μM) caused concentration-dependent decreases in CYP1A2 and CYP2B6 activity, and CYP1A2 mRNA levels, and bell-shaped curves were observed for CYP2B6 mRNA levels and CYP3A4/5 activity. In this study, toxicity to the hepatocytes was observed at brigatinib concentrations >2.5 μM by the lactate dehydrogenase leakage assay. Brigatinib was a weak inducer of CYP2B6 at concentrations ≤2.5 μM.	40% based on simulations from a physiologically-based PK model. The concomitant use of moderate CYP3A inhibitors with Alunbrig should be avoided. If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced by approximately 40% (i.e. from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a moderate CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inhibitor. . . **Effect of CYP3A Inducers on Brigatinib** In a crossover drug interaction study in healthy subjects (Study AP26113-15-105, N = 20), coadministration of multiple 600 mg daily doses of rifampicin (a strong CYP3A inducer) with a single 180 mg brigatinib dose decreased brigatinib C_{max} by 59.5%, AUC_{∞} by 80.4% (5--fold), and AUC_{120} by 80.0% (5-fold), relative to a single 180 mg brigatinib dose given alone. The concomitant use of strong CYP3A inducers with brigatinib including, but not limited to, rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, and St. John's wort should be avoided. Moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50% based on simulations from a physiologically-based PK model. The concomitant use of moderate CYP3A inducers with brigatinib-, including but not limited to efavirenz, modafinil, bosentan, etravirine, and nafcillin, should be avoided. **Effect of Brigatinib on CYP3A Substrates** In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. In patients with cancer, coadministration of multiple 180 mg daily doses of Alunbrig with a single 3 mg oral dose of midazolam, a sensitive CYP3A substrate, decreased midazolam C_{max} by 16%, AUC0-INF by 26%, and AUC0-last by 30%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib reduces plasma concentrations of coadministered drugs that are predominantly metabolized by CYP3A.

Key Safety Findings	Relevance to Human Usage
	Therefore, coadministration of brigatinib with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus) should be avoided as their effectiveness may be reduced. **Effects of Brigatinib on Transporter Substrates** Coadministration of brigatinib with substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine), OCT1, MATE1, and MATE2K may increase their plasma concentrations. Patients should be closely monitored when brigatinib is coadministered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

Abbreviation: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; CYP, cytochrome P 450; MATE, multidrug and toxin extrusion protein; NOAEL, no-observed-adverse-event level; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; SAE, Serious adverse events; TEAE, treatment emergent adverse events.

Part II: Module SIII - Clinical Trial Exposure

Table SIII.1 Duration of Exposure (Studies AP26113-11-101, AP26113-13-201 and AP26113-13-301)

Duration of exposure	Patients	Person time (person-months)
<1 month	46 (9.35)	17.41
1 to <3 months	60 (12.20)	111.84
3 to <6 months	44 (8.94)	192.89
6 to <12 months	74 (15.04)	646.34
12 to <24 months	79 (16.06)	1389.24
>=24 months	189 (38.41)	6513.15
Total person time	492 (100.00)	8870.87

(Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29)
Last patient last visit/contact date: Study 301: 2021-01-29.
Analysis includes patients in higher or lower doses other than the recommended dose.
Person time is defined as the sum of the treatment exposure of all patients in each category.
4 patients (3 patients in study 201 and 1 patient in study 301) enrolled did not get treatment.

Table SIII.2 Age Group and Gender (Studies AP26113-11-101, AP26113-13-201 and AP26113-13-301)

Age group	Patients		Person time (person-months)	
	Male	Female	Male	Female
18 – <65 years	165 (74.32)	196 (71.53)	3004.06	3836.58
65 - <75 years	38 (17.12)	62 (22.63)	654.06	924.94
75 - <85 years	18 (8.11)	15 (5.47)	275.98	174.00
>=85 years	1 (0.45)	1 (0.36)	1.12	0.13
Total	222 (100.00)	274 (100.00)	3935.21	4935.66

Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29)
Last patient last visit/contact date: Study 301: 2021-01-29.
Analysis includes patients in higher or lower doses other than the recommended dose.
Person time is defined as the sum of the treatment exposure of all patients in each category.

[redacted]

Table SIII.3 Starting Dose (Studies AP26113-11-101, AP26113-13-201 and AP26113-13-301)

Dose of exposure	Patients	Person time (person-months)
30 mg QD	3 (0.61)	6.31
60 mg QD	3 (0.61)	7.20
90 mg QD	127 (25.81)	1897.89
120 mg QD	11 (2.24)	107.43
60 mg BID	7 (1.42)	82.17
90 mg QD/180 mg QD	278 (56.50)	5913.69
180 mg QD	44 (8.94)	654.95
90 mg BID	4 (0.81)	71.66
240 mg QD	10 (2.03)	117.68
120 mg BID	3 (0.61)	11.79
300 mg QD	2 (0.41)	0.10
Total	492 (100.00)	8870.87

(Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29)

Last patient last visit/contact date: Study 301: 2021-01-29.
Analysis includes patients in higher or lower doses other than the recommended dose.
Person time is defined as the sum of the treatment exposure of all patients in each category.
4 patients (3 patients in study 201 and 1 patient in study 301) enrolled did not get study treatment.

Table SIII.4 By Racial or Ethnic Origin (Studies AP26113-11-101, AP26113-13-201 and AP26113-13-301)

Ethnic origin	Patients	Person time (person-months)
Race		
White	334 (67.34)	5762.76
Black or African	8 (1.61)	101.62
Asian	145 (29.23)	2861.11
Other/Unknown	9 (1.81)	145.38
Ethnicity		
Hispanic or Latino	22 (4.44)	420.99
Not Hispanic or Latino	474 (95.56)	8449.87
Total	496 (100.00)	8870.87

(Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29)

Last patient last visit/contact date: Study 301: 2021-01-29.
Analysis includes patients in higher or lower doses other than the recommended dose.
Person time is defined as the sum of the treatment exposure of all patients in each category

[redacted]

Table SIII.5 By Eastern Cooperative Oncology Group Status (Studies AP26113-11-101, AP26113-13-201 and AP26113-13-301)

ECOG Performance Status	Patients	Person time (person-months)
0	167 (33.67)	3903.70
1	304 (61.29)	4735.84
2	25 (5.04)	231.33
Total	496 (100.00)	8870.87

(Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29)

Last patient last visit/contact date: Study 301: 2021-01-29.
Analysis includes patients in higher or lower doses other than the recommended dose.

Person time is defined as the sum of the treatment exposure of all patients in each category.

Table SIII.6 Special Populations

Population	Patients	Person Time
Pregnant women	0	0
Lactating women	0	0
Renal impairment (severe)	8	Single doses in 8 subjects with severe renal impairment
Hepatic impairment(mild to severe)	18	Single doses in 18 subjects with hepatic impairment
Cardiac impairment (patients with comorbidities of the cardiac disorder SOC)	80	1270.14

Abbreviation: SOC, System Organ Class.

Source: Renal Impairment (study AP26113-15-108), hepatic impairment (study AP26113-15-107) and cardiac impairment (Database Cutoff Date: Study 101: 2016-05-31, Study 201: 2017-09-29.

Last patient last visit/contact date: Study 301: 2021-01-29)

Person time is defined as the sum of the treatment exposure of all patients in each category.

Expanded Access Program Exposure

As of the DLP of 31-October-2024, a total of 1,332 patients were exposed through the Expanded Access Program outside of the clinical development program.

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Had significant, uncontrolled, or active CV disease, specifically including, but not restricted to: myocardial infarction within 6 months prior to the first dose of brigatinib; unstable angina within 6 months prior to first dose; congestive heart failure within 6 months prior to first dose; history of clinically significant (as determined by the treating physician) atrial arrhythmia; any history of ventricular arrhythmia; cerebrovascular accident or transient ischemic attack within 6 months prior to first dose.	
Reason for exclusion:	Would have affected efficacy endpoints and safety outcomes.
Is it considered to be included as missing information?:	No
Rationale:	On the basis of the brigatinib safety profile, hypertension and bradycardia are known related toxicities. Pre-clinical data suggest cardiovascular findings. There is no plan to have a study in significant, uncontrolled or active CV disease population.

Was pregnant or breastfeeding	
Reason for exclusion:	Embryofetal and developmental toxicity was shown in nonclinical studies. On the basis of this nonclinical finding, brigatinib may cause fetal harm when administered to a pregnant woman. It is unknown whether brigatinib is excreted in human milk and available data cannot exclude potential excretion in human milk.
Is it considered to be included as missing information?:	No
Rationale:	Brigatinib should not be used during pregnancy unless the clinical condition of the mother requires treatment. If brigatinib is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to a fetus. Available data cannot exclude potential excretion in human milk; therefore, breastfeeding should be stopped during treatment with brigatinib.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table SIV.2 Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities (below):	
• Patients with: ○ renal impairment ○ hepatic impairment ○ CV impairment	**Population** / **Persons** Renal impairment (severe) / 8 Hepatic impairment (mild to severe) / 18 Cardiac impairment (patients with comorbidities of the cardiac disorder System Organ Class) / 80
• Immunocompromised patients	Not applicable
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Limited population
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

[redacted]

Part II: Module SV – Post authorisation Experience

SV.1. Post authorisation Exposure

Cumulatively, worldwide exposure for brigatinib since launch was estimated to be approximately 14,828 patient years (PYs).

SV.1.1. Method used to calculate exposure

The methodology used to calculate the exposure assumes an average daily dose (ADD) of 178.3 mg of brigatinib based on the current Reference Safety Information (RSI).

SV.1.2. Exposure

Based on the above methodology, the patient exposure can be estimated to be 5,409,994 ADDs cumulatively, corresponding to approximately 14,828 PYs of brigatinib treatment cumulatively.

[redacted]

[redacted]

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

No systematic examination of the abuse potential of brigatinib was performed in the nonclinical and clinical studies. There is no information regarding the dependence potential in animals or humans. Evaluation of adverse events (AEs) does not reveal evidence of euphoria, sedation, or mood alteration.

Part II: Module SVII – Identified and Potential Risks

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

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

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

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Adverse drug reactions (ADRs) that occurred in <25% of patients and Grade 3-4 severity in ≤5% of the patients:
Upper respiratory infection, decreased appetite, insomnia, headache, dizziness, dysgeusia, palpitations, constipation, abdominal pain, dry mouth, stomatitis, dyspepsia, flatulence, pruritus, arthralgia, musculoskeletal chest pain, pain in extremity, musculoskeletal stiffness, blood creatinine increased, oedema, pyrexia, pain, non-cardiac chest pain, weight decreased, memory impairment, tachycardia, blood cholesterol increased, and chest discomfort.

ADRs that occurred in >25% of patients and Grade 3-4 severity reported in ≤5% of the patients:

Nausea, diarrhea, vomiting, rash, and fatigue.

ADRs for which frequency was mostly based on laboratory findings with minimal clinical impact or can be managed by adequate supportive therapy:

Anemia, lymphocyte counted decreased, APTT (activated partial thromboplastin time) increased, white blood cell count decreased, neutrophil count decreased, decreased platelet count, hyperbilirubinaemia, hyperglycaemia, hyperinsulinaemia, hypophosphataemia, hypokalaemia, hypomagnesaemia, hypercalcemia, and hyponatraemia.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

ADRs with clinical consequences of Grade 3-4 severity reported in ≤5% of patients:

Pneumonia, pancreatitis, and peripheral neuropathy.

Known risks that require no 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):

Not applicable.

Known risks that do not impact the risk-benefit profile:

Not applicable.

Other reasons for considering the risks not important:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the list of safety concerns in the Initial RMP

Important Identified Risks	Risk-Benefit Impact
Pulmonary toxicity (including early-onset pulmonary events [EOPE] and later-onset pneumonitis)	Pulmonary toxicity was frequently observed in the brigatinib clinical development program. Pulmonary AEs such as dyspnoea, hypoxia, pneumonitis, pneumonia and interstitial lung disease (ILD) have significant impact on patient

Important Identified Risks	Risk-Benefit Impact
	quality of life; they can cause severe distress and require medical intervention. Early detection could mitigate seriousness including monitoring of symptoms and dose modifications, as appropriate; implementation of a PAC to enhance detection by increasing awareness of the risk by general health care professionals who may not be experienced in the use of anticancer medicines and brigatinib.
Hypertension	Hypertension was frequently observed in the brigatinib clinical development program. Many cases of hypertension are mild with minimal impact on the patient. More severe cases of hypertension may require medical treatment. Early detection could mitigate seriousness and monitoring of blood pressure and dose modifications, as appropriate with treatment according to standard guidelines to control blood pressure.
Bradycardia	Bradycardia was frequently observed in the brigatinib clinical development program. Most cases of bradycardia are mild with minimal impact on the patient. More severe bradycardia may require medical intervention. It is possible to detect bradycardia at an early stage with monitoring of heart rate and dose modifications, as appropriate. This could mitigate seriousness.
DDI with strong CYP3A inhibitors and strong and moderate CYP3A inducers	Coadministration of brigatinib with strong CYP3A inhibitors and strong and moderate CYP3A inducers will affect the concentrations of brigatinib and could result in toxicity or lack of efficacy. Toxicity could result in excess AEs; lack of efficacy could result in tumor growth. In mild cases, there will be minimal impact on the patient; however, severe cases may require medical intervention. The risk of DDI is decreased with the provision of specific guidance concerning this risk.
Important Potential Risks	**Risk-Benefit Impact**
Hepatotoxicity	Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were frequently observed in the brigatinib clinical development program. While mild cases of hepatotoxicity will cause little impact on the patient, severe cases may require medical intervention and liver transplantation. The risk of hepatotoxicity can be minimized with monitoring of hepatic function and overall health, as well as paying attention to other

Important Identified Risks	Risk-Benefit Impact
	drugs which may affect hepatic function or brigatinib concentration.
Myopathy, including rhabdomyolysis and cardiomyopathy	Creatine phosphokinase (CPK) elevations, usually asymptomatic, were frequently observed in the brigatinib clinical development program. Detection at an early stage by monitoring for symptoms of myopathy and dose modifications, as appropriate, could mitigate seriousness of CPK elevations and myopathy.
Pancreatitis	Elevations of amylase and lipase were frequently observed in the brigatinib clinical development program. While amylase and lipase elevations may be transient or asymptomatic, and related to underlying lung cancer, if the clinical pancreatitis is diagnosed, these cases could require medical intervention. Detection at an early stage by monitoring of amylase and lipase and dose modifications, as appropriate, could mitigate seriousness.
Retinal degeneration, macular degeneration	Retinal degeneration and macular degeneration have not been seen in patients; however, vision disorders and vision impairment were seen in patients. In mild cases, there will be minimal impact on the patient; however, severe cases may require medical intervention and may lead to vision loss. Detection at an early stage including ophthalmologic evaluation and dose modifications, as appropriate, to attend to and address visual changes, could mitigate seriousness and may help prevent or minimize these risks.
Embryofetal and developmental toxicity	Embryofetal and developmental toxicity is likely to have impact on the fetus. However, there is limited data to quantify or qualify the effect of lung cancer itself or of chemotherapeutic agents on pregnancy outcomes and embryofetal toxicity. Prescribers are to avoid the use of brigatinib in patients who are or are capable of becoming pregnant and male patients who are sexually active with women of childbearing potential and are informed of the need for adequate contraception in such situations.

Missing Information	Risk-Benefit Impact
Effects on male and/or female fertility	No human data on the effect of brigatinib on fertility are available. On the basis of repeat-dose toxicity studies in male animals, brigatinib may cause reduced fertility in males.

Missing Information	Risk-Benefit Impact
	The clinical relevance of these findings to human fertility is unknown.
Long-term safety	Ongoing clinical studies and maintenance studies aim to provide additional information about the safety with long-term use of the product. There is no evidence to suggest a different safety profile with long-term use.
DDI with CYP3A4 substrates	In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. In patients with cancer, coadministration of multiple 180 mg daily doses of Alunbrig with a single 3 mg oral dose of midazolam, a sensitive CYP3A substrate, decreased midazolam C_{max} by 16%, AUC0-INF by 26%, and AUC0-last by 30%, relative to a 3 mg oral dose of midazolam administered alone. Brigatinib reduces plasma concentrations of co-administered medicinal products that are predominantly metabolized by CYP3A.

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

Considering brigatinib now has been available in the EU market for more than 5 years, the safety risk profile (including EOPEs) is considered to be well characterized, there is increased awareness of EOPE risk among the prescribers since the initial product approval and lack of EOPEs in Brigatinib-5007 study representing real world setting, the MAH proposes the removal of the additional risk minimisation measure of the PAC for the risk of EOPEs in the EU. As such upon removal of PAC requirement in EU and in accordance with GVP Module V Rev. 2 guidance on the RMP format, the Important Identified risk of "Pulmonary toxicity" is removed from Table SVIII.1 Summary of Safety Concerns and other relevant sections. The Sponsor will continue to monitor this risk as a safety concern in the scope of the Periodic Benefit Risk Evaluation Report (PBRER).

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

Not applicable.

SV VII.3.2. Presentation of the Missing Information

Not applicable.

Part II: Module SVIII – Summary of the Safety Concerns

Table SVIII.1 Summary of safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including Post-authorisation Safety Studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable.

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-authorisation Efficacy Studies

None.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

PAC:

The aRMM of PAC for the important identified risk of "Pulmonary toxicity (including EOPEs) has been removed. Please refer to Section SVII.2 for more details.

V.3. Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of RMP for Alunbrig (Brigatinib)

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

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

This summary of the RMP for Alunbrig 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 Alunbrig's RMP.

I. The Medicine and What It Is Used For

Alunbrig is authorised as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib and as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously not treated with an ALK inhibitor (see SmPC for the full indication). It contains brigatinib as an active substance and it is given by mouth.

Further information about the evaluation of Alunbrig's benefits can be found in Alunbrig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/alunbrig-epar-risk-management-plan-summary_en.pdf

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 the case of Alunbrig, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Alunbrig 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 Alunbrig. 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).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C. Post-authorisation Development Plan

II.C.1. Studies Which Are Conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Alunbrig.

II.C.2. Other Studies in Post-authorisation Development Plan

There are no studies required for Alunbrig.

[redacted]

Part VII: Annexes

Table of Contents

[redacted]

Annex 4: Specific Adverse Drug Reaction Follow-Up Forms

[redacted]

Annex 6: Details of Proposed Additional Risk Minimisation Activities

[redacted]

[redacted]

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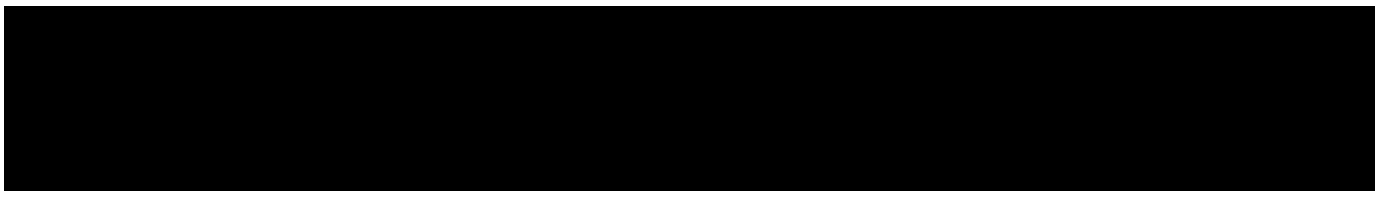

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

[redacted]

[redacted]

Annex 6 Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.