16 September 2021
EMA/CHMP/41191/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gavreto

International non-proprietary name: pralsetinib

Procedure No. EMEA/H/C/005413/0000

Note

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

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List of abbreviations

ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration vs time curve
AUC_{0-24}	Area under the plasma concentration-time curve from zero to 24 hours
$AUC_{0-\infty}$	Area under the plasma concentration vs time curve from time 0 to infinity
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BID	Twice daily
BLQ	Below the limit of quantification
BOIN	Bayesian optimal interval
BOR	Best overall response
BW	Body weight
Cave	Average plasma concentration
CBR	Clinical benefit rate
CCDC6	Coiled-coil domain-containing 6
CHMP	Committee for Medicinal Products for Human Use
CL_{plasma}	Plasma clearance
CL/F	Apparent oral clearance, unadjusted for bioavailability
Cmax	Maximum plasma concentration
CMA	Conditional marketing authorisation
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
ctDNA	Circulating tumor deoxyribonucleic acid
Ctrough	Trough plasma concentration
%CV	Percent coefficient of variation
CxDy	Cycle x Day y
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
DUSP6	Dual specificity phosphatase 6
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Endothelial growth factor receptor
EFD	Embryofoetal development
EMA	European Medicines Agency
E-R	Exposure-response
ESMO	European Society for Medical Oncology

EU	European Union
F	Oral bioavailability
FDA	Food and Drug Administration of the United States
FGFR2	Fibroblast growth factor receptor 2
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GoF	Goodness-of-fit plots
hERG	Human ether à go go–related gene
HV	Healthy volunteers
IC50	50% of maximal inhibition concentration
IC90	90% of maximal inhibition concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILD	Interstitial lung disease
ISF	Interstitial fluid
JAK	Janus kinase
Kd	Dissociation constant
KDR	Kinase insert domain receptor
KIF5B	Kinesin family member 5B
K-M	Kaplan-Meier
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
MATE	Multidrug and toxin extrusion protein
MDP	Measurable disease population
MedDRA	Medical Dictionary for Regulatory Activities
MKI	Multikinase inhibitor
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NGS	Next generation sequencing
NOEL	No-observed-effect-level
NOAEL	No-Observed-Adverse-Effect-Level
NPC	Numerical predictive checks
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PBT	Persistence, Bioaccumulation and Toxicity
PD	Progressive disease
PDX	Patient-derived xenograft
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
Pop PK	Population pharmacokinetics
PPI	Proton pump inhibitor
PR	Partial response

PS	Performance status
PT	Preferred Term
PTC	Papillary thyroid cancer
pvcVPCs	Prediction and variance corrected visual predictive checks
PXR	Pregnane X receptor
QD	Once daily
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT corrected for heart rate by the Fridericia method
QWBA	Quantitative whole-body autoradiography
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during transfection
RMP	Risk Management Plan
RP2D	Recommended Phase 2 dose
SA	Scientific advice
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SmPC	Summary of Product Characteristics
SPRY4	Sprout receptor tyrosine kinase signaling antagonist 4
STAT5	Signal transducer and activator of transcription 5
StdDev	Standard deviation
t1/2	Apparent elimination half-life
TEAE	Treatment-emergent adverse event
TGI	Tumour growth inhibition
Tmax	Time of maximum plasma concentration
TK	Toxicokinetics
TKI	Tyrosine kinase inhibitor
TRKC	Tropomyosin receptor kinase C
TTR	Time to response
UGT	uridine 5'-diphospho-glucuronosyltransferase
USA	United States of America
V/F	Apparent volume of distribution, unadjusted for bioavailability
VEGFR2	Vascular endothelial growth factor receptor 2
Vss	Apparent volume of distribution at steady-state
Vz/F	Apparent volume of distribution during the terminal phase, unadjusted for bioavailability

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Blueprint Medicines (Netherlands) B.V. submitted on 30 April 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Gavreto, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2019.

During the procedure, the applicant has changed from Blueprint Medicines (Netherlands) B.V. to Roche Registration GmbH.

The applicant applied for the following indication:

Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0266/2019 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above mentioned Regulation.

New active Substance status

The applicant requested the active substance pralsetinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific Advices on the development of treatment of RET-fusion positive metastatic NSCLC subject to the present application:

- EMEA/H/SA/4091/2/2019/SME/I
- EMEA/H/SA/4091/1/2019/SME/III

The Scientific Advices pertained to the following Quality, Non-Clinical and Clinical aspects:

- designation of starting materials for the drug substance
- specifications including stability of drug substance
- proposed analytical tests and specification strategy for the drug product release and stability
- nonclinical safety data package
- efficacy data set obtained from the single-arm trial
- patient population from the single-arm trial
- safety database
- study design of the confirmatory trial

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Blanca Garcia-Ochoa

The application was received by the EMA on	30 April 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	08 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 January 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2021

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	01 September 2021
A SAG on Gavreto has taken place on	07 September 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Gavreto on	16 September 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking a Marketing Authorisation for the treatment of adult patients with rearranged during transfection (RET)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy.

2.1.2. Epidemiology

With an estimated 1.8 million deaths per year, lung cancer is the leading cause of cancer death worldwide. In Europe, about 470,000 patients developed lung cancer in 2020 and more than 380,000 people died from lung cancer, which represents one fifth (19.6%) of all deaths from cancer in the EU (Globocan, 2020). The two main categories of lung cancer are NSCLC (approximately 85% of lung cancers) and small cell lung cancer (SCLC) (Zappa and Mousa, 2016). NSCLC subtypes include adenocarcinoma (most common for both men and women in Europe with up to 68% of NSCLC), squamous cell carcinoma (25% to 30% of all lung cancer) and large cell carcinoma (5% to 10% of lung cancer) (Szumera-Ciećkiewicz *et al*, 2013; Zappa and Mousa, 2016).

Approximately 75% of lung adenocarcinomas harbour genetic alterations that promote the RTK/RAS/RAF signalling pathway including drivers such as KRAS, EGFR, ALK, ROS1, BRAF, MET, NTRK, and RET, among others (Inamura, 2017; Rosell and Karachaliou, 2016). Oncogenic RET fusions have

been identified in 1 to 2% of NSCLC and the RET fusions are typically found in adenocarcinoma histology, though occasionally also in squamous cell carcinoma (Lin *et al*, 2015; Takeuchi *et al*, 2019).

2.1.3. Biologic features

RET is a receptor tyrosine kinase expressed in several neural, neuroendocrine and genitourinary tissue types that normally requires ligand and co-receptor binding for activation (Mulligan, 2014). Aberrant activation of RET is a critical driver of tumour growth and proliferation across several solid tumours (Mulligan, 2014).

Oncogenic activation of RET can occur via two primary mechanisms (Drilon *et al*, 2018). First, chromosomal rearrangements can produce hybrid proteins that fuse the RET kinase domain with a partner protein that often contains a dimerization domain (Romei *et al*, 2016; Kohno *et al*, 2012; Takeuchi *et al*, 2012; Lipson *et al*, 2012). Second, point mutations can directly or indirectly activate the kinase (Donis-Keller *et al*, 1993; Mulligan *et al*, 1993; Hofstra *et al*, 1994). Both mechanisms of oncogenic activation result in constitutively active, ligand-independent RET kinase activity and activation of downstream signalling pathways (Drilon *et al*, 2018).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Most patients with NSCLC present with advanced stage unresectable disease (ESMO Guidelines 2019) and, if untreated, these patients are expected to die within an average of 9.4 months of diagnosis; only 18% of all patients with lung cancer are alive five years or more after diagnosis (Campbell *et al*, 2018; NCCN 2020).

In addition, the disease itself is associated with many symptoms that need to be managed (*e.g.,* cough, dyspnoea, weight loss, chest pain, chronic obstructive pulmonary disease, bone pain, headaches, anaemia and paraneoplastic syndromes) (Simoff *et al*, 2013; Spiro *et al*, 2007).

RET-fusion positive NSCLC tumours tend to lack mutations in other known driver genes and are commonly found in a younger population of non-smokers (Michels *et al*, 2016; Lin *et al*, 2015; Tsuta *et al*, 2014; Lipson *et al*, 2012; Takeuchi *et al*, 2012; Stransky *et al*, 2014; Jordan *et al*, 2017). For NSCLCs, including lung adenocarcinomas, no significant difference has been reported in progression-free survival (PFS) or overall survival (OS) between untreated patients with RET-positive and RET-negative tumours (Wang *et al*, 2012).

2.1.5. Management

Patients with *RET* fusion-positive NSCLC typically receive the same standard-of-care treatment as patients with NSCLC who do not have a driver mutation (ESMO guidelines, 2020; Belli *et al*, 2021). Standard first-line systemic treatment for patients with advanced, non-resectable NSCLC lacking a driver mutation is platinum doublet-based cytotoxic chemotherapy and/or immunotherapy with checkpoint inhibitor. Currently recommended subsequent therapies after progression on platinum doublet-based therapy consist generally of immune checkpoint inhibitor monotherapy, single agent chemotherapy, or docetaxel in combination with ramucirumab (Planchard *et al*, 2018). Subsequent therapy for refractory patients after these treatment options is best supportive care, or enrolment in a clinical trial.

Of note, in February 2021, Retsevmo (selpercatinib) was approved in Europe for the treatment of cancers that display RET gene alterations: *RET*-fusion positive NSCLC, *RET*-fusion positive thyroid cancer and *RET*-mutant medullary-thyroid cancer (MTC). More specifically in NSCLC, Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive NSCLC who

require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

About the product

Pralsetinib (formerly known as BLU-667) is a tyrosine kinase inhibitor that targets oncogenic RET fusions (including KIF5B-RET and CCDC6-RET).

The CHMP adopted a positive opinion for use of Gavreto in the following indication:

Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

Therapy should be initiated by a physician experienced in the administration of anticancer medicinal products.

Patient selection for treatment of RET fusion-positive advanced NSCLC should be based on a validated test method.

Posology

The recommended dose is 400 mg pralsetinib once daily on an empty stomach. Treatment should be continued until disease progression or unacceptable toxicity.

If vomiting occurs after taking a dose of pralsetinib, the patient should not take an additional dose but continue with the next scheduled dose.

Missed doses
If a dose of pralsetinib is missed, the patient should make up for the missed dose as soon as possible on the same day. The regular daily dose schedule for pralsetinib should be resumed the next day.

Dose modifications for adverse reactions
Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation.

Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg once daily. Gavreto should be permanently discontinued in patients who are unable to tolerate 100 mg orally once daily.

Recommended dose modifications for adverse reactions are indicated in Table 1.

Table 1. Recommended dose modifications for Gavreto for adverse reactions

Adverse reaction	**Severity[a]**	**Dose modification**
Pneumonitis/Interstitial lung disease (ILD) (see section 4.4 of the SmPC)	Grade 1 or 2	Interrupt treatment with Gavreto until resolution. Resume at a reduced dose. Permanently discontinue Gavreto for recurrent pneumonitis/ILD.
	Grade 3 or 4	Permanently discontinue for pneumonitis/ILD.
Hypertension	Grade 3	Interrupt treatment with Gavreto for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.

	Grade 4	Permanently discontinue Gavreto.
Transaminase elevations	Grade 3 or 4	Interrupt treatment with Gavreto and monitor aspartate aminotransferase (AST) and alanine aminotransferase (ALT) once weekly until resolution to Grade 1 or baseline. Resume at a reduced dose. If transaminase elevation recurs at Grade 3 or higher, permanently discontinue treatment with Gavreto.
Haemorrhagic events	Grade 3 or 4	Withhold Gavreto until resolution to Grade 1. Resume at a reduced dose. Discontinue Gavreto for life-threatening or recurrent severe haemorrhagic events.
QT prolongation	Grade 3	Interrupt treatment with Gavreto for QTc intervals >500 ms until QTc interval returns to <470 ms. Resume at the same dose if risk factors that cause QT prolongation are identified and corrected. Resume treatment at a reduced dose if other risk factors that cause QT prolongation are not identified.
	Grade 4	Permanently discontinue Gavreto if the patient has life-threatening arrhythmia.
Other clinically significant adverse reactions (see section 4.8 of the SmPC)	Grade 3 or 4	Interrupt treatment with Gavreto until improvement to ≤Grade 2. Resume at a reduced dose. Permanently discontinue for recurrent Grade 4 adverse reactions.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03

Type of Application and aspects on development

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

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

The applicant claims the final clinical study report for ARROW (BLU-667-1101, phase I/II), which will be submitted in Q4 2022, will include longer term follow up of efficacy from 281 RET fusion-positive NSCLC patients including data from 116 treatment-naïve patients enrolled through October 2020 and safety data. The applicant considers that the data to be provided in the final ARROW clinical study report will be sufficient to comprehensively assess and confirm a positive benefit-risk.

The ongoing Phase 3 AcceleRET Lung trial is proposed as an Annex II PAES, rather than as a specific obligation of the CMA. This is an open-label, randomized, controlled multicentre phase III study in RET fusion-positive NSCLC patients (BLU-667-2303). This study is designed to assess the efficacy of pralsetinib as compared to Investigator's choice platinum-based chemotherapy regimen for patients with metastatic NSCLC harbouring an oncogenic RET fusion and who have not received prior systemic therapy.

- Unmet medical needs will be addressed

The applicant claims that, given the unprecedented overall response rate (ORR) and duration of response (DOR) of pralsetinib regardless of line of therapy in the RET fusion-positive NSCLC population, its beneficial activity in the central nervous system (CNS), its safety profile as well as the improvement to patient care it can provide (*i.e.* oral, once daily precision therapy that can be administered in the home in an outpatient setting), pralsetinib will be of major therapeutic advantage to this population, and thus will address an unmet medical need.

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

The applicant claims that, to date, it has been shown that pralsetinib has a favourable benefit-risk in patients with RET-fusion positive advanced NSCLC. Supportive data from the AcceleRET Lung Phase 3 trial will further confirm the benefit/risk observed in the ARROW trial and will increase the safety database and demonstrate the impact of pralsetinib on PFS, ORR, DOR and OS compared to SOC platinum-containing anticancer regimens. This will further confirm the conclusions on the benefit/risk profile of pralsetinib in the proposed population, however it is the applicant's position that these data are not needed in support of an initial EU marketing authorisation and conditional marketing authorisation at this time is justified.

Postponing the submission of the MAA until completion of the ARROW study would lead to a delay of approximately two years in time to approval. A delay of two years is excessive in the setting of a fatal disease with an important medical need, considering metastatic NSCLC patients in a 1L setting have a median OS of approximately 10-30 months (Keytruda SmPC, 2021; Taxotere SmPC, 2020), and patients in a 2L treatment setting have a median survival time of approximately 8-13 months (Alimta SmPC, 2020; Fehrenbacher et al, 2018; Herbst et al, 2016; Opdivo SmPC, 2020).

Considering the unprecedented efficacy and DOR observed in the ARROW study, as well as the manageable safety profile, the applicant claims that immediate availability of pralsetinib outweighs the risk inherent in the fact that additional data are still required.

2.2. *Quality aspects*

2.2.1. Introduction

The finished product is presented as hard capsules containing 100 mg of pralsetinib as active substance.

Other ingredients are:

Capsule content: hypromellose, cellulose microcrystalline pregelatinised starch, sodium hydrogen carbonate, citric acid , and magnesium stearate.

Capsule shell: brilliant blue FCF (E133), hypromellose, and titanium dioxide (E171)

Printing ink: shellac , propylene glycol (E1520), potassium hydroxide , and titanium dioxide (E171)

The product is available in a high density polyethylene (HDPE) bottle with child-resistant cap (polypropylene) and foiled induction seal liner and desiccant sachet (silica gel) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name is (cis)-*N*-((S)-1-(6-(4-fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1H-pyrazol-3-ylamino)pyrimidin-2-yl)cyclohexanecarboxamide corresponding to the molecular formula $C_{27}H_{32}FN_9O_2$. It has a relative molecular mass of 533.61 g/mol and the following structure:

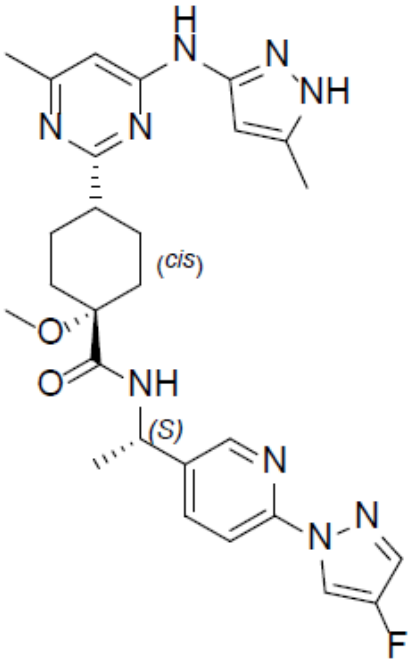

Figure 1 : Active substance structure

In the molecular structure, stereochemistry is indicated for the cyclohexane ring. This relates to configurational isomerism or geometric isomerism, which occurs due to the possibility of different

spatial positions across the ring system, in this case resulting in the cis-isomer. As the cyclohexane ring constitutes configurational isomerism, it is endorsed that this ring system does not imply chirality at this position. Hence, there is only one stereogenic carbon atom contained in the molecule resulting in the S-form of pralsetinib. The enantiomer of the active substance (R-form) is controlled as specified impurity in the active substance specification.

The chemical structure and absolute stereochemistry of pralsetinib has been unambiguously established by a combination of analytical characterization techniques which include single crystal X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), Fourier transform infrared spectroscopy (FT-IR), and ultraviolet absorption spectroscopy (UV). Solid state characterisation of relevant polymorphic forms A, B and C have been conducted using X-Ray Powder Diffraction (XRPD), differential scanning calorimetry (DSC, to further characterise monohydrate), thermal gravimetric analysis (TGA), dynamic vapour sorption analysis (DSV), microscopy and scanning electron microscopy (SEM).

The active substance is a non-hygroscopic white to off-white to yellow solid. Pralsetinib solubility in aqueous solvents has been studied and it shows that the active substance is practically insoluble in water; the solubility of pralsetinib in aqueous buffers slightly increases with acid pH. The solubility in various solvents has also been studied and it shows that pralsetinib is freely soluble in methanol.

A polymorphic screening has been performed to study occurrence of polymorphic forms and their interconversion. The active substance exists in multiple solid forms, including the stable forms A, B and C. A detailed discussion on polymorphic forms of the active substance has been provided. Interchangeability between the forms has been thoroughly investigated. Relevant polymorphic forms have been identified as A, B and C. The different polymorphic forms can be differentiated by XRPD. The choice of pralsetinib monohydrate (Form C) has been adequately justified. The manufacturing process produces consistently form C. Data of 18 batches, including three registration batches, convincingly demonstrates that form C is obtained. Stability data demonstrates that there is no change in the polymorphic form of the active substance during storage.

Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site

The synthesis of the active substance is described in five steps, while comprises four actual synthetic steps (bond breaking/formation) and a crystallisation/purification step using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
Criticality of material input and process/operating parameters have been laid down in the process description.

A risk-based scientific development approach was used to design and develop the manufacturing process and control strategy for the active substance.

The approach to assigning critical process parameters (CPPs) incorporates a statistical treatment of laboratory data from multi-variate process mapping studies conducted, evaluation of manufacturing batch history data, and quality risk assessments. The applicant has confirmed that no design space is claimed

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. The impurity discussion has satisfactorily focused on all relevant aspects, i.e. organic impurities (in starting materials, intermediates and active substance as well as process impurities), genotoxic impurities, residual solvents and elemental/inorganic impurities.

Control strategy for organic impurities has been extensively discussed and is ensured by adequate specifications for starting materials, intermediates, active substance and controlled reaction conditions. Fate, carry-over and control of potential impurities (unchanged or as derivatives) from the starting materials through intermediates to the final active substance has been satisfactorily addressed.

The finished product is out of scope of ICH M7 (indication: advanced cancer). However, a risk assessment in line with ICH M7 has been presented. All actual and potential impurities likely to be present in the active substance have been evaluated for potential genotoxicity. Starting materials, intermediates, reagents as well as potential impurities and degradation products were considered. No genotoxic impurities were found. Reports for the QSAR analysis have not been provided and impurities investigated have not been classified according to ICH M7. However, as the finished product is out of scope of ICH M7, the evaluation of genotoxic impurities is considered sufficient.

Control strategy for residual solvents has been extensively discussed and justified. All solvents used in synthesis of starting materials and the active substance have been addressed and are controlled.

Control of additional possible impurities has been introduced in the active substance specification and the method description has been presented. However, method validation is pending. Therefore, the CHMP recommended to submit the method validation report for additional possible impurities testing as a Type IB variation (classification B.II.d.1.z) post-approval . .

Screening of intentionally added elementals as well as ICH Q3D class 1 and 2A elements has been conducted on representative active substance batches. Complete risk assessment in line with ICH Q3D have been conducted. Other inorganic impurities such as inorganic salts that are potential by-products are removed during washing/work-up, filtration and isolation procedures.

An extensive description of the development of the active substance from the early clinical batches to the current process performance qualification (PPQ) batches has been provided. Process development has been satisfactorily addressed. It has been confirmed that the same synthetic route overall has been used during development made implying that the bond-forming chemistry has remained unchanged.

The active substance is packaged in a container which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), identity (HPLC), assay (HPLC), specified impurities (chiral HPLC, HPLC), residual solvents (HS-GS), elemental impurities (ICP-MS), solid form confirmation (PXRD), water content (KF), residue on ignition (gravimetric), other organic impurities (GC-MS, IC, GC) .

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The overall control strategy of residual solvents in regulatory starting materials, intermediates and final active substance have been provided and is considered acceptable.

Genotoxic impurities could be generated or introduced from the reagents and solvents used in the proposed commercial manufacturing process .

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines, except the method for two specified impurities for which a recommendation to complete the validation has been raised (see discussion above, REC 001). In addition, at the time of opinion, the stability indicating nature of the HPLC method used for identification, assay and impurities had not been fully demonstrated. Therefore, the CHMP recommended that the applicant to address this and conduct additional forced degradation studies under the harsher conditions . The applicant will include the results of the additional forced degradation studies as a Type IB variation (classification B.II.d.1.z) post approval [REC 002]. Satisfactory information regarding the reference standards used for testing has been presented.
Batch analysis data of commercial and pilot scale manufactured by Process A and Process B of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer using commercial manufacturing process stored in the intended commercial package for up to 12 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided and packaged in the commercial packaging material. The batch scale difference between registration batches and the commercial scale batches is less than a 10-fold increase. Therefore, registration batches are considered representative of the commercial manufacturing process.

Data from up to 18 months and 12 months at the long-term and 6 months at the accelerated storage condition from three supportive active substance batches manufactured with intended commercial process at the site where clinical trials were made. were also provided.

The packaging configuration for the supportive batches is comparable with the intended for marketing.

The parameters tested were description, assay, impurities, enantiomeric impurity, solid form confirmation, water content and microbial enumeration.

The data show minimal variation with no significant trends for the active substance stored up to 12 months at 25°C/60% RH or 6 months at 40°C/75% RH. All test parameters remained within the pre-defined acceptance criteria throughout the duration of testing for commercial and supportive batches.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant degradation was observed after exposure to light stress.

Results on stress conditions: thermal stress (105°C for 14 days), oxidative stress for 14 days at ambient temperature and protected from light), acidic stress (14 days at ambient temperature and protected from light), basic stress (14 days at ambient temperature and protected from light) were also provided on one batch. Based on the totality of the forced degradation studies, pralsetinib is stable to extreme thermal, oxidative, acidic and basic stress conditions. Therefore, this active substance does not require any special storage conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as light blue opaque size 0 (22 mm long x 7 mm wide) hard capsules, with "BLU-667" printed on the capsule shell body and "100 mg" printed on the capsule shell cap in white ink.

Based on the clinical development program, a solid oral dosage form was the starting point and the initial objective for the pharmaceutical development of the finished product. The quality target product profile (QTPP) was an integral part of the development process that expanded on the initial objective to guide the selection and optimization of desirable attributes and quality targets for the finished product. The QTPP connects the desired product attributes with specific development targets and then links them to the resulting qualities of the intended commercial product.

The active substance is taken forward to be made into a spray dried dispersion (SDD) intermediate prior to being formulated into the finished product (capsules).

Potential finished product critical quality attributes (CQA) have been derived from the QTPP and/or prior knowledge as a means to design a quality product and a manufacturing process which consistently delivers the intended performance of the product. The preliminary identification of the finished product CQAs was performed with consideration of relevant quality attributes of the finished product components (e.g. active substance), process development studies, and process knowledge based on previous experience. In addition, ICH Q8 (R2), Q9 and Q10 guidelines were used as benchmarks to guide development with the aim of enabling continuous improvement in the context of a lifecycle approach to product development and process validation.

Based on these assessments, attributes were identified as potentially critical to the spray dried dispersion (SDD) intermediate and capsule quality. These attributes were selected in accordance with ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, including consideration of analytical and manufacturing capabilities, desired product quality attributes, and intended product performance with regard to safety and efficacy.

Pralsetinib is a low solubility-high permeability active substance and is classified as a BCS Class 2 active substance based on criteria for solubility and intestinal permeability in the *ICH M9 Guideline Biopharmaceutics Classification System-based Biowaivers*.

Hence solid-state properties of the active substance are relevant for the dosage form. Due to its low intrinsic aqueous solubility, the active substance is formulated as an amorphous dried dispersion. The manufacturing process involves complete dissolution of the active substance during the spray-drying process to obtain an anhydrous amorphous form of pralsetinib as spray dried dispersion (SDD), the finished product intermediate, thereby rendering solid-state properties of the intermediate more relevant than the active substance. The specification for the finished product intermediate includes control of polymorphic form and particle size.

The active substance is slightly soluble to practically insoluble in aqueous media, at pH = 1.0 to 8.0, and it is more soluble in acidic aqueous media than in basic aqueous media. In simulated biological fluids, pralsetinib is practically insoluble in fasted-state simulated intestinal fluid, sparingly soluble in fasted-state simulated gastric fluid, and slightly soluble in fed-state simulated intestinal fluid.

The compatibility of the SDD intermediate with a range of commonly used pharmaceutical excipients has been assessed. The data obtained were used to aid selection of appropriate excipients during formulation development.

A compatibility study was performed between the active substance and the excipients. There was no change in the solid-state form of pralsetinib over the duration of the excipient compatibility study. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The objective of the formulation development was to develop 10 mg, 30 mg and 100 mg immediate release capsule formulations containing pralsetinib. Only the 100 mg strength is proposed for marketing. The intended formulation (intermediate and capsule) was developed at the initial manufacturer for products used in clinical trials . Following the introduction of the capsule formulation into clinical studies, a new manufacturer of the finished product intermediate and a new manufacturer of the capsules were introduced, which are the commercial sites proposed. The formulation and the unit operations in the manufacture of the intermediate and the finished product have not changed during the course of development. However, process optimisation changes have been conducted.
A comparability exercise on batches of the finished product intermediate and the finished product, respectively, has been conducted. Comparable quality and solid-state characteristics have been demonstrated and it has been justified that changes do not impact quality and manufacturability of the finished product intermediate and the finished product. In addition, stability of the amorphous form of the active substance in the finished product intermediate and the finished product when stored in appropriate packaging closed correctly has been demonstrated. Solid form conversion does not occur. Transparency and traceability with regard to batches mentioned in the dossier and their use in clinical studies have been ensured. Bridging between development formulations and final formulation is established. The commercial formulation has been used to manufacture finished product batches, which have been or will be used in clinical studies and correspond to the formulation used for the finished product registration batches.
Solid-state properties and solubility of the finished product intermediate and influence on finished product performance have been satisfactorily provided. The specification for the intermediate includes control of polymorphic form and particle size. Control of polymorphic form is also included in the active substance specification (crystalline active substance) and the finished product specification (amorphous active substance), hence solid-state is controlled throughout manufacture.
Development of the final commercial dissolution method and evaluation of its discriminatory power against capsule and process attributes that could impact product performance was carried out. The solubility of praseltinib SDD in representative dissolution buffers was determined. The effects of surfactants and sinkers on pralsetinib solubility in the neutral pH range were also studied. To confirm the suitability of the method, three capsule batches representative of the commercial process were tested using the proposed dissolution method. It was observed that very consistent profiles can be obtained using the proposed dissolution parameters. Discriminatory power of the dissolution method was studied Therefore, it is concluded that the proposed commercial dissolution method is discriminatory with respect to meaningful variations in the material attributes and manufacturing process parameters. The dissolution profile utilizing the commercial dissolution method is generally comparable for pralsetinib capsules manufactured throughout the development program.

The primary packaging is high density polyethylene (HDPE) bottle with child-resistant cap (polypropylene) and foiled induction seal liner and desiccant sachet (silica gel). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product manufacturing process comprises the manufacturing of a spray dried dispersion (SDD) intermediate by spray drying the active substance to produce an amorphous drug dispersion, followed by intra-granular blending with excipients, roller compaction, extragranular blending and filling into capsule shell. The process is considered to be a standard manufacturing process.

The design of experiments applied to the spray drying process was focused on the parameters which had the potential to influence the CQAs of the SDD. For the capsule manufacturing process, comprehensive studies to enhance process understanding and evaluate the interplay between multiple unit operations were conducted. However, no design space is claimed for capsule manufacture.

The pralsetinib SDD intermediate and capsule formulation contain commonly used excipients and utilize standard unit operations for the production of solid oral dosage forms, hence validation data for commercial scale is not required in the dossier. The PPQ batches were manufactured in accordance with manufacturing process of the commercial finished product. The PPQ protocols and reports were provided. The process verification will continue throughout the life cycle of the product in accordance with the relevant guidelines.

The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (HPLC, HPLC-UV), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur.), dissolution (Ph. Eur.), water content (KF), active substance physical form (PXRD), and microbial enumeration (Ph. Eur.).

A justification for the omission of microbial testing and disintegration in the finished product release specification has been provided.
Total aerobic microbial count (TAMC), total yeasts and molds count (TYMC) and absence of specified organism (*E. coli*) testing of the finished product has been performed during development. All registration batches placed on ICH stability studies are tested for microbial enumeration at the initial time point(s) and annually thereafter. In addition, low water activity levels observed in the finished product indicate that the amount of water available in the capsules is insufficient to support the growth of a representative microbial population, and therefore the risk of microbial contamination in this non-sterile oral dosage product is extremely low. Based on this evaluation, in accordance with ICH Q6A, microbial enumeration testing will not be part of the commercial release specification but will remain on the shelf life specification.
To date, no degradation products above the identification threshold have been observed in the finished product during clinical release and stability.

Discussion on elemental impurities in line with ICH Q3D has been provided. Potential sources of elemental impurities have been outlined in an overall manner stating excipients, active substance, water, manufacturing equipment and container closure system. A combination of component approach and finished product approach has been used. Five finished product batches, including batches representative of the commercial process and sites proposed, have been screened for one intentionally added element used in the active substance synthesis as well as for ICH Q3D class 1 and 2A elements. Levels were well-below 30% of the permitted daily exposure limit for each element. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity control in the finished product specification.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that there is no risk on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for 6 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Three primary (registration) batches of the SDD intermediate and three supportive SDD batches manufactured with used in clinical trials and registration active substance batches, respectively, were placed under long term (25°C/60% RH) conditions for up 12 months and under accelerated (40°C/75% RH) conditions for up 6 months according to the ICH guidelines. The SDD registration and supportive batches were manufactured at the commercial site using the commercial process and packaged in the commercial container closure system.

Three primary (registration) capsules batches were placed under long term (25°C/60% RH) conditions for up 18 months and accelerated (40°C/75% RH) conditions for up 6 months according to the ICH guidelines. The capsules registration batches were manufactured at the commercial site using the commercial process (Process III) and packaged in commercial container closure system. The capsules registration batches were manufactured with active substance sourced from pralsetinib used in the sites during the clinical development program. Three supporting capsule batches manufactured at the commercial manufacturing site using the commercial process and produced with active substance registration batches (produced at the commercial active substance manufacturing site) were placed on long term (25°C/60% RH) conditions for up 12 months and accelerated (40°C/75% RH) conditions for up 6 months according to the ICH guidelines.

The available data supports a 24-month shelf life for the capsules, 100 mg.

A bracketing design aligned with ICH Q1D was used within the registration stability program in order to assess the stability profile of multiple packaging fill counts.

As supportive stability data, two capsules batches manufactured with commercial Process using 6 month aged SDD were also placed on long term (25°C/60% RH) and accelerated (40°C/75% RH) Sites used during the clinical development program conditions. A 6 month hold time is established for the intermediate pralsetinib SDD in the commercial packaging configuration where the hold time begins from the date active substance is used for SDD manufacturing. This hold time is aligned with the maximum hold time represented in confirmatory capsule stability studies which used 6-month aged SDD. Finished product stability data up to 12 months under long-term condition using 6-month aged SDD show little to no change or variability on stability and supports the assignment of a SDD hold time of 6 months.

This is further supported by the SDD long term and accelerated stability studies, with data available through 12 months under long term storage conditions.

Samples were tested for appearance, assay, degradants, water content, solid form, dissolution, particle size distribution and microbial limit testing. The analytical procedures used are stability indicating. No significant trends or changes in any test attribute of the SDD and the capsules have been observed in the registration and the supporting stability batches throughout the duration of the long term and accelerated conditions.

A preliminary bulk stability study was performed on capsules, 100 mg development batch manufactured at the intended commercial manufacturing site with the intended commercial process. The batch was packaged in the intended bulk packaging and it was stored at ambient warehouse conditions (15°C – 25°C) and tested after 9 months and 12 months of storage. All results for appearance, assay, degradants, dissolution, water content and microbial evaluation were within the proposed commercial specifications following bulk storage for up to 12 months. A confirmatory bulk hold stability of the capsule, 100 mg commercial batch has been initiated. The batch was packaged in accordance with commercial bulk packaging . The bulk storage configuration represents the worst-case scenario, without desiccant bags between the bulk packaging, as is the case for the commercial packaging configuration. Therefore, the available data supports the stability of bulk 100 mg capsule for this 6 months at ambient warehouse conditions (15°C – 25°C).

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed in appearance, active substance solid form, assay, degradation products, or dissolution. The photostability data shows that the capsules are not sensitive to light.

A force degradation study (acidic, basic, hydrogen peroxide) was performed. A development open dish stress study was also performed for SDD and capsules. No significant trends or changes in test attribute for SDD and capsules have been observed.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

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

The active substance exists in multiple solid forms, including the stable forms A, B and C. The different polymorphic forms can be differentiated by XRPD. The choice of pralsetinib monohydrate (Form C) has been adequately justified. The manufacturing process produce consistently form C. Stability data demonstrates that there is no change in the polymorphic form of the active substance during storage. The manufacturing process of the finished product involves complete dissolution of the active

substance during the spray-drying process to obtain an anhydrous amorphous form of the active substance as spray dried dispersion (SDD).At the time of the CHMP opinion, there are two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the submission of the analytical method validation report for specified impurities and the stability-indicating nature of the HPLC method used for identification, assay and impurities . These have been raised as recommendations. In addition, further forced degradation studies under the harsher conditions should be conducted and be presented as part of the relevant variation post approval.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

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

- to submit the method validation report of specified impurities as a Type IB variation (classification B.II.d.1.z) post-approval.

- stability-indicating nature of the HPLC method used for identification, assay and impurities should be demonstrated, additional forced degradation studies under the harsher conditions should be conducted. The applicant will include the results of the additional forced degradation studies as a Type IB variation (classification B.II.d.1.z) post approval.

Non-clinical aspects

2.2.7. Introduction

Gavreto contains pralsetinib (also known as BLU-667, BLU123244, or X581238), an inhibitor of RET kinase and oncogenic RET mutants. The non-clinical efficacy and safety of pralsetinib were characterized through a battery of pharmacology (potency, selectivity, anti-tumour activity, safety), pharmacokinetics (PK) (absorption, distribution, metabolism, excretion, drug interactions and toxicokinetics (TK)) and toxicology studies (single dose toxicity, repeat-dose toxicity, genotoxicity, phototoxicity, local tolerance, impurities, immunotoxicity, ecotoxicity and reproduction toxicity).

2.2.8. Pharmacology

Primary pharmacodynamic studies

In vitro

Binding and inhibition of RET was investigated *in vitro* in purified enzymes assays including wild-type RET, oncogenic RET mutants and fusion kinases, in which pralsetinib was compared to other RET binding chemical entities (Report BPM-0015). Highly potent binding to all types of RET was confirmed for pralsetinib whereas binding of the other multikinase inhibitors, such as cabozantinib, vandetanib, and regorafenib, occurred with varying affinity to RET mutants and fusions Table 2).

Table 2. Biochemical activity of cabozantinib, vandetanib, regorafenib, ponatinib, and pralsetinib against wild-type RET, RET Mutants, and RET fusion proteins

Compound	Mean IC50 (nM)				
	RET	RET V804L	RET V804M	RET M918T	CCDC6-RET
Pralsetinib	0.43	0.33	0.38	0.40	0.45
Cabozantinib	11	45	162	8	34
Vandetanib	4	3597	726	7	20
Regorafenib	12	53	70	25	15
Ponatinib	0.6	4	2	0.8	0.8

Abbreviations: CCDC6 = coiled-coil domain-containing 6; IC50 = half-maximal inhibitory concentration; RET = rearranged during transfection. Source: Report BPM-0015.

To document the selectivity of pralsetinib (at 1 ⌠M) on RET, the applicant investigated binding and inhibition in a panel of over 450 kinases *in vitro*. Measurement of dissociation constant (Kd) demonstrated that pralsetinib exhibited a Kd value < 50 nM for 21 kinases (Reports BLU005-03-s, BLU005-04-p). It was shown that pralsetinib mainly and most potently binds to RET, however, affinity for Janus kinase (JAK)1, JAK2, and tropomyosin receptor kinase C (TRKC) was shown, as Kd values within 10-fold of RET were demonstrated.

A second selectivity study, testing the ability of pralsetinib to inhibit the enzymatic activity across a panel of 374 kinases, demonstrated that pralsetinib (at 0.3 ⌠M) inhibited the activity of 22 kinases over 50% (Report BPM-0022). It was further shown that pralsetinib is a more potent inhibitor of RET than any other kinase tested and only two other kinases are inhibited by pralsetinib with an half-maximal inhibitory concentration (IC_{50}) within 20-fold of RET inhibitory activity, *i.e.,* JAK1 and DDR1.

Pralsetinib was further investigated *in vitro* in relevant cancer cell lines expressing RET to explore potency. Studies were conducted in Ba/F3 cells, LC2/ad cells as well as human MTC TT and MZ-CRC-1 cell lines, expressing KIF5B-RET, CCDC6-RET fusion, RET C634W and RET M918T mutations, respectively. In these investigations, pralsetinib potently inhibited RET autophosphorylation, RET-dependent signalling and RET-dependent cell proliferation (Table 3) (Reports BPM-0016 and BPM-0017). Furthermore, it was shown that proliferation of parental Ba/F3 cells not expressing a KIF5B-RET fusion was poorly inhibited by pralsetinib (IC_{50} = 1873.1 nM), confirming that pralsetinib is selective for cell lines dependent on oncogenic RET.

Table 3. Effects of pralsetinib, cabozantinib, and vandetanib on proliferation of ret-driven cell lines

Compound	Ba/F3-KIF5B-RET IC50 (nM)	Ba/F3-KIF5B-RET (V804L) IC50 (nM)	Ba/F3-KIF5B-RET (V804M) IC50 (nM)	TT (C634W RET) IC50 (nM)	MZ-CRC-1 (M918T RET) IC50 (nM)	LC2/ad (CCDC6-RET) IC50 (nM)
Pralsetinib	16.5	15.3	4.6	15.4	4.2	3.7
Cabozantinib	341.4	3022.6	5582.4	554.9	62.8	328.3
Vandetanib	792.9	9227.6	8360.1	551.7	15.2	45.9

Abbreviations: CCDC6 = coiled-coil domain containing 6; IC_{50} = half-maximal inhibitory concentration; KIF5B = kinesin family member 5B; RET = rearranged during transfection. Source: Reports BPM-0016 and BPM-0017

The activity of pralsetinib against known receptors that are associated with dose-limiting cardiovascular toxicity in humans, *i.e.,* KDR/VEGFR2 and FGFR2, as well as JAK2, was investigated in relevant well-established cell lines (Report BPM-0018). The studies showed that pralsetinib inhibited

these pathways with reduced potency compared to RET inhibition, with a 14-, 40-, and 12-fold more potent binding to RET than KDR/VEGFR2, FGFR2, and JAK2, respectively, confirming the lower potency for other kinases as also shown in the enzyme assays (Table 4). The toxicological effects attributed to KDR/VEGFR, FGFR2 and JAK2 inhibition were investigated further in repeat-dose studies in rats and monkeys (see section 2.3.4 Toxicology).

Table 4. Cellular activity of pralsetinib on RET, KDR/VEGFR2, FGFR2, and JAK2

Assay	Cell Line	Phosphorylation IC50 (nM)
Phospho-RET	Ba/F3-KIF5B-RET	5.0
Phospho-KDR/VEGFR2	HUVEC	70
Phospho-FGFR2	Kato III	201
Phospho-STAT5 (JAK Signalling Pathway)	TF-1	58

Abbreviations: FGFR2 = fibroblast growth factor receptor 2; IC_{50} = half-maximal inhibitory concentration; JAK = Janus kinase; KDR = kinase insert domain receptor; RET = rearranged during transfection; STAT5 = signal transducer and activator of transcription 5; VEGFR2 = vascular endothelial growth factor receptor 2. Source: Reports BPM-0016 and BPM-0018.

In vivo

The capacity of pralsetinib to inhibit tumour growth was investigated in mice, using allografted tumours expressing the KIF5B-RET fusion (Figure 2) and xenografted tumours expressing KIF5B-RET and CCDC6-RET fusions as well as the RET C634W mutation (Figure 3 and Figure 4) (Reports BPM-0019 and CPB-P16-5665, 1110-003, BPM-0020, CPB-P16-5645, E0400-U1608). Tumour control, measured as tumour growth inhibition (TGI) and inhibition of phosphorylation, and tumour regression, was shown to be dose-dependent and was in some cases complete at the highest doses tested. The dose levels tested seemed to be well tolerated with either no effects observed or only minimal non-adverse effects observed on body weight.

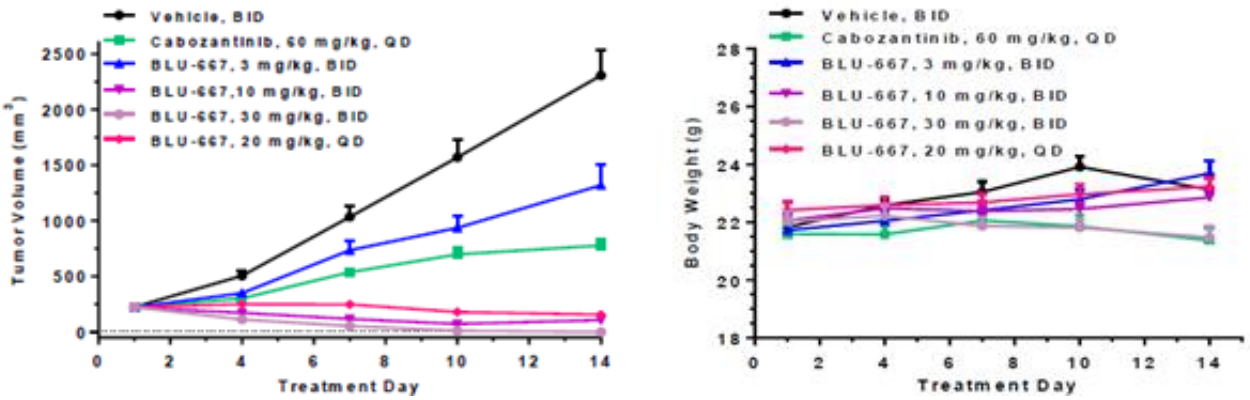

Figure 2. Efficacy and body weight measurements for pralsetinib in the KIF5B-RET driven Ba/F3 allograft model

Abbreviations: BID = twice daily; BLU-667 = pralsetinib; RET = rearranged during transfection; QD = once daily. Source: Report CPB-P16-5665.

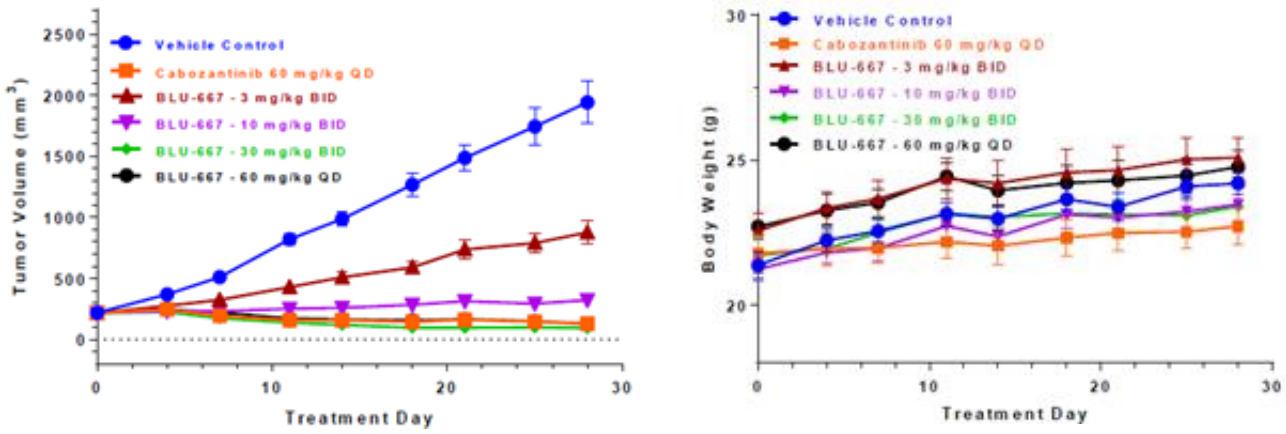

Figure 3. Efficacy and body weight measurements with pralsetinib in a KIF5B-RET non-small cell lung cancer patient-derived xenograft model

Abbreviations: BID = twice daily; BLU-667 = pralsetinib; PDX = patient-derived xenograft; QD = once daily; RET = rearranged during transfection. Source: Report 1110-003.

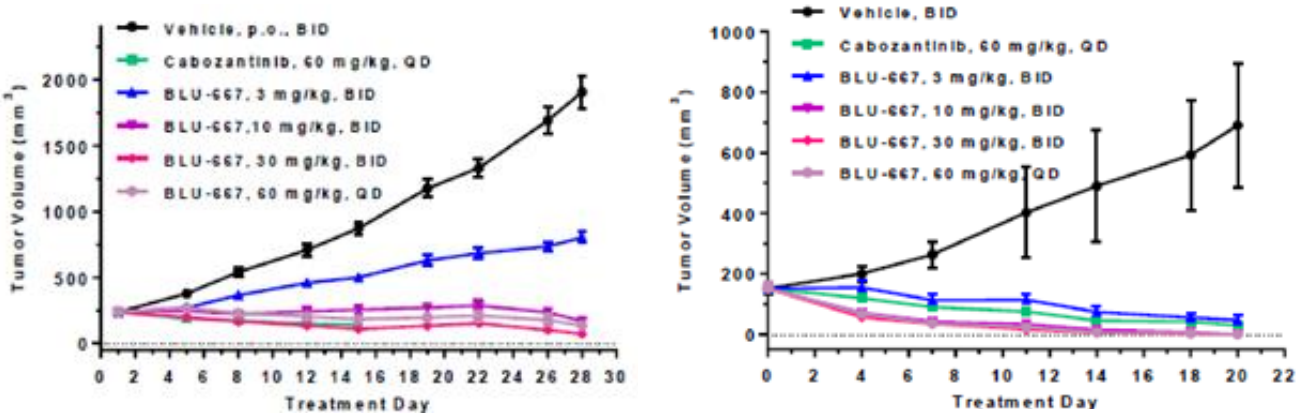

Figure 4. Efficacy with pralsetinib in a medullary thyroid cancer cell line xenograft (left) and a RET fusion positive colorectal cancer patient-derived xenograft (right)

Abbreviations: BID = twice daily; BLU-667 = pralsetinib; CCDC6 = coiled-coil domain-containing 6; PDX = patient-derived xenograft; QD = once daily; RET = rearranged during transfection. Source: Reports CPB-P16-5645 and E0400-U1608.

The anti-tumour activity of pralsetinib on brain metastases was investigated in a Ba/F3-KIF5B-RET-luc brain orthotopic inoculation model (Report CPB-P18-21802). Pralsetinib administered orally with 10 and 30 mg/kg twice daily (BID) resulted in increased survival compared to vehicle control, which points towards an extended activity of pralsetinib on intercranial tumours (Figure 5).

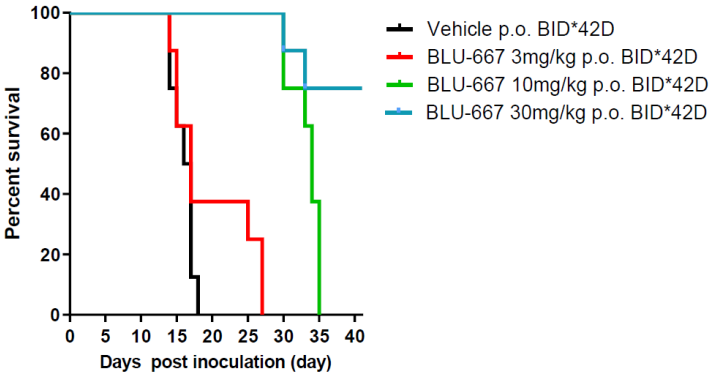

Figure 5. Survival curve for pralsetinib in the Ba/F3-KIF5B-RET-luc brain orthotopic inoculation model

Abbreviations: BID = twice daily; BLU-667 = pralsetinib; p.o. = per os (oral); RET = rearranged during transfection. Source: Report CPB-P18-21802.

These data were confirmed in an xenografted tumour model expressing the CCDC6-RET fusion showing a significant dose-dependent intracranial TGI with no intracranial tumours remaining at the end of the study at the highest dose level (30 mg/kg BID)(Report E0400-U1804)(Figure 6). Distribution studies in rats were performed to further investigate the distribution of unbound pralsetinib from plasma to brain (see section 2.3.3 Pharmacokinetics).

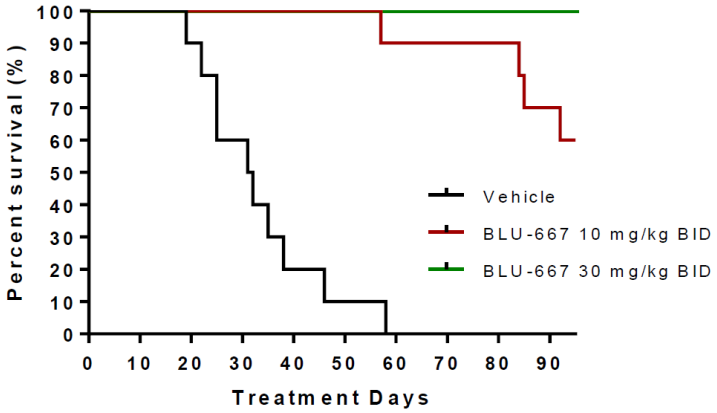

Figure 6. Survival curve for pralsetinib in an intracranially inoculated colorectal cancer patient-derived xenograft model

Abbreviations: BID = twice daily; BLU-667 = pralsetinib; RET = rearranged during transfection. Source: Report E0400-U1804.

To correlate the dose levels at which tumour control was observed to achieved plasma concentrations, a compilation of PK/pharmacodynamic data based on allografted tumour models was presented (Report BPM-0020), showing that the mouse plasma concentration required for 90% inhibition of RET phosphorylation across all experiments was determined to be 769 ng/mL (human maximum plasma concentration at steady state (Cmax,ss) at 400 mg: 2830 ng/ml)(Figure 7).

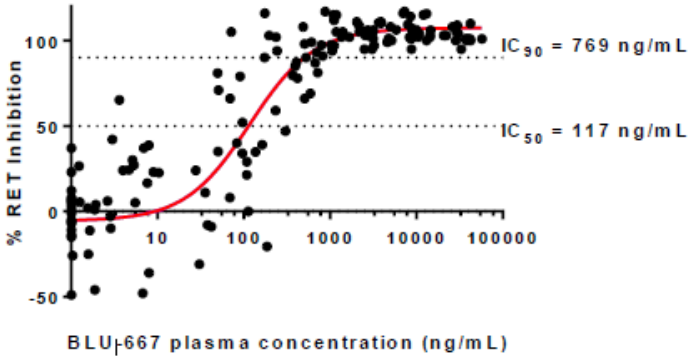

Figure 7. Pharmacokinetic/pharmacodynamic profile of pralsetinib in the Ba/F3-KIF5B-RET and Ba/F3-KIF5B-RET (V804L) allograft models

Abbreviations: RET = rearranged during transfection; BLU-667 = pralsetinib; IC = inhibitory concentration

Secondary pharmacodynamic studies

The selectivity of pralsetinib for binding to other kinases was discussed in the previous section. The potential of pralsetinib to interact with other targets besides kinases, including receptors, transporters and enzymes was investigated *in vitro* and is described in the safety pharmacology section.

Safety pharmacology programme

Potential activity of pralsetinib on the cardiovascular system was investigated in *in vitro* and *in vivo* studies. A non-GLP *in vitro* study investigated the effect of pralsetinib on the hERG channel current in Chinese hamster ovary cells stably transfected with hERG complementary deoxyribonucleic acid (cDNA) and expressing hERG channels, at near-physiological temperature (Report CPB-25-15-010A-0169). The IC_{50} for the inhibitory effect of pralsetinib on hERG potassium current was 5.18 µM (Hill coefficient = 0.92), suggesting a low potential for prolonging the QT interval. This was explored further in repeat-dose studies in monkeys up to 10 mg/kg/day, where electrocardiogram (ECG) measurements have been included (see section 2.3.4 Toxicology).

Cardiovascular effects were furthermore investigated in two separate non-GLP *in vivo* studies in Sprague Dawley rats, where higher systolic, diastolic, and mean blood pressure, with a concomitant decrease in heart rate was observed at a single oral dose of 25, 50, or 200 mg/kg pralsetinib (Report WIL-124581 and WIL-124606). Furthermore, lower body temperature was observed in the 200 mg/kg group. The no-observed-effect-level (NOEL) was 10 mg/kg pralsetinib. No clinical observations were however associated with any of the dose levels tested.

The inhibitory function of pralsetinib on a panel of pharmacological targets including receptors, transporters, and enzymes was investigated in a non-GLP *in vitro* study (Reports 100023499 and 100023915). Pralsetinib was shown to have some inhibitory effect against 5-HT2A and Na+ channel site 2, which have the potential to impact CNS and cardiovascular function. However, in the follow-up functional study, pralsetinib inhibited the 5-HT2A and Na+ channel site 2 with IC_{50} values corresponding to free maximum plasma concentration (Cmax) concentrations about 30-fold above free Cmax concentrations in humans at the recommended therapeutic dose. Furthermore, the inhibitory effects against 5-HT2A or Na+ channel site 2 were also investigated in rat or monkey studies (see section 2.3.4 Toxicology).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted.

2.2.9. Pharmacokinetics

Methods of analysis

Table 5summarizes the validation of the methods to measure pralsetinib in K_2EDTA rat and monkey plasma in support of the GLP pivotal TK studies (Reports BLU-R5992 and BLU-R5954).

No formal validation was performed to support the bioanalytical methods of pralsetinib in mouse and dog plasma, however, standard operating procedures were followed to ensure accuracy of concentration measurements.

Table 5. Summary of analytical method validation for the determination of pralsetinib in rat, and monkey plasma samples from toxicokinetic studies

	Rat Plasma	**Monkey Plasma**
Method	BTM-2134-R0	BTM-2135-R0
Calibration model	Linear weighted $1/x^2$	Linear weighted $1/x^2$
MS/MS interface	TurboIonSpray	TurboIonSpray
Validated dynamic range	5.00 to 2000 ng/mL	5.00 to 2000 ng/mL
Precision (%CV) within-assay	≤ 6.2	≤ 9.4
Precision (%CV) between-assay	≤ 4.6% (7.6% at LLOQ)	≤ 5.3% (11.9% at LLOQ)
Accuracy (%bias)	≤ –9.3% (–8.8% at LLOQ)	≤ –13.3% (–12.4% at LLOQ)
Stability	Stable for at least 18 hours at ambient temperature	Stable for at least 18 hours at ambient temperature
Freeze-thaw stability	At least 3 freeze/thaw cycles at –70ºC and –20 C	At least 3 freeze/thaw cycles at –70ºC and –20 C
Recovery	100.3%	92.5%
Processed extract stability	Stable for at least 123 hours at ambient temperature	Stable for at least 94 hours at ambient temperature
Long-term sample storage stability	93 days at –20ºC and –70ºC	117 days at –20ºC and –70ºC

Abbreviations: %CV= %coefficient of variation; LLOQ= Lower limit of quantitation; MS/MS= tandem mass spectrometry. Source: Reports BLU-R5992, BLU-R5992A2; BLU-R5992A2 LTS and SS, BLU-R5954, BLU-R5954A2, BLU-R5954A2 QC-LTS.

Absorption

The plasma PK properties of pralsetinib upon single-dose administration in non-clinical species are summarized in Table 6.

Table 6. Cross species comparison of single intravenous dose pharmacokinetics and oral bioavailability of pralsetinib

PK Parameter	Rat	Dog	Monkey
CLplasma (mL/min/kg)	14.6 ± 1.6	2.0 ± 0.3	6.5 ± 3.0
Vss (L/kg)	3.3 ± 0.4	0.5 ± 0.1	1.7 ± 0.2
t1/2 (h)	3.5	3.5 ± 0.2	3.7 ± 1.2
Oral F (%)	100	100	100

Abbreviations: CLplasma = plasma clearance; F = bioavailability; PK = pharmacokinetics; t1/2 = apparent terminal elimination half-life; Vss = apparent volume of distribution at steady state. Source: Reports CPB-P15-10033R02, CPB-P15-10082d01, and CPB-P15-10082K01.

The TK of pralsetinib were investigated in rats and monkeys in GLP-compliant 28-day and 13-week repeated-dose toxicology studies (Reports WIL-124570, WIL-124571, 00124768, and 00124770) (Table 7). In rats, a greater than dose proportional increase in exposure was observed after repeat oral dosing while the increase was approximately dose proportional in monkeys, with non-linear kinetics. T½ was consistent across species as well as a complete oral bioavailability (100%).

Accumulation occurred to some extend in rats (2.36 to 2.64 for males and 2.32 to 3.27 for females after repeated dosing for 13 weeks) whereas accumulation was minimal in monkeys. There were no significant gender differences in terms of either Cmax or area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24}) in the pivotal studies. Adequate exposure was achieved in plasma via the proposed clinical route at the intended clinical dose of 400 mg per day.

Table 7. Summary of pralsetinib toxicokinetics in pivotal 28-day and 13-week repeat-dose studies in rats and monkeys

Study ID	Daily Dose (/)	Animal AUC_{0-24} (ng.h/ml)		Cmax ng/mL		T ½	
		♂	♀	♂	♀	♂	♀
Sprague Dawley rats							
WIL-12570 28 day	10	22000	40600	1970	3690	-	-
	20	64300	82100	5120	6680		
	30	125000	101000	7180	9120		
	75*	166000	223000	11100	14500		
00124770 13 week	5	9040	12800	751	1280	-	-
	10	33300	42300	2360	3580	-	-
	20	101000	108000	6570	8420	-	5.01
Cynomolgus monkey							
WIL-124571 28 day	0	NA	NA	NA	NA		
	5/2.5#	9890/4780	15700/6190	1530/703	2390/866		
	15/7.5#	56100/28400	38000/25800	7020/3190	4730/3320		
	40	157000/-	135000/-	10900/-	10700/-		
00124768 13 week	2	4370	5030	485	478	5.84	-
	5	15700	13400	1620	1120	4.19	-
	10	43200	31900	2790	2850	-	-

Abbreviations: AUC0-24 = area under the plasma concentration-time curve from zero to 24 hours; Cmax = maximum plasma concentration; NA = not applicable. *Day 1 AUC values, as the group was terminated early due to mortalities/morbidity, # dose reduction due to unacceptable toxicity in the high dose group, and initial mid dose group. Note: The AUC and Cmax values presented are from the end of the study unless otherwise mentioned.

Distribution

The *in vitro* protein binding of pralsetinib (10 µM) was determined in 100% plasma from mouse, rat, dog, monkey, and human using rapid equilibrium dialysis (Report 1905093). Protein binding of pralsetinib was similar across species and showed a high binding (>95% bound), *i.e.,* 2.45%, 4.2% and 2.9% unbound pralsetinib in rats, monkeys and humans, respectively. The *in vitro* blood partitioning of pralsetinib was studied in fresh blood from mouse, rat, dog, monkey, and human (Report CPB-P15-10118). Blood-to-plasma ratios for pralsetinib were similar across species and distribution was greater in plasma compared with blood.

In vivo studies were conducted to assess the distribution of pralsetinib and its metabolites to blood and tissues using oral gavage administration in rats (Report 00124834). In Sprague Dawley rats, accumulation primarily occurred in excretory organs, *i.e.,* liver and kidney. There was a clear decrease in radioactivity in all tissues over time with no retention in blood or plasma. In Long Evans rats, high levels of radioactivity were detected in the uveal tract and the pigmented skin. [14C]-pralsetinib–derived radioactivity concentrations were still present in the uveal tract at the end of the study, indicating that pralsetinib has an affinity for pigmented tissue. The ophthalmic findings and phototoxic potential of pralsetinib were further investigated in repeat dose toxicity studies in monkeys and rats and two *in vitro* phototoxic investigations (see section 2.3.4 Toxicology).

No distribution of pralsetinib to the brain was observed in the quantitative whole-body autoradiography (QWBA) distribution study in Sprague Dawley rats (Report 00124834). However, a separate microdialysis assay in rats investigating the distribution to the brain and striatal interstitial fluid (ISF) was conducted (Report Key 1598). The sensitivity in the microdialysis assay is higher than for the QWBA study (LLOQ: 2.75 ng/g vs. 781 ng/g) and thus the microdialysis assay is considered to give a more precise indication of the brain penetration in rats. Though the QWBA study showed limited penetration in brain, the microdialysis assay showed a brain penetration of unbound pralsetinib corresponding to a factor of 0.14 from plasma to brain tissue (ISF), indicating that distribution occurs to the rat brain.

Of note, the 90% of maximal inhibition concentration (IC_{90}) of pralsetinib for RET inhibition in human brain ISF is used as indicator for efficacy in treating brain tumour metastases in the clinical trials. The predicted total plasma concentration in rats required to achieve a corresponding IC_{90} of pralsetinib for RET inhibition in human brain ISF is 1514 ng/ml, and with mean steady state maximum and trough plasma concentrations of pralsetinib dosed at 400 mg once daily (QD) in NSCLC patients at 2830 and 1150 ng/mL, respectively, the concentrations are near or above the systemic concentration predicted to achieve brain IC_{90} of pralsetinib for RET inhibition.

Placental transfer and excretion in milk has not been investigated.

Metabolism

In vitro, pralsetinib undergoes limited to moderate metabolism in humans, rats, mice, monkeys and dogs in microsomes and hepatocytes (Reports CPB-P15-10033, 150604, 150521). A total of 18 metabolites of pralsetinib derived from oxidation, defluorination, glucuronidation, and GSH conjugation were identified (Report BLU-R9667). Direct N-glucuronide conjugation was the major metabolic pathway of pralsetinib in *in vitro* incubations in human hepatocytes, oxidation and glutathione conjugation were less frequent. In monkeys, moderate metabolism occurs, though at a lower level than in human hepatocytes, whereas limited metabolism occurs in the other non-clinical species. No human specific metabolites were detected *in vitro*. *In vivo* metabolism studies in rats and monkeys are included in the section on excretion below.

Excretion

In vivo, it was shown that the metabolites are primarily excreted via bile in bile duct cannulated rats, both after oral and IV administration, and via faeces after a single oral dose in monkeys, and that limited excretion occurs via urine (≤ 5%) (Reports BLU-R5482AM1, BLU-R9705). In rats, pralsetinib is primarily excreted as oxidative metabolites or as GSH and glucuronide conjugates via the bile. In faeces, unchanged [14C]-pralsetinib was the most significant drug-related component in both rats and monkeys with a few metabolites derived from oxidation, cysteine conjugation, and glucuronidation conjugation also being observed. This supports the *in vitro* observation of limited metabolism occurring for pralsetinib.

Pharmacokinetic drug interactions

A study was conducted to assess the potential of pralsetinib to inhibit cytochrome P450 (CYP450) catalytic activity *in vitro* in human liver microsomes (Report 1812081). Pralsetinib showed concentration-dependent inhibition of CYP2C8 (via mixed inhibition), CYP2C9 (via competitive inhibition), CYP2C19 and CYP2D6, as well as concentration- and time-dependent inhibition of CYP3A4/5 (via competitive inhibition). Pralsetinib was furthermore shown to induce mRNA levels and enzyme activity of CYP1A2, CYP2B6, CYP3A4, CYP2C8 and CYP2C9 in a concentration-dependent manner in primary cultures of human hepatocytes (Reports 1811301, 1910112) and exhibited limited concentration-dependent activation of human pregnane X receptor (PXR) in an *in vitro* assay (Report CYP0915-R10b).

In vitro data indicate that pralsetinib is mainly catalysed by CYP3A4 with minor contribution of CYP1A2 and CYP2D6 (Report BLU-R9696). Moreover, *in vitro* studies with recombinant UGT showed that UGT1A4 was the major enzyme responsible for the formation of the N-glucuronide of pralsetinib. UGT1A1 and UGT1A3 were also capable of forming pralsetinib N-glucuronide, but only at low levels (Report BLU-R5500).

Moreover, *in vitro* studies showed that pralsetinib is a substrate for human P-glycoprotein (P-gp) and Breast cancer resistance protein (BCRP) and may at the same time have the potential for drug interactions with substrates of the following transporters: P-gp, OATP1B3, MATE1, MATE2K, BCRP, OATP1B1, (OAT1, OAT3, and BSEP to a limited degree) (Report 19BLUPP1R1).

Other pharmacokinetic studies

The PK profile of pralsetinib formulated as capsules and a spray dried dispersion was investigated in cynomolgus monkeys either with or without pre-treatment with the proton pump inhibitor famotidine (Report WIL-124618). Only minor non-significant differences were observed between the two formulations and pre-treatment with famotidine did not influence the PK profile.

2.2.10. Toxicology

A general toxicity study program was performed, with rats, Beagle dogs and cynomolgus monkeys. The rat and cynomolgus monkey were used in GLP-compliant 28-days and 13-week repeat dose toxicity studies, which were preceded by 7 days non-GLP studies as well as single dose studies in both species. Furthermore, a few dose range studies were performed in order to discern any differences between different batches and vehicles (single dose studies) used. An enhanced embryofoetal development (EFD) study (GLP compliant) in rats was performed in order to discern any possible reprotoxic effect. No carcinogenicity studies were performed.

Single dose toxicity

The major findings of the single dose oral gavage toxicity studies in rats, dogs and monkeys are summarized in Table 8In rats, doses of up to 300 mg/kg were tolerated, whereas in the dog and monkey, severe clinical signs resulting in euthanasia or death were observed at 75 mg/kg and 300 mg/kg respectively. Multiple dark red areas on the surface of the small and large intestines (mucosal epithelium erosion and ulceration) were observed in dead animals after a single dose of pralsetinib (300 mg/kg monkeys).

Table 8. Summary table of the single dose toxicity studies

Study design	Observed max non-lethal dose	Major findings
WIL-124550 (Non-GLP) Sprague Dawley rat - 3M 10[a], 100[a], 300[a] or 300[b] mg/kg Oral gavage	300 mg/kg	No clinical signs noted up to 48 hours post dosing
WIL-124557 (Non-GLP) Beagle dog - 3M (4M) 5[b], 25[b], 25[c], 75[b] mg/kg/day (25[b] mg/kg (plus 6 µg/kg pentagastrin [IM] pre-treatment)) Oral gavage	25 mg/kg	Mortality 3/3 at 75 mg/kg; emesis, salivation and/or diarrhoea at ≥ 25 mg/kg without pentagastrin pre-treatment; soft faeces and emesis at 25 mg/kg with pentagastrin pre-treatment; decreased defecation at 5 mg/kg.
WIL-124569 (Non-GLP) Cynomolgus monkey - 3M 10[d], 30[d], 300[d] mg/kg Oral, via nasogastric tube	30 mg/kg	Mortality 1/3 at 300 mg/kg, pale body and pale facial area noted in all animals.
WIL-124591 (Non-GLP) Cynomolgus monkey - 3M 30[d] mg/kg Oral, via nasogastric tube	30 mg/kg	Swollen abdominal area noted; no other findings.

[a] (10% HS15 in 20% BP-β-CD/ NA); [b] vehicle 1 (CMC-Na: 1% Tween 80 in dH2O/ NA); [c] vehicle c (50% Labrasol in dH2O/ NA); [d] (CMC-Na: 1% Tween 80 in citrate buffer/ NA)

Repeat dose toxicity

The major findings of the repeat dose toxicity studies in rats, dogs and monkeys are summarized in Table 9. In the repeat dose studies of 28 days and 13 weeks duration, the following were recorded: clinical observations, detailed physical examinations, body weight measurements, food consumption measurements, ophthalmic evaluations, serum chemistry, haematology and coagulation assessments, complete necropsy, organ weight determinations, histopathologic evaluation, and TK. In the cynomolgus monkey studies, ECG recordings were also performed, but no functional effects on the cardiovascular system were noted based on ECG analyses and in-life examinations.

Table 9. Summary table of the repeat dose toxicity studies

Study design	NOEL/ NOAEL	Major findings
Sprague Dawley rat		
WIL-124551 (Non-GLP) 6 M Oral gavage	15 mg/kg/day AUC_{0-24} 17100 h*ng/mL	**200 mg/kg/day:** Early death/moribundity **≥50 mg/kg/day:** Clinical findings and lower BW and food consumption, lower liver

0, 15, 50 and 200 mg/kg/day Duration: 7 days	Cmax 1930 ng/mL	weights, histological changes in multiple tissues **≥15 mg/kg/day:** Clinical pathologies, lower spleen and thymus weights
WIL-124592 (Non-GLP) 6 F Oral gavage 15 and 50 mg/kg/day Duration: 7 days	50 mg/kg/day	Well tolerated at all dose levels with no significant clinical observations noted in the treatment groups.
WIL-124570 (GLP) Main study 10 M/F Recovery 5 M/F TK animals 3 M/F 9 M/F Oral gavage 0, 10, 20, 30, 75 mg/kg/day Duration: 28 days	STD_{10} 30 mg/kg/day AUC_{0-24} (M/F) 125000/101000 h*ng/mL Cmax (M/F) 7180/9120 ng/mL	**75 mg/kg/day:** Mortality/moribundity (38% M, 42% F). Euthanasia of remaining animals on Day 8/9 due to severe BW loss, lower food consumption. Clinical signs: dermal atonia, unkempt appearance, scabbing on the forelimb(s) Histopathology: mineralization of multiple organs, decreased cellularity of multiple haematopoietic and lymphoid organs, and haemorrhage, inflammation and/or necrosis in multiple organs, increased physeal thickness in the sternum, decreased lymphoid cellularity in the Peyer's patch, and necrosis in the pancreas **≥30 mg/kg/day:** Clinical signs: flailing upon handling, vocalization upon handling, thin body condition, body that was cool to the touch, pale extremities, swollen abdominal area, laboured respiration, exophthalmus of the right eye, red material around eye(s) and/or nose, scabbing on the facial area, and/or yellow material on the urogenital area **≥20 mg/kg/day:** Lower BW gain (M), lower mean BW (M). Histopathology: increased physeal thickness in the femur, incisor and odontogenic degeneration, odontogenic vacuolation, and odontoblast necrosis in the teeth **≥10 mg/kg/day:** Decreased bone marrow cellularity, mineralization of the glandular stomach Haematology: decreased mean RBC, HB, HT and RETIC Clinical pathology: Increased ALT, AST, SDH, Cholesterol, TRIG, urea nitrogen, creatinine, Ca, K, decreased albumin and protein Note: The off-target, non-severely toxic pharmacologic effects (i.e., thickened physeal cartilage (femur), hyperphosphatemia with corresponding mineralization in the glandular stomach, incisor tooth degeneration and decreased bone marrow cellularity with corresponding lower erythrocyte parameters) were either resolving or resolved after the 14-day recovery period with the exception of incisor tooth degeneration.

00124770 (GLP) Main study 10 M/F Recovery 5 M/F TK animals 3 M/F 9 M/F Oral gavage 0, 5, 10, 20 mg/kg/day Duration: 13 weeks	10 mg/kg/day AUC_{0-24} (M/F) 33300/42300 h*ng/mL Cmax (M/F) 2360/3580 ng/mL	**20 mg/kg/day:** Clinical signs: hunched posture and/or thin, broken teeth (F and 1 M), lower BW gain, lower mean BW, lower food consumption Serum chemistry: increased urea nitrogen Macroscopic and microscopic findings: teeth (dentin matrix alteration, ameloblast degeneration, odontoblast degeneration, and odontoblast necrosis), tooth fractures, decreased lymphoid cellularity in the thymus, tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which corresponded with lower mean testis and epididymis weights, gross observations of soft and small testis, degeneration of the corpus luteum in the ovary. **≥10 mg/kg/day:** Lower mean BW (M) Haematology: Lower RBC, RETIC (M), higher MCV, MCH Serum chemistry: increased ALP, ALAT, ASAT, cholesterol and phosphorous, K (F), decreased albumin (F), TP (F) and A/G ratio (F) Macroscopic and microscopic findings: minimal odontoblast degeneration (M), minimal to mild tubular degeneration/atrophy in the testis with secondary cellular debris in the lumen of the epididymis, minimal degeneration of the corpus luteum **≥5 mg/kg/day:** Haematology: lower WBC, lymphocyte, eosinophil and basophil counts, lower RETIC (F), higher PLT Macroscopic and microscopic findings: minimal decreased haematopoiesis
Beagle dog		
WIL-124558 (Non-GLP) 3 M Oral gavage 0, 3, 10, 30 mg/kg/day Duration: 7 days	3 mg/kg/day AUC_{0-24} 24500 h*ng/mL Cmax 2600 ng/mL	**30 mg/kg/day:** Moribundity, BW loss (9.1% on Day 3), decreased food consumption Histology: acute microscopic haemorrhage in lungs **≥10 mg/kg/day:** Histology: GALT necrosis and depletion
Cynomolgus monkey		
WIL-124572 (Non-GLP) 3 M Oral gavage (nasogastric) 0, 10, 30, 150/75 mg/kg/day Duration: 7 days	10 mg/kg/day AUC_{0-24} 42700 h*ng/mL Cmax 4570 ng/mL	**150/75 mg/kg/day:** Mortality/moribundity 3/3 animals Macroscopic findings: dark red discoloration and/or areas along the surface of the stomach, duodenum, jejunum, ileum, cecum, and colon **≥30 mg/kg/day:** Moribundity 1/3 at 30 mg/kg Clinical signs: hunched posture, hypoactivity, partial closure of eyes, diarrhoea, pale gums, ataxia, prostration, pale/cool body and/or extremities, shallow respiration, decreased respiration rate, piloerection. tremors (mild), red nasal discharge, red/brown material on various body surfaces, dermal atonia. Cause of death: GI toxicity, with secondary bacterial sepsis

		Haematology: decreases in absolute RETIC, absolute neutrophils and absolute monocytes, higher mean ALAT, ASAT, phosphorus, CK, LDH Macroscopic findings: small spleen, decreased organ weight: absolute thymus weight and absolute spleen weight. Microscopic findings: gastrointestinal tract, axillary and mandibular lymph nodes, bone marrow, thymus, spleen, GALT and mesenteric lymph node, and lung
WIL-124571 (GLP) 5 M/F Nasogastric gavage 0, 5/2.5, 15/7.5, 40 mg/kg/day Dose reduction on Day 4 (F) and 5 (M) due to severe toxicity in the high dose groups, Group 3 animals had a 2-day dosing holiday before dosing with 7.5 mg started on Day 6 (F) and 7 (M) Duration: 28 days	NOAEL 5/2.5 mg/kg/day AUC_{0-24} (M/F) 4780/6190 h*ng/mL Cmax (M/F) 703/866 ng/mL HNSTD 7.5 mg/kg/day AUC_{0-24} (M/F) 28400/25800 h*ng/mL Cmax (M/F) 3190/3320 ng/mL	**40 mg/kg/day:** Mortality 3 M and 4 F, early termination on Day 5 (M) and 4 (F) Clinical signs: diarrhoea, red material in faeces, ataxia, hunched posture, cool and/or pale extremities and/or body, hypoactivity, prostrate, dermal atonia, and decreased respiration rate, BW loss Clinical pathology: increased prothrombin and activated partial thromboplastin times, ALAT, ASAT, cholesterol and phosphorous, creatinine and urea nitrogen. Decreased serum calcium, TP, albumin, globulin, Cl, Na Macroscopic findings: red/dark red areas of the stomach and red/dark red areas and/or raised areas of the small and large intestines, small spleen, and/or small thymus Cause of death/morbidity: (9/10 animals) bacterial sepsis secondary to gastrointestinal inflammation Microscopic findings: foci of neutrophilic inflammation often containing bacterial colonies in the lymph nodes, spleen, and/or salivary gland, as well as reduced cellularity of sternal bone marrow. **15 mg/kg/day:** Mortality 1 M (bacterial sepsis secondary to colonic intussusception and skin and GI lesions). Clinical signs observed for this animal: cool and pale extremities, hypoactivity, shallow respiration, partial closure of both eyes, prostrate, open wound on left hindlimb, and red material on hindlimbs and anogenital area. 9% BW loss. Macroscopic findings: intussusception of the colon, dark red areas of the stomach and duodenum, raised areas in the jejunum, cecum, and colon, small thymus, and mass in the subcutis of the urogenital region Microscopic findings: ulcerative/erosive inflammation often with intralesional bacterial colonies and gas formation in the skin, subcutis, oesophagus, and intestines. intusseption confirmed. **15/7.5 mg/kg/day:** Clinical signs: (most observations related to a single F) hunched posture, decreased defecation, thin body condition, dermal atonia, emesis containing food or clear, white, yellow, or red material, salivation, clear material around mouth, reddened facial area, and/or red material on forelimb(s), increased activated partial thromboplastin times (M), increased absolute neutrophils, higher total WBC (M) Decreased globulins, TP (F), Ca, Increased urine specific gravity, decreased total urine volume (correlated to dehydration/decreased water consumption (M)

		Microscopic findings: reduced lymphoid cellularity of the thymus (F), reduced cellularity of the sternal bone marrow, physeal dysplasia of the femur (M) After recovery period: Minimally decreased lymphoid cellularity of the thymus (1 F), everything else had recovered. **≥2.5/5 mg/kg/day:** Increased ALAT and ASAT Microscopic findings: Lower thymus weight (F)
00124768 (GLP) 4 M/F Oral gavage 0, 2, 5, 10 mg/kg/day Duration: 13 weeks	10 mg/kg/day AUC_{0-24} (M/F) 43200/31900 h*ng/mL Cmax (M/F) 2790/2850 ng/mL	**10 mg/kg/day:** Lower RBC, HB, HT, MCV (M); Higher RETIC (M), PLT (M), RCDW (F) Organ weight; lower thymus weight (F, Absolute and relative to body and brain weight) Microscopy: minimal to mild decreased lymphoid cellularity **5 mg/kg/day:** Lower HB (F)

Abbreviations: ALAT= alanine transferase, ASAT= aspartate transferase, BW= body weight, Ca= calcium, HB= haemoglobin, HT= haematocrit, K= potassium, LDH= lactate dehydrogenase, MCV= mean cell volume, PLT= platelet count, RBC= red blood cell count, RETIC= reticulocyte count, RCDW= red cell distribution width, SD= Sprague Dawley, WBC= white blood cell count.

Secondary Pharmacology Leading to Toxicity Observed in Rats and Monkeys

Overall, the adverse effects observed in repeated-dose studies using rats and monkeys were consistent with off-target pharmacological effects of pralsetinib, or the sequelae thereof.

The following adverse effects were attributed to the pharmacologic effect of VEGFR2 (also known as KDR) inhibition:

- Primary vascular effects on the physeal cartilage in the femur in rats and monkeys and on the teeth in rats (Chen and Cleck, 2009; Fletcher *et al*, 2010; Patyna *et al*, 2008). Physeal dysplasia is a lesion often encountered secondary to impairment of VEGF-dependent angiogenesis. Incisor degeneration has been previously described after VEGF and FGFR tyrosine kinase inhibition;
- Gastrointestinal lesions in monkeys. Altered gut barrier is a known sequela of VEGF pathway inhibition in non-clinical toxicity species and in humans (Chen and Cleck, 2009);
- Degeneration of the corpus luteum in the ovary in rats. The development of the corpus luteum depends on proliferation of blood vessels within the theca interna (Fraser, 2006) and treatment with VEGFR inhibitors is known to result in reduced ovarian weight and decreased number of corpora lutea in animals (Patyna *et al*, 2008; Wedge *et al*, 2005).

The following adverse effects were attributed to the pharmacologic effect of FGFR signalling inhibition:

- Primary tissue mineralization effects in rats. This has been observed with other investigational compounds (Brown *et al*, 2005; Yanochko *et al*, 2013) where soft tissue mineralization was associated with FGFR inhibition due to its physiologic role of suppressing 1,25-dihydroxy-vitamin D3-mediated phosphate absorption from the gut.

The following adverse effects were attributed to the pharmacologic effect of JAK2 inhibition:

- Primary cellular effects on the bone marrow and erythron parameters in rats and monkeys due to the reliance upon JAK2 for erythropoietin signalling (Broxmeyer, 2013; Parganas *et al*, 1998; Quelle *et al*, 1994; Springuel *et al*, 2015).

The following adverse effects were attributed to stress response rather than to pralsetinib-related off-target effects:

- Decreased cellularity of lymphoid organs corresponding with changes in the hemogram, notably decreased lymphocytes with increased neutrophils and monocytes in rats (Everds et al, 2013).

Interspecies comparison

The observed toxicities in the 28-day repeat dose toxicity study in monkeys, are seen at exposures similar or slightly above clinical exposure levels (*e.g.,* from 15 mg/kg/day). The high dose level of 10 mg/kg/day in the 13-week study is also considered to be the no-observed-adverse-effect-level (NOAEL), and the area under the plasma concentration vs time curve (AUC) on Day 91 is 43200 and 31900 h*ng/mL. In the rodent studies the NOAEL is at exposures similar or below clinically relevant exposures. Severe toxicity and mortality were observed at exposure multiples of 3 to 5-fold the clinically relevant exposure (following the maximum recommended dose of 400 mg/day) (Table 10).

Table 10. Comparison of animal and human/clinical exposure

Study ID	**Daily Dose (/)**	**Animal AUC (ng.h/ml)**		**Animal:Human Exposure Multiple**	
		♂	♀	♂	♀

Sprague Dawley rats					
WIL-12570 28 day	10 20 30 75*	22000 64300 125000 166000	40600 82100 101000 223000	0.5 1.5 2.8 3.8	0. 9 1.9 2.3 5.1
00124770 13 week	5 **10** 20	9040 **33300** 101000	12800 **42300** 108000	0.2 **0.8** 2.3	0.3 **1.0** 2.5
Cynomolgus monkey					
WIL-124571 28 day	5/2.5# 15/7.5# 40	9890/4780 56100/28400 157000/-	15700/6190 38000/25800 135000/-	0.2/0.1 1.3/0.6 3.6/-	0.4/0.1 0.9/0.6 3.1
00124768 13 week	2 5 **10**	4370 15700 **43200**	5030 13400 **31900**	0.1 0.4 **1.0**	0.1 0.3 **0.7**

Clinical AUC 0-tau,ss 43900 h*ng/ml(Study 1101), at a dose of 400 mg/day

*Day 1 AUC values, as the group was terminated early due to mortalities/morbidity, # dose reduction due to unacceptable toxicity at the high dose level, and initial mid dose level (15 mg/kg/day).

Genotoxicity

Conventional studies of genotoxicity (Ames test in Salmonella strains TA1537, TA98, TA100, TA1535 and *E. coli* WP2 *uvrA* (study WIL-124573), micronucleus assay in TK6 Cells (study 00124797) and bone marrow micronucleus assay following oral administration to rats (study 00124769)) were conducted with pralsetinib.

A weak positive signal was detected in the *in vitro* micronucleus test in TK6 cells, however, the %increase observed was within historical control ranges, and only 2 to 3-fold the concurrent control. The positive control (vinblastine sulfate) showed a 21-fold increase in the same trial (trial 1, 27 hours incubation, without S9). In a repeated trial, the pralsetinib treated groups did not show any increase compared to concurrent control, whereas mitomycin treated group, was increased 27-fold compared to concurrent negative control. Therefore, pralsetinib is considered negative for genotoxicity in the tested ranges.

Carcinogenicity

No carcinogenicity studies were conducted with pralsetinib.

Reproduction Toxicity

In a fertility and early embryonic development study in rats, males were dosed for 28 days prior to mating and continuing through 1 day prior to euthanasia. Females were dosed for 14 days prior to mating and continuing through Gestation Day 7. No test article-related findings were noted on male or female reproduction (mating, fertility, and pregnancy indices), oestrous cyclicity, or spermatogenesis at the tested doses of 5, 10 and 20 mg/kg /day orally. However, post-implantation loss was observed at doses as low as 5 mg/kg (approximately 0.3 times the human exposure (AUC) at the clinical dose of 400 mg based on toxicokinetic data from the 13-week rat toxicology study). At the 20 mg/kg dose level (approximately 2.5 times the human exposure) 82% of female rats had totally resorbed litters, with 92% post-implantation loss (early resorptions). A dosage level of 10 mg/kg/day was considered the NOAEL for early embryonic toxicity.

Moreover, adverse effects were observed in the GLP-compliant 13-week repeat dose toxicity study with respect to reproductive organs in rats (Report 00124770). At 20 mg/kg/day the following was observed in males: tubular degeneration/ atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis which corresponded with lower mean testis and epididymis weights, respectively, and gross observations of soft and small testis, and in females: degeneration of the corpus luteum in the ovary. No adverse findings were observed with respect to the reproductive tissues in the 28-day studies in Sprague Dawley rats and cynomolgus monkeys (Reports WIL-124570 and WIL-124571, respectively) nor in the 13-week study in cynomolgus monkeys (Report 00124768).

A GLP-compliant embryofoetal development (EFD), extended dose range study was performed in Sprague Dawley rats (Report 00124766). The following parameters and endpoints were evaluated in this study: clinical signs, body weights, body weight gains, gravid uterine weights, food consumption, TK parameters, gross necropsy, intrauterine growth and survival, and foetal morphology (internal, external, and skeletal findings). It was not possible to establish a NOAEL for reproductive toxicity, as multiple malformations were observed in both visceral (kidney and ureter) and skeletal (vertebral rib, costal cartilage and vertebral central anomalies) tissues at dose levels of 5 and or 10 mg/kg/day as well as reduced ossification of ribs. These dose levels were below the maternal NOAEL dose level of 30 mg/kg/day (corresponding to 180 mg/m2/day and AUC_{0-24} was 90,600 ng*h/mL and the Cmax was 8700 ng/mL). All females in dose groups of 20 or 30 mg/kg/day had 100% post implantation loss (all early resorptions), and similarly in the 10 mg/kg/day group an increased number of post-implantation loss and a resulting lower mean litter proportion of viable foetuses were observed. Therefore, pralsetinib is considered a teratogenic drug, at exposures below levels causing maternal toxicity. Dose levels causing reproductive toxicity are also below human exposure levels.

No prenatal and postnatal development studies, and juvenile animal studies were conducted with pralsetinib.

Local Tolerance

Local tolerance of pralsetinib in the gastrointestinal tract of Sprague Dawley rats and cynomolgus monkeys has been characterized in the GLP-compliant 28-day and 13-week toxicology studies (Reports WIL-124570, WIL-124571, 00124770, and 00124768). In both rats and monkeys, GI complications were observed at the high dose levels. In cynomolgus monkeys, doses of 15 and 40mg/kg/day caused gastrointestinal epithelial erosion and ulceration (related to VEGFR inhibition), which was also deemed to be cause of death. In rats, 28 days of pralsetinib treatment with 30 mg/kg/day was associated with tissue mineralization within the glandular stomach mucosa. This was attributed to FGFR inhibition-mediated hyperphosphatemia. Following 13-week treatment in rats, 5 mg/kg/day were associated with observations of mineralization within the glandular stomach mucosa.

No changes were observed in oropharyngeal/oesophageal tissues that was deemed pralsetinib related in neither rat nor monkey.

Other toxicity studies

Immunotoxicity

Although no dedicated immunotoxicity studies were conducted with pralsetinib, some of the toxicological findings reported in repeat-dose toxicity studies were related to its actions on immune system (*i.e.,* decreased cellularity of multiple haematopoietic and lymphoid organs in rats, and bone marrow cellularity and decreased cellularity of lymphoid organs in monkeys).

Impurities

In silico and *in vitro* assessment of a number of impurities were performed (see section 2.2 Quality aspects). Two non-clinical GLP compliant 14-day repeat dose studies were performed in rats, in order to qualify impurities 1 and 2 (Study No 00124746), BLU136228 and BLU136229 (Study No 00124665). No additional toxicities were observed in the two studies.

Phototoxicity

Two neutral red uptake phototoxicity assays were performed to evaluate the phototoxic potential of pralsetinib: one in BALB/c 3T3 mouse fibroblasts (Study No 20143108, GLP) and one in 3T3 fibroblasts (Study No WIL-124562, non-GLP). Pralsetinib was found to be negative for phototoxicity in both studies.

2.2.11. Ecotoxicity/environmental risk assessment

A phase I estimation of exposure as well as Persistence, Bioaccumulation and Toxicity (PBT) screening resulted in the log Kow below the trigger value of 4.5, and the Predicted Environmental Concentration surfacewater (PEC surfacewater) below the action limit of 0.01 µg/L. Therefore, no definitive PBT assessment, nor any further ERA studies were performed or proposed to be performed.

Table 11. Summary of main study results

Substance (INN/Invented Name): Pralsetinib			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	EC A.8 OECD 107 OPPTS 830.7550	log Pow at pH 5 : 3.0 log Pow at pH 7 : 4.0 log Pow at pH 9 : 3.9	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, default or refined (*e.g.* prevalence, literature)	0.0031	g/L	> 0.01 threshold (N)
Other concerns (*e.g.* chemical class)			(N)

2.2.12. Discussion on non-clinical aspects

Pharmacology

The non-clinical development has been conducted in line with ICH guidelines M3 (R2) (Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals) and S9 (Non-clinical evaluation for anticancer pharmaceuticals). Pralsetinib is indicated as monotherapy for the treatment of adult patients with RET fusion-positive advanced NSCLC and is administered as a repeat dose.

The potency and selectivity of pralsetinib were evaluated *in vitro* using biochemical and cellular signalling assays and the anti-tumour activity of pralsetinib was evaluated *in vitro* and *in vivo* in mouse tumour allograft and xenograft models. The potency and dosing regimens were compared to already marketed RET inhibitors, where it was shown that pralsetinib elicited a superior inhibition and selectivity of RET kinases *in vivo*. From a non-clinical point of view, exposure-response (E-R) relationship appears to be justified. *In vitro* and *in vivo* proof of concept is considered well established.

The activity of pralsetinib against known receptors that are associated with dose-limiting cardiovascular toxicity in humans, *i.e.,* KDR/VEGFR2 and FGFR2, as well as JAK2, was investigated in relevant cell lines. Although pralsetinib inhibited other kinases with reduced potency compared to RET inhibition, toxicological effects attributed to KDR/VEGFR, FGFR and JAK2 inhibition were observed in the repeat-dose studies in rats and monkeys at low exposure margins. Furthermore, in an *in vitro* investigation, pralsetinib was shown to have some inhibitory effect against 5-HT2A and Na+ channel site 2, however, the observed inhibition was considered be of limited clinical relevance at the recommended therapeutic dose.

According to the ICH S9 guideline, in the absence of specific concerns regarding safety pharmacology (*i.e.,* cardiac, respiratory or CNS effects) in patients, safety pharmacological studies are not required to support marketing authorisation of products within the scope of ICH S9. Based on the available non-GLP *in vitro* data and general toxicology studies in monkeys and rats, a low risk for cardiac effects is identified. Of note, According to ICH S7B, rats and mice are not appropriate species to investigate cardiovascular effects, as the ionic mechanisms of repolarization in these species differ from larger species, *i.e.,* humans. However, as rats were not used to investigate QT prolongation, the use of the rat species to investigate cardiovascular effects *in vivo* in this study is acceptable. Data from receptor binding assays against a panel of pharmacological targets including receptors, transporters and enzymes, as well as the follow-up biochemical assays suggest low risk of off-target CNS or respiratory effects for pralsetinib at clinically relevant doses. This is also supported by general toxicity studies in rats and monkeys where no adverse findings related to CNS or respiration were observed. Furthermore, clinical data from the ongoing ARROW trial does not suggest an increased risk associated with cardiac effects, CNS or respiratory disorders (see section 2.6 Clinical safety).

Pharmacokinetics

The PK (absorption, distribution, metabolism, excretion (ADME)) of pralsetinib were evaluated in non-clinical species used for pharmacology and safety testing of pralsetinib (rat and monkey). The PK after both single and repeat dosing appear well described in rats, where a nonlinear and greater than dose proportional relationship was observed with signs of accumulation. In monkeys, the increase in exposure was approximately dose proportional with limited signs of accumulation. Oral bioavailability was complete in both species (100%).

Distribution was evaluated in adult rats, however, in line with ICH S9 distribution in pregnant and nursing rats was not described. Potential accumulation was observed in pigmented tissue, specifically in the eye and uveal tract, where pralsetinib was still measured in significant amounts at the end of the study. However, no relevant effects were observed in repeat-dose toxicity studies or in an *in vitro* phototoxicity study. Therefore, this finding does not give rise to toxicological concern.

A rat microdialysis assay showed a brain penetration of unbound pralsetinib corresponding to a factor of 0.14 from plasma to brain tissue (ISF). This indicates that distribution occurs to the rat brain. Data from the study supports the use of pralsetinib to treat brain tumour metastases in NSCLC patients.

Toxicology

Toxicology was investigated sufficiently in rats and cynomolgus monkey. The dog was also investigated as a non-rodent species, but due to species specific toxicities, related to p38 MAPK inhibition, and exacerbated toxicities following this inhibition, the dog was not suitable for further toxicity studies beyond single dose or 7 days repeat-dose studies. The pivotal toxicity studies were conducted in compliance with GLP guidelines.

In studies of up to 13 weeks duration in rats and cynomolgus monkeys, the primary findings at exposures similar to steady state human exposures (AUC) at 400 mg once daily in patients with advanced NSCLC included physeal dysplasia in the rat (2 times margin) and haematological effects (1 times margin) in both species. Additional adverse findings at higher exposures include degenerative changes in male and female reproductive organs (2 times margin) and increases in blood phosphorus with corresponding mineralization in soft tissues in rats (≥2 times margin), and myocardial haemorrhage in rats (4.4 times margin). Increased blood pressure was observed in rats after a single dose of 25 mg/kg (2 times). The No-Observed-Adverse-Effect-Level (NOAEL) of pralsetinib in the 13-week studies was 10 mg/kg/day in both species, corresponding to exposure (AUC) margins of 1 times relative to the human exposures. Regarding local exposure and toxicity, there was no evidence of gastrointestinal disturbance in either species up to the NOAEL dose of 10 mg/kg (0.9 times human margin). At higher doses in monkeys, gastrointestinal ulcerations and haemorrhage were observed.

Some of the observed toxicities can be attributed by to off-target pharmacological actions of pralsetinib, such as KDR (VEGFR2), FGFR and JAK2. Severe toxicities were observed in the 28-day studies at exposure levels slightly above or up to 5-fold the clinical exposure following maximum recommended daily dose of 400 mg. The SmPC section 5.3 reflects the findings from the repeat-dose toxicity studies.

With respect to reproductive toxicity studies, a fertility and early embryonic development study and an extended dose range EFD study were performed in rats. No pralsetinib-related findings were noted on male or female reproduction, oestrous cyclicity or spermatogenesis at the tested doses of 5, 10 and 20 mg/kg /day orally in the fertility and early embryonic study. However, based on lower intrauterine survival, a dosage level of 10 mg/kg/day was considered to be the NOAEL for early embryonic toxicity. Fertility parameters were not included in the repeat-dose studies, but histological evaluation of reproductive organs in rats, in the 13-week study, showed reproduction toxicity for both sexes. In the EFD study, multiple visceral and skeletal malformations were observed, as well as developmental variation, even from the lowest dose level of 5 mg/kg/day. 100% post implantation loss was seen at 20 mg/kg/day and above. The maternal NOAEL was considered to be 30 mg/kg/day, hence the reprotoxic effects of pralsetinib were seen below doses causing maternal toxicity.

Pralsetinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay and was negative in both in vitro human lymphocyte chromosome aberration assay and in vivo rat bone marrow micronucleus tests. Consistent with ICH guideline S9, the following non-clinical studies were not conducted: carcinogenicity studies, a confirmatory embryofoetal toxicity study in a second species, studies on pre/postnatal development, studies in juvenile animals, and immunotoxicity studies.

The findings from the toxicity studies are briefly presented in the SmPC.

2.2.13. Conclusion on the non-clinical aspects

An adequate program of *in vitro* and *in vivo* pharmacology was conducted, supporting the intended clinical use of pralsetinib. Non-clinical proof of concept as an inhibitor of rearranged during transfection (RET) kinase and oncogenic RET mutants appear well-established.

The pharmacokinetics of pralsetinib are well described.

Toxicology was investigated sufficiently in rats and cynomolgus monkeys. The toxicities observed were linked to secondary pharmacology, *e.g.,* inhibition of JAK2, VEGFR2 and FGFR signalling. Severe toxicities were observed at exposure levels slightly above or up to 5-fold the clinical exposure following maximum recommended daily dose of 400 mg.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 12. Overview of studies contributing clinical pharmacology data

Study Identifier Status	Study Objective	Study Design	Subjects (No. (M/F) Type Age: Mean [Range])	Treatments (Dose, Dosage Form) [Product ID]	Route	Pralsetinib Formulation	Data Included in PopPK Analysis
Pharmacokinetics, Pharmacodynamics, and Exposure-response in Patients with NSCLC							
BLU-667-1101 *Phase 1*: complete *Phase 2*: ongoing; enrolment open	*Phase 1 (dose escalation)*: Maximum tolerated dose, recommended Phase 2 dose, PK, and safety of pralsetinib *Phase 2 (expansion [registration-enabling])*: Efficacy, safety, PK, and pharmaco-dynamics of pralsetinib	Phase 1/2, open-label, 2-part first-in-human study	404 patients with RET-fusion NSCLC, thyroid cancer, or other RET-altered solid tumours (227M/177F) 58.1 years [18 - 87 years]	*Phase 1*: Escalation from 30 to 600 mg QD (BID: 100/100 mg, 200/100 mg)[a], *Phase 2*: 400 mg QD	Oral, fasted (2 h)	10, 30, or 100 mg HPMC capsules	Yes
Mass-balance in Healthy Subjects							
BLU-667-0103 Complete	ADME and mass-balance of pralsetinib	Open-label	6 healthy subjects (6M/0F) 30.3 years [23 - 40 years]	Pralsetinib ~310 mg (~100 µCi) single dose: 3 × 100 mg capsules 1 × ~10	Oral, fasted (10 h)	100 mg HPMC capsules + ~10 mg (~100 µCi) [^{14}C]pralsetinib	No

				mg capsule containing (100 µCi [^{14}C]pralsetinib		in capsule	
Pharmacokinetics in Healthy Subjects							
BLU-667-0102 Complete	Bioequivalence, comparing four 100 mg tablets with four 100 mg capsules of pralsetinib	Open-label, randomized, 2-period crossover	90 healthy subjects (63M/27F) 42.1 years [19 - 55 years]	Pralsetinib 400 mg single dose: 4 × 100 mg tablets 4 × 100 mg capsules	Oral, fasted (10 h)	100 mg tablet (20AZ0802.HQ0 0001) 100 mg HPMC capsule (18J03G)	Yes (capsule arm only)
Effect of Extrinsic Factors in Healthy Subjects							
BLU-667-0101 Complete	Food effect, compare PK of pralsetinib with or without food (standardized high-fat, high-calorie meal)	Open-label, randomized, 2-period crossover	20 healthy subjects (13M/7F) 39.4 years [22 - 51 years]	Pralsetinib 200 mg single dose: 2 × 100 mg capsules	Oral, fed or fasted (10 h)	100 mg HPMC capsule (18E07G)	Yes (fasted arm only)
BLU-667-0104 Complete	Drug-drug interaction, effect of coadministered itraconazole or rifampin on PK of pralsetinib	Open-label, 2-part, fixed-sequence, 2-period	Part 1: 25 healthy subjects (19M/6F) 40.8 years [22 - 55 years] Part 2: 25 healthy subjects (20M/5F) 39.6 years [21 - 54 years]	Part 1: Pralsetinib single dose: 2 × 100 mg capsules ± itraconazole 200 mg BID on Day 1, 200 mg QD on Days 2-14 Part 2: Pralsetinib single dose: 4 × 100 mg capsules ± rifampin 600 mg QD on Days 1-16	Oral, fasted (10 h)	100 mg HPMC capsule (19C24G)	Yes (pralsetinib only arm)
BLU-667-0105 Complete	Drug-drug interaction, effect of esomeprazole and gastric pH alteration on PK of pralsetinib	Open-label, fixed-sequence, 2-period	36 healthy subjects (31M/5F) 35.6 years [19 - 54 years]	Pralsetinib single dose: 4 × 100 mg capsules ± esomeprazole 40 mg QD on Days 1-6	Oral, fasted (10 h)	100 mg HPMC capsule (19C24G)	Yes (pralsetinib only arm)

Abbreviations: ADME= Absorption, distribution, metabolism, excretion; BID= twice daily; CSR= Clinical study report; E-R= exposure-response; F= female, HPMC= hydroxypropyl methylcellulose; ID= identification; M=male; MTD= maximum tolerated dose; No.= number; NSCLC= non-small cell lung cancer; PopPK= population pharmacokinetics; PK= pharmacokinetic(s); QD= once daily; RET= rearranged during transfection. Note: [a] The BID dosing regime was not explored further, and a recommended phase 2 dose for BID dosing was not defined.

The clinical pharmacology of pralsetinib was studied in the ongoing phase I/II efficacy and safety study in patients with RET-fusion NSCLC, thyroid cancer, and other RET-altered solid tumours (BLU-667-1101; only data from patients with NSCLC were included in the PK analyses for the current submission), and in five Phase I clinical pharmacology studies in healthy subjects. An overview of these studies is available in Table 12

2.3.2. Pharmacokinetics

Bioanalysis and models

A liquid chromatography/tandem mass spectrometry (LC-MS/MS) bioanalytical method was submitted for the determination of pralsetinib concentration in support of all the clinical studies. The bioanalytical method was validated successfully. The PK of pralsetinib were described by noncompartmental analyses and/or by population PK (Pop PK) analysis. The Exposure-Response (E-R) relations were investigated by means of graphical analysis and time-dependent models using Pop PK derived exposure metrics and selected measures of efficacy and safety.

Population PK model

The Pop PK of pralsetinib was described by a one-compartment linear model with several absorption transit compartments depending on the capsule manufacturing process. The final dataset for the Pop PK model comprised data from 491 subjects of which, 61% were patients (298: 161 patients with NSCLC and 137 patients with RET-altered thyroid cancer) and 39% (193) healthy volunteers (HV). The Pop PK model accounts for time-dependency or additional covariate effects in long-term use of pralsetinib. Data exclusions due to below the limit of quantification (BLQ) were >10% of total observations. Including BLQ values had minimal impact.

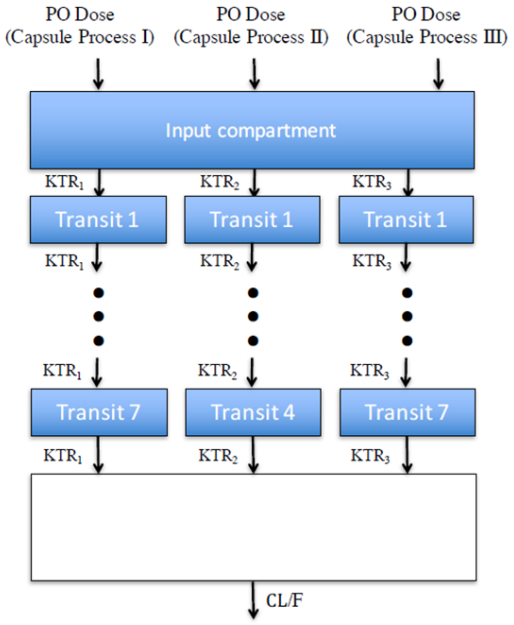

Figure 8. Schematic of the population PK Model

Abbreviations: KTR1= absorption transit rate constant for capsule Process I; KTR2= absorption transit rate constant for capsule Process II; KTR3= absorption transit rate constant for capsule Process III; V/F= apparent volume of distribution; CL/F= apparent oral clearance

The significant covariates included in the final model were Asian race on apparent volume of distribution (V/F), NSCLC patients on oral bioavailability (F), age on apparent oral clearance (CL/F), concomitant CYP3A4 weak inducer use on F, NSCLC patients administered capsule Process I on F, and capsule Process III on the absorption transit rate for HV.

Table 13. Parameter estimates for the final Population PK model

Parameter Name	Estimated Value (95% CI)*
Apparent Clearance (CL/F, L/h)	13.8 (12.9 - 14.7)
Covariate Effect of Age on CL/F	-0.489 (-0.612 - -0.360)
Apparent Volume of Distribution (V/F, L)	395 (373 - 421)
Covariate Effect of Race (Asians) on V/F (Fold)	0.783 (0.669 - 0.894)
Rate of Transit Absorption for Capsule Process I (KTR_1, 1/h)	5.51 (4.95 - 6.13)
Rate of Transit Absorption for Capsule Process II (KTR_2, 1/h)	3.22 (3.03 - 3.41)
Rate of Transit Absorption for Capsule Process III (KTR_3, 1/h)	7.69 (7.12 - 8.23)
Relative Bioavailability for Patients with NSCLC Compared to Healthy Volunteers (Fold)	1.43 (1.25 - 1.60)
Covariate Effect of Capsule Process I on Bioavailability (Fold)†	0.759 (0.667 - 0.858)
Covariate Effect on Weak CYP3A4 Inducers on Bioavailability (Fold)†	0.738 (0.629 - 0.883)
Between Subject Variability for CL/F (% CV)	48 (44.3 - 52.1)
Between Subject Variability for V/F (% CV)	46.9 (43.0 - 51.4)
Correlation between CL/F-V/F	0.742 (0.682 - 0.792)
Between Subject Variability for KTR (%)	34.1 (31.5 - 38.0)
Between Occasion Variability for Bioavailability (%)	35.2 (30.3 - 40.2)
Between Occasion Variability for KTR (%)	26.8 (19.4 - 34.0)
Residual Unexplained Variability for Healthy Volunteers (Proportional) (% CV)	26.5 (25.9 - 27.1)
Residual Unexplained Variability for Study BLU-667-1101 (Proportional) (% CV)	38 (36.4 - 39.6)

*95% CI derived from SIR using 1000 samples with 500 resamples; † F in patients with NSCLC = 1.43 · 0.759 (if Process I) · 0.738 (if CYP3A4 inducer use).

Sample importance resampling using 1000 samples with 500 resamples were used to generate 95% CIs for parameter estimates. None contained the null. The final model was also evaluated by prediction and variance corrected visual predictive checks (pvcVPCs), numerical predictive checks (NPC) and goodness-of-fit (GoF) plots. GoF plots for the final model are shown in Figure 9, Figure 10 and Figure 11.

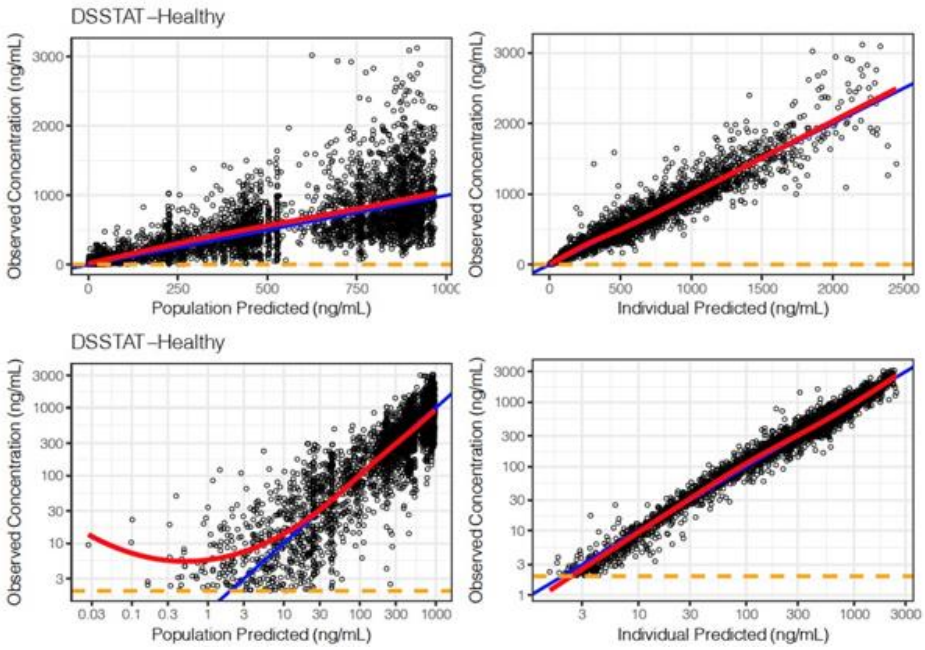

Figure 9. Individual predicted, and population predicted vs. observed concentrations in healthy volunteers

Abbreviations: Healthy= healthy volunteers

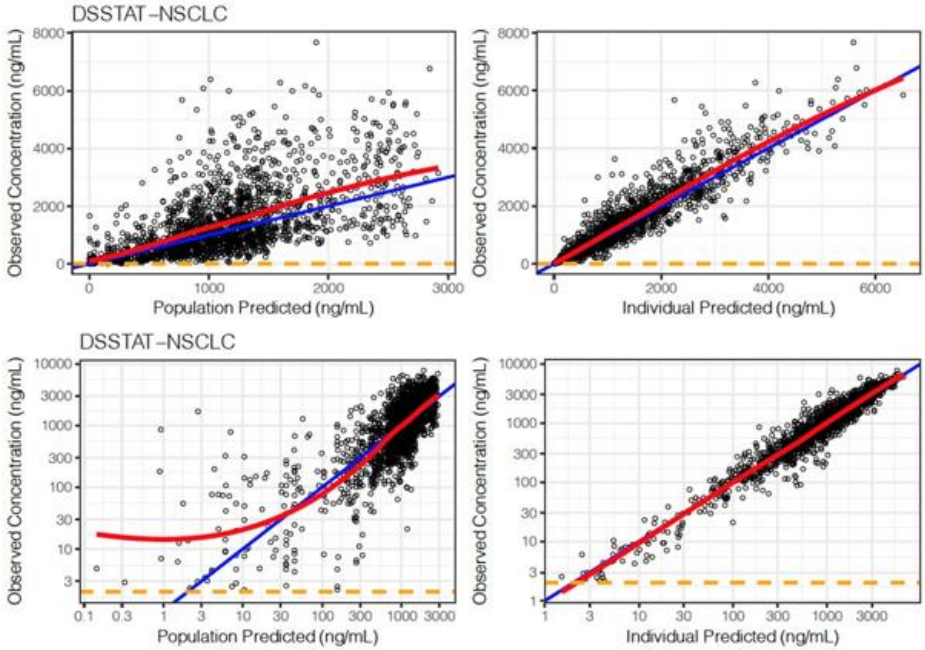

Figure 10. Individual predicted, and population predicted vs. observed concentrations in patients

Abbreviations: NSCLC= non-small cell lung cancer

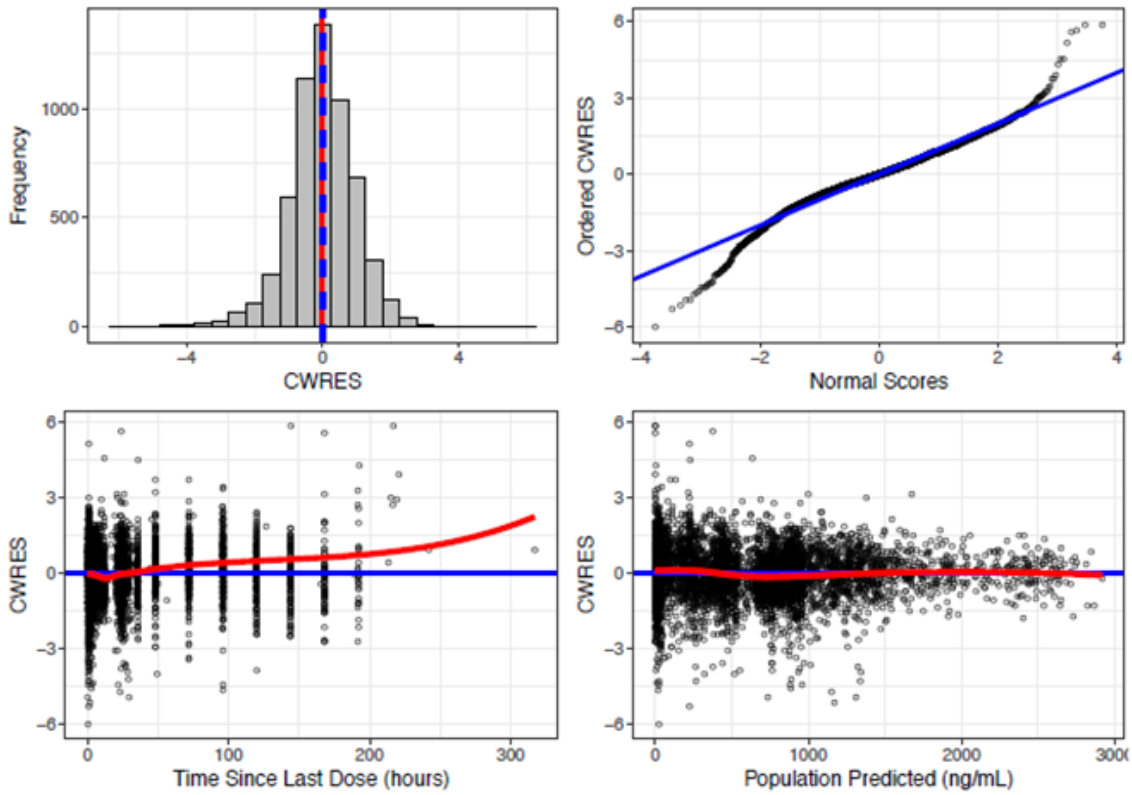

Figure 11. CWRES plots for the final population PK model

Note: The solid blue lines represent the line of identify or zero, the red lines represent the trend in the data (Loess smooth) or the mean.

The pvcVPCs stratified by population showed the model could adequately capture the trend of observations in both HV and patients (Figure 12).

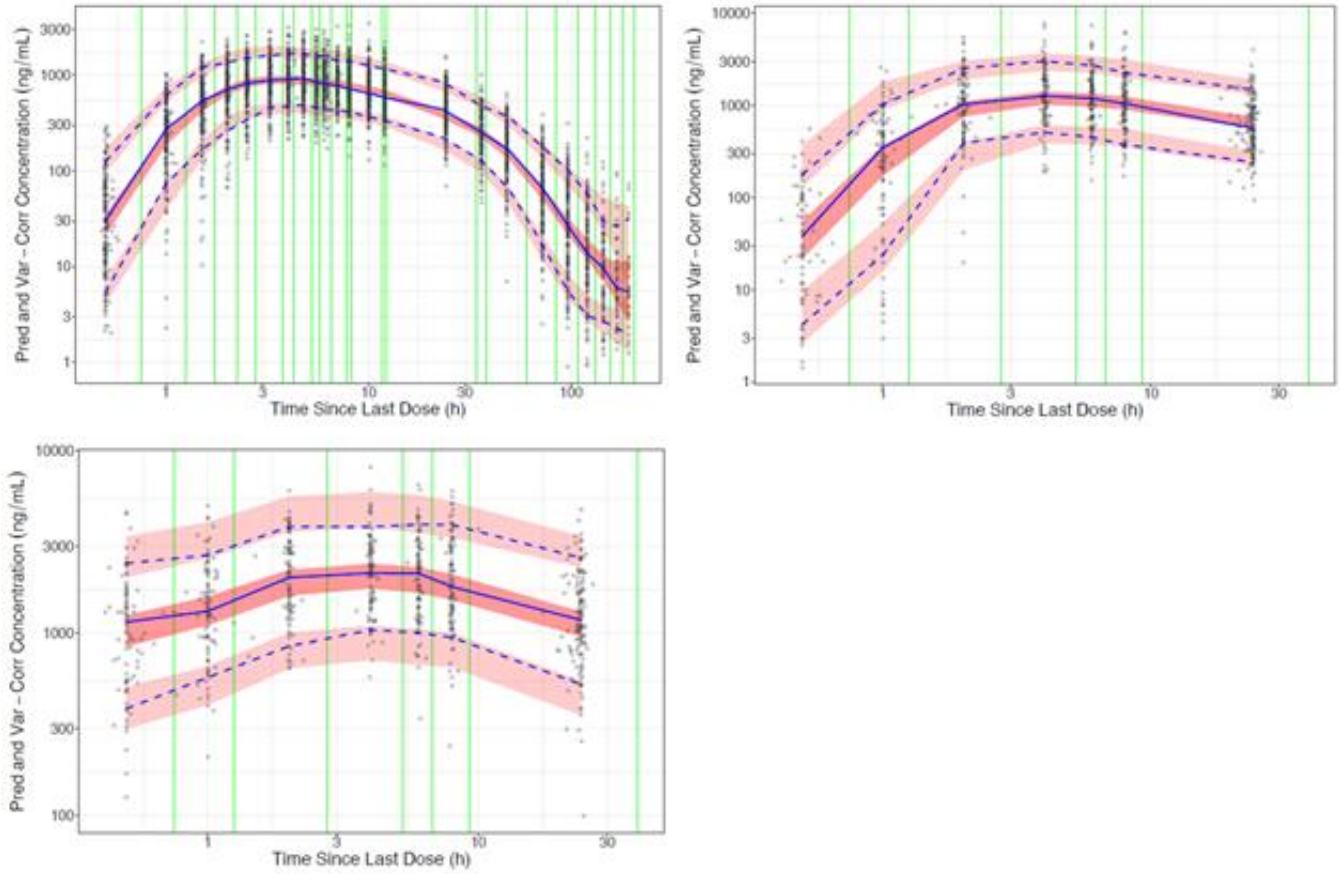

Figure 12. pvcVPC for the final pralsetinib model in healthy volunteers and patients

Upper left pane: Healthy volunteers; Upper right pane: Patients with NSCLC (C1D1); Lower left pane: Patients with NSCLC (C1D5). Note: Open circles= individual observed, dashed blue lines= observed 10th & 90th percentiles of the observed data, solid blue line= observed median concentration, shaded red areas= 95% prediction interval around the model predicted 10th, 50th and 90th percentiles, green lines= bin limits. Log-log scale is used.

Effects of covariates

The impact on pralsetinib exposure metrics of covariates included in the final model were evaluated by means of Forest plots (Figure 13). CYP3A4 Weak Inducer (n=25) and Capsule Process 1 had effects on pralsetinib exposure exceeding the 80-125% range.

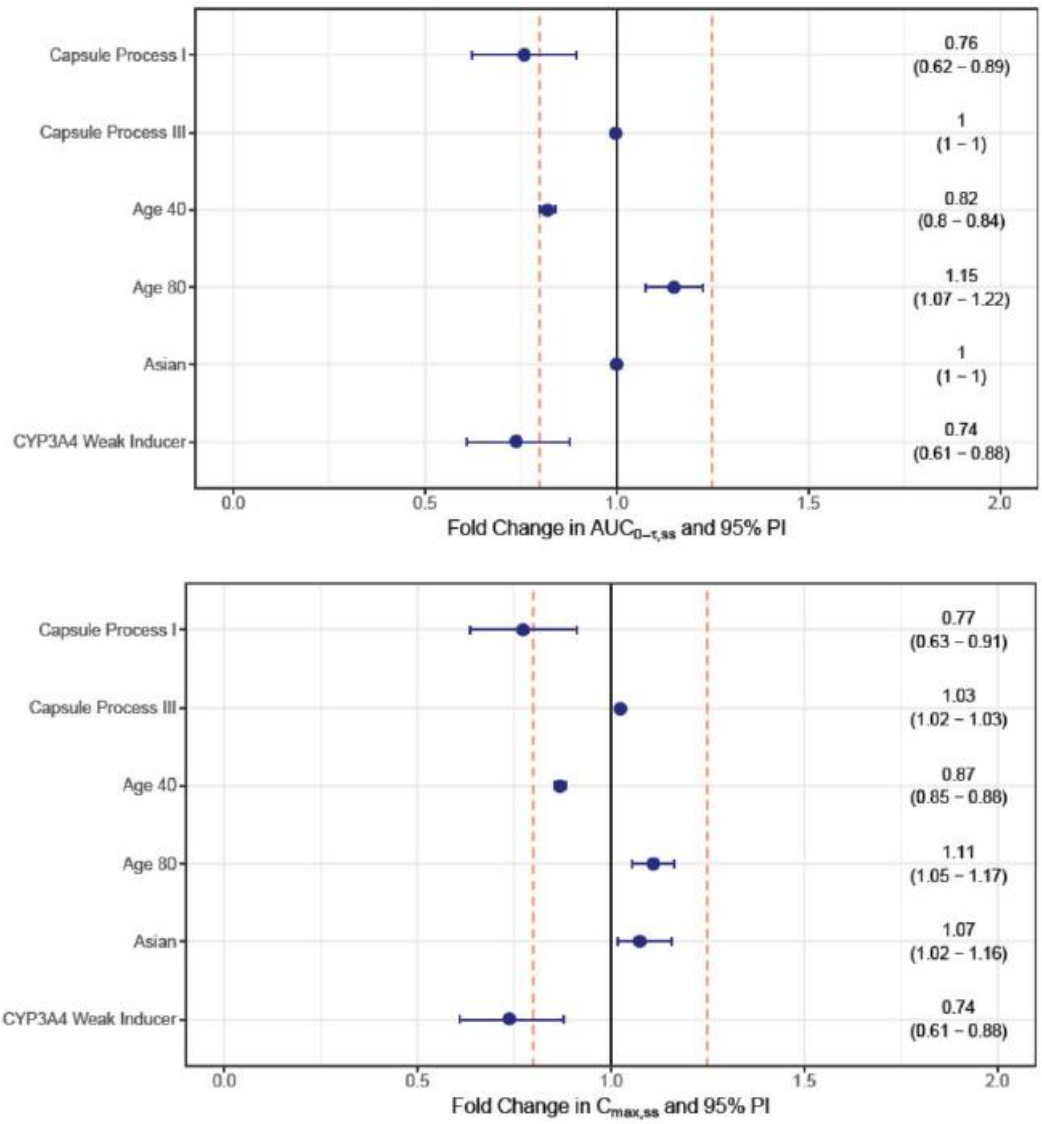

Figure 13. Model-predicted Effect of Covariates on Fold Change in Pralsetinib Exposure

Abbreviations: AUC0-τ,ss = area under the plasma concentration-time curve over the dosing interval (τ) at steady state; Cmax,ss = maximum plasma concentration at steady state; CYP3A4 = cytochrome P450 b3A4; NSCLC = non-small cell lung cancer; PI = prediction interval. Note: The solid black line represents the median of the simulated reference individual, defined as a non-Asian patient with NSCLC who was treated with pralsetinib at a dose of 400 mg QD administered as Process II capsules under fasted conditions, with a population median age of 60 years, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80% to 125% range of the reference individual. The blue dots and error bars represent the median and 95% PI of the covariate effect based on 1000 simulated individuals within each group including uncertainty on the fixed effect. Healthy subjects are not included in the plot.

Source: Population PK Report BLUE201906

The recommended dose of pralsetinib is 400 mg QD. No effects of body size descriptors on exposure were observed. The weight span across patients were 34.9 – 128 kg which represents a 4-times dosing difference in mg/kg. Additional plots of exposure versus weight showed no correlation in healthy volunteers. A slight exposure decrease with increasing body weight was observed in NSCLC patients at C1D1 (process II) (Figure 15). The exposure difference at weight extremes (34.9 – 121.8 kg) were 3x

more pronounced at steady-state (C1D15) than after first dose in the NSCLC population showing a clear relation between weight and pralsetinib exposure at steady-state (Figure 15).

Previously developed population models for pralsetinib in healthy volunteers, patients with NSCLC and patients with RET altered thyroid cancer were combined and evaluated (report BLUE202015). In the combined model, the structure was unchanged from previous models. Effects of body weight were included as a covariate on CL/F and V/F with estimated allometric exponents 0.265 and 0.496, respectively, and median weight 73.5 kg. The effect of race on V/F was removed and the effect on F of use of CYP3A4 inducers replaced with an effect on CL/F. Included were also an age threshold for effect of age on CL/F and an effect of thyroid cancer on KTR (C1D1). The diagnostics indicate the combined model performs well and can adequately capture pralsetinib observations in patients with NSCLC or RET-altered thyroid cancer at C1D1 and C1D15.

The effect of weight is shown in Figure 14 using 40 kg and 100 kg for the 2.5 and 97.5th percentiles (34.9 – 121.8 kg are the weight extremes in NSCLC).

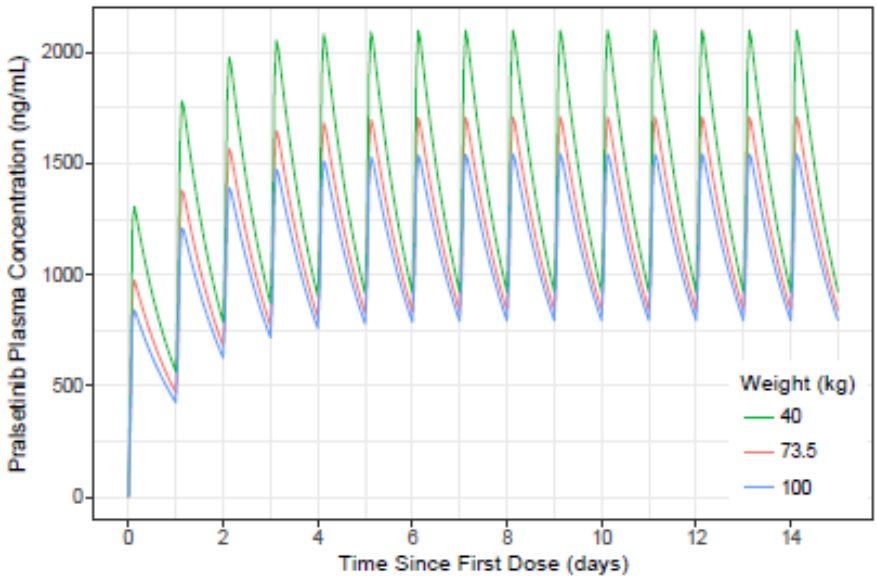

Figure 14. Model predicted effect of body weight on pralsetinib exposure

The plot indicate that low weight patients experience markedly higher Cmax exposures than median weight or obese patients. This can be accepted if there is no increased risk for safety events for this patient subgroup.

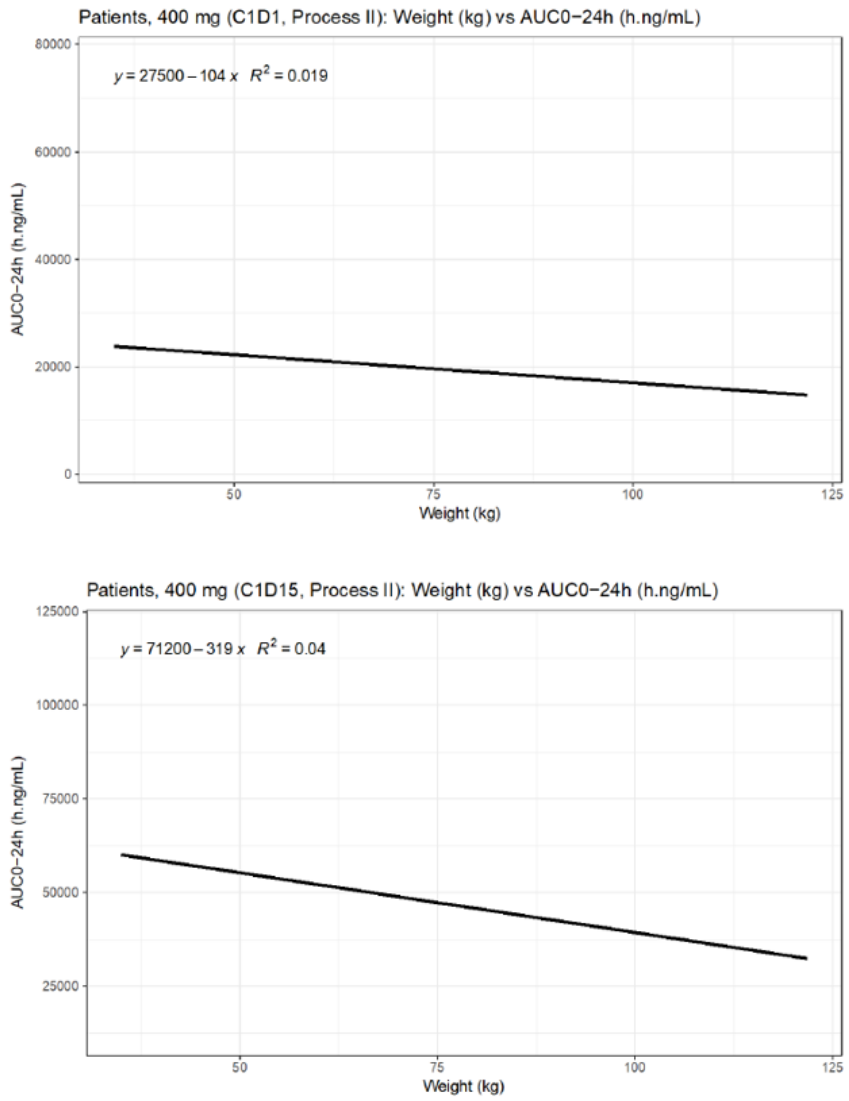

Figure 15. Correlation between body weight and AUC in patients with NSCLC

Abbreviations: AUC= overall exposure; NSCLC= non-small cell lung cancer

PK simulations of brain exposure

A plasma concentration of 769 ng/mL (or unbound concentration of 1.696 ng/mL; fu,p=0.008) was required to achieve 90% inhibition of RET phosphorylation (systemic IC_{90}) in mice (see section 2.3.2 Pharmacology). This translates to 212 ng/mL in human plasma (fu,p=0.029). In rats, a partition coefficient of unbound brain to unbound plasma for pralsetinib was determined by microdialysis to ~0.14 (see section 2.3.3 Pharmacokinetics). Therefore, a systemic concentration of 1514 ng/mL is required in patients to achieve a concentration of 212 ng/mL and thus IC_{90} in the brain. Pop PK simulations in 1000 virtual NSCLC patients (re-sampled from Study 1101) indicated that about 90% and 40% of NSCLC patients would maintain adequate brain exposure based on Cmax and trough plasma concentration (Ctrough), respectively, during the dosing interval of 400 mg QD (Figure 16).

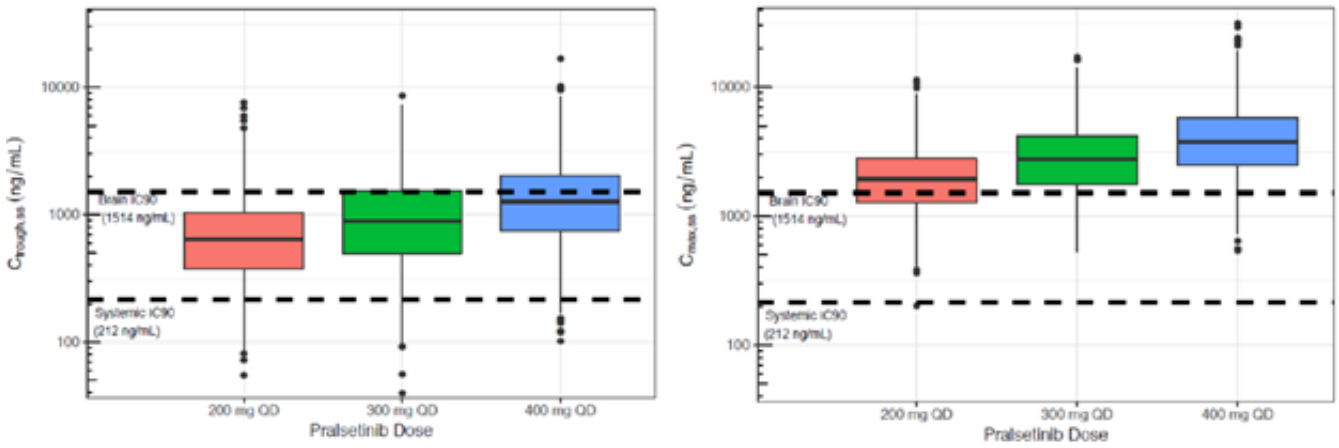

Figure 16. Simulated Plasma Ctrough,ss and Cmax,ss of Pralsetinib in Patients with NSCLC

Abbreviations: Cmax,ss = maximum plasma concentration at steady state; Ctrough,ss = trough plasma concentration at steady state; IC_{90} = 90% of maximal inhibition concentration; NSCLC = non-small cell lung cancer; QD = once daily; RET = rearranged during transfection. Note: The solid lines within each box represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (ie, interquartile range), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * interquartile range of the hinges respectively, and values outside the whiskers are represented with dots. The data are simulated from 1000 patients with NSCLC assuming capsule Process 3, with patient demographics sampled from Study BLU-667-1101 with replacement. The top horizontal dashed line indicates the predicted brain IC_{90} of pralsetinib for RET inhibition in humans (1514 ng/mL), and the bottom horizontal dashed line indicate the predicted plasma IC_{90} of pralsetinib for RET inhibition in humans (212 ng/mL).

Source: Population PK Report BLUE201906.

Exposure-response relationships

The relation between pralsetinib exposure and efficacy measures (PFS and CNS PD) and grade 3+ adverse event (AEs) (pneumonia, anaemia, hypertension and lymphopenia) were evaluated using time-dependent Cox-proportional hazard models. The time-varying exposure was defined as the average exposure in the 28-day period before a safety event or as the average exposure between measures of efficacy. The summary metric, average plasma concentration (C_{ave}), was the primary exposure metric and the hazard was evaluated following an increase in C_{ave} by 400 ng/mL ($C_{ave}400$). The results of the models were concordant with the results presented in the clinical study report.

Absorption

Table 14. Summary of Pralsetinib pharmacokinetics in patients with NSCLC and healthy subjects

Study Identifier (Location)	Pralsetinib Treatment	N	GeoMean (%CV) [a]							
			C_{max} (ng/L)	T_{max} (h)	AUC_{0-24} (h•ng/mL)	AUC_{0-last} (h•ng/mL)	$AUC_{0-\infty}$ (h•ng/mL)	CL/F (L/h)	V_z/F (L)	$t_{1/2}$ (h)
Patients with NSCLC										
BLU-667-1101 (CSR BLU-667-1101)	**Single dose (Cycle 1 Day 1)**									
	60 mg	1	513 (-)	2.00 (2.00 - 2.00)	4280 (-)	4290 (-)	5370 (-)	11.2 (-)	159 (-)	9.89 (-)
	100 mg	3	197 (72.8)	4.03 (2.03 - 6.03)	2240 (-)	2600 (64.6)	3790 (-)	26.4 (-)	608 (-)	19.8 (-)
	200 mg	6	316 (49.5)	3.04 (1.98 - 7.98)	4100 (47.1)	4070 (42.1)	5550 (51.9)	36.0 (51.9)	781 (39.0)	17.7 (12.0)
	300 mg	4	634 (17.2)	1.94 (1.72 - 7.90)	9890 (-)	9360 (17.5)	10900 (-)	27.5 (-)	485 (-)	12.2 (-)
	400 mg	87	1610 (70.4)	4.00 (1.92 - 23.7)	22700 (67.5)	21900 (73.9)	33800 (68.8)	11.8 (68.8)	228 (74.7)	14.7 (6.48)
	600 mg	2	2070 (-)	2.00 (2.00 - 2.00)	64100 (-)	35000 (-)	87800 (-)	6.84 (-)	126 (-)	12.8 (-)
BLU-667-1101 (CSR BLU-667-1101)	**Repeat dose, steady state (Cycle 1 Day 15)**									
	60 mg QD	1	408 (-)	1.97 (1.97 - 1.97)	5310 (-)	5380 (-)	-	11.3 (-)	-	-
	100 mg QD	2	560 (-)	3.98 (3.97 - 4.00)	8400 (-)	8400 (-)	-	11.9 (-)	222 (-)	12.9 (-)
	200 mg QD	6	605 (77.3)	3.97 (2.00 - 4.08)	7010 (108)	7030 (108)	-	28.5 (108)	555 (77.9)	14.9 (5.19)
	300 mg QD	4	1180 (35.8)	3.12 (0.98 - 24.0)	20700 (30.2)	20900 (29.2)	-	14.5 (30.2)	748 (-)	25.8 (-)
	400 mg QD	77	2830 (52.5)	4.00 (0.98 - 22.8)	43900 (60.2)	44400 (57.0)	-	9.10 (60.2)	268 (82.5)	22.2 (13.5)
	600 mg QD	1	4240 (-)	8.00 (8.00 - 8.00)	78700 (-)	79100 (-)	-	7.62 (-)	-	-

Study Identifier (Location)	Pralsetinib Treatment	N	GeoMean (%CV) [a]							
			C_{max} (ng/L)	T_{max} (h)	AUC_{0-24} (h•ng/mL)	AUC_{0-last} (h•ng/mL)	$AUC_{0-\infty}$ (h•ng/mL)	CL/F (L/h)	V_z/F (L)	$t_{1/2}$ (h)
Healthy Subjects										
BLU-667-0101 (CSR BLU-667-0101)	2 × 100 mg capsule, single dose, fed	20	1181 (33.6)	8.501 (4.01 - 24.09)	13530 (41.9)	26590 (29.2)	26680 (29.1)	7.495 (29.1)	140.9 (28.7)	13.179 (2.0004)
	2 × 100 mg capsule, single dose, fasted	20	578.6 (48.8)	4.002 (2.00 - 8.00)	7502 (40.4)	11880 (46.6)	11990 (46.0)	16.67 (46.0)	307.7 (39.5)	13.153 (3.2638)
BLU-667-0102 (CSR BLU-667-0102)	4 × 100 mg tablet, single dose, fasted	90	1782 (38.4)	3.250 (1.00 - 12.00)	26020 (34.3)	49330 (37.5)	49490 (37.6)	8.083 (37.6)	190.7 (36.2)	16.927 (4.91)
	4 × 100 mg capsule, single dose, fasted	87	1048 (49.8)	4.744 (2.00 - 24.03)	14780 (47.1)	28270 (51.7)	28430 (51.9)	14.07 (51.9)	327.6 (46.5)	16.912 (6.38)
BLU-667-0103 (CSR BLU-667-0103)	3 × 100 mg capsule + ~10 mg [^{14}C] capsule, single dose, fasted	6	956.1 (29.4)	4.044 (2.00 - 4.78)	-	22980 (39.6)	23050 (39.4)	13.41 (39.4)	242.9 (46.9)	12.682 (1.96)
BLU-667-0104 (CSR BLU-667-0104)	2 × 100 mg capsule, single dose, fasted (pralsetinib alone)	25	594 (73.4)	2.00 (1.50 - 10.0)	7098 (74.3)	11380 (80.8)	11550 (80.0)	17.3 (80.0)	365 (80.7)	16.1 (9.82)
	4 × 100 mg capsule, single dose, fasted (pralsetinib alone)	25	1168 (52.5)	1.55 (1.49 - 10.0)	16840 (52.5)	31100 (51.6)	31200 (51.4)	12.8 (51.4)	261 (52.7)	14.4 (3.47)
BLU-667-0105 (CSR BLU-667-0105)	4 × 100 mg capsule, single dose, fasted (pralsetinib alone)	36	1001 (44.7)	2.02 (1.50 - 12.0)	15350 (41.4)	27490 (46.7)	27600 (46.6)	14.5 (46.6)	305 (49.2)	15.1 (4.30)

Abbreviations: AUC0-∞ = area under the plasma concentration-time curve from time 0 to infinity; AUC0-24 = area under the plasma concentration-time curve from time 0 to 24 hours post-dose; AUC0-last = area under the plasma concentration-time curve from time 0 to the last measurable concentration above the lower limit of quantitation; CL/F = apparent oral clearance, unadjusted for bioavailability; Cmax = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; N = number of subjects in the pharmacokinetic population; NSCLC = non-small cell lung cancer; QD = once daily; Tmax = time of maximum plasma concentration; t1/2 = apparent elimination half-life; Vz/F = apparent volume of distribution during the terminal phase, unadjusted for bioavailability.

[a] Median (range) for Tmax and arithmetic mean (standard deviation) for t1/2.

Source: NCA PK Report BLUE201904, Table 5, Table 6; CSR BLU-667-0101, Table 11-2; CSR BLU-667-0102, Table 11-2; CSR BLU-667-0103, Table 11-3; CSR BLU-667-0104, Table 11-3, Table 11-6; CSR BLU-667-0105, Table 11-2.

Absolute bioavailability

No absolute bioavailability study in humans was conducted.

Relative bioavailability/Bioequivalence

The median time to peak concentration (Tmax) ranged from 2.0 to 4.0 hours following single doses of pralsetinib 60 mg to 600 mg (0.15 to 1.5 times the recommended dose of 400mg) (Table 14).

Pralsetinib C_{max} and AUC increased inconsistently over the dose range of 60 mg to 600 mg once daily (0.15 to 1.5 times the recommended dose); PK was linear in the dose range of 200 and 400 mg in healthy volunteers. Pralsetinib plasma concentrations reached steady state by 3 to 5 days.

At the recommended dose of 400 mg once daily under fasting conditions, the mean steady state Cmax of pralsetinib was 2830 ng/mL and the mean steady state area under the concentration-time curve (AUC0-24h) was 43900 h•ng/mL. The mean accumulation ratio was ~2-fold after repeated dosing.

The relative bioequivalence studies showed that the exposure was larger for capsules of process II compared with process I, and a non-clinically relevant larger Cmax for capsules of process III compared with process II. In the target population, capsules of process I were used for the dose escalation part of study 1101, whereas capsules of process II were primarily used for the extension part of the study. The majority of the efficacy and safety is based on treatment with capsules of process II. The capsules for marketing are from process III. No clinically relevant differences between exposure of capsule II and III are evident.

Influence of food

In study BLU-667-0101 the effect of food was examined. The study was an open-label, randomized, 2-period crossover study in 20 healthy adults (7 female and 13 male). The objective was to compare the PK of pralsetinib given as a single 200 mg dose when administered with or without a standardized high-fat meal. Blood samples for analysis of pralsetinib in plasma were taken at prespecified time points for up to 192 hours after administration. Following administration of a single dose of 200 mg pralsetinib with a high-fat meal (approximately 800 to 1000 calories with 50 to 60% of calories from fat), the mean (90% CI) Cmax of pralsetinib was increased by 104% (65%, 153%), the mean (90% CI) area under the plasma concentration vs time curve from time 0 to infinity (AUC0-∞) was increased by 122% (96%, 152%), and the median Tmax was delayed from 4 to 8.5 hours, compared to the fasted state (Figure 17, Table 14).

Comparing Cmax and $AUC_{0-\infty}$ after administration of 400 mg pralsetinib from study 1101 (2 hours fasting before and 1 hour after intake of pralsetinib in NSCLC patients) and study 0102, 0104 and 0105 (intake of pralsetinib after an overnight fast in healthy volunteers), Cmax was 38-61% higher and $AUC_{0-\infty}$ was 8-22% higher when fasting was 2 hours compared with administration of pralsetinib after an overnight fast. The difference is considered to be caused by the difference between healthy subjects and NSCLC patients. A simulation-based analysis revealed no clinically relevant changes in exposure when pralsetinib is administered after at least 2 hours of fasting and 1 hour before the next meal and when administered after 10 hours of fasting.

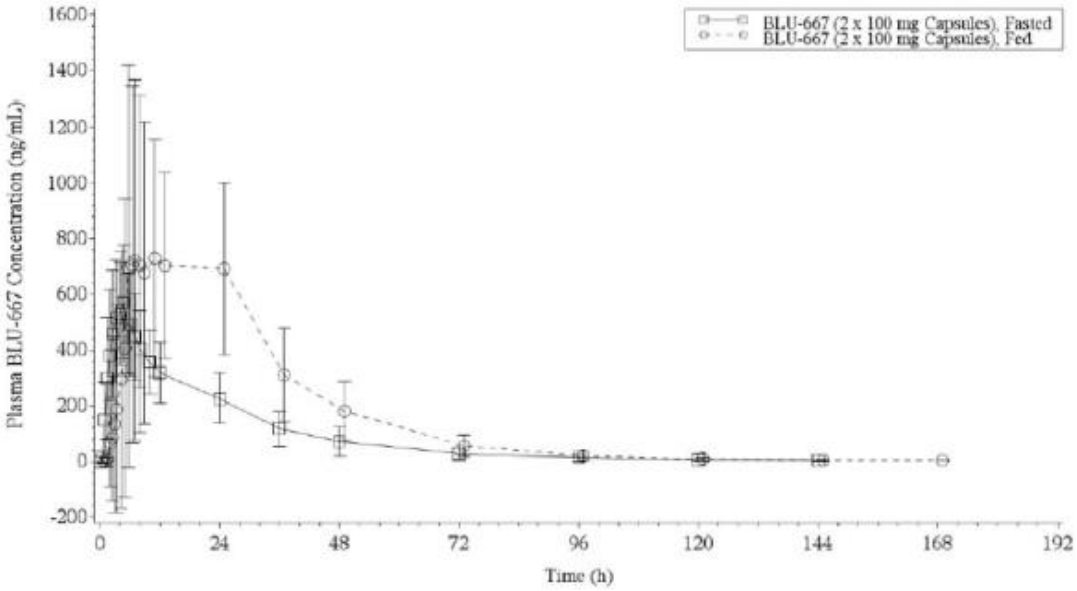

Figure 17. Mean plasma concentration-time profiles after administration of 200mg pralsetinib under fasted and fed conditions

Abbreviations: BLU-667= pralsetinib. Note: The data for fed conditions are offset to the right to enhance clarity.
Source: CSR BLU-667-0101

Distribution

In patients with NSCLC treated with pralsetinib at a dose of 400 mg, the volume of distribution was 228 L after single dose and 268 L at steady state indicating that pralsetinib was extensively distributed to tissue. The geometric mean apparent volume of distribution during the terminal phase, unadjusted for bioavailability (Vz/F) was similar in patients with NSCLC and healthy subjects. In the clinical mass-balance study in healthy subjects, the blood-to-plasma ratio was 0.6-0.7 and *in vitro* studies showed a high level of protein binding (see section 2.3.3 Pharmacokinetics).

Elimination

Study BLU-667-0103 was an open-label study to assess the absorption, metabolism, excretion, and mass-balance of [14C] pralsetinib after a single oral dose in 6 healthy adult male subjects. In the mass balance study, T½ of pralsetinib was 12.7 hours, and clearance was 13.4L/h for pralsetinib. In the NSCLC population (study BLU-667-1101), T½ was 14.7 hours after a single dose of 400 mg and and 22.2 hours following multiple doses of 400 mg pralsetinib. Clearance was 9.1 L/h at steady state (Table 14). The mean total recovery of the administered radioactivity was 78.6%, 6.06% in urine (4.8% as unchanged) and 72.5% in faeces (66% as unchanged), indicating that excretion in faeces was the major elimination pathway for [14C]pralsetinib in humans.

Different half-life between pralsetinib (13 hours) and total radioactivity (20 hours) were observed.

Metabolism

A small proportion of pralsetinib was metabolised after the single oral dose of [14C]pralsetinib (study BLU-667-0103). Pralsetinib oxidative metabolism was mainly mediated by CYP3A4 (phase I), with minor contribution of CYP1A2 and CYP2D6. The phase II metabolism was mainly catalysed by UGT1A4, with minor contribution of UGT1A1 and UGT1A3. In the mass balance study, around 5% of the radioactivity in plasma was represented by metabolites of pralsetinib. The main metabolite was made by glucuronidation (M709), whereas the minor metabolites (M453 and M549b) were made by

oxidation. In faeces and urine, pralsetinib accounted for the majority of the radioactivity, 96.4% and 91.5% respectively, and demonstrated that the majority of the parent drug was excreted unchanged.

Dose proportionality and time dependencies

Dose proportionality

In healthy subjects there was a dose proportional increase in exposure, whereas this was not the case in patients with NSCLC, neither at single dose or at steady state (Table 14). Although only few individuals received doses lower or higher than 400 mg, the exposure more than doubled for an increase in dose of 100 mg over the range 200 to 400 mg.

Time dependency

The exposure at steady state was around two-fold for doses of 100, 200, 300 and 400 mg compared with exposure for single dose (Table 14). There was no indication that this 2-fold higher exposure was dose dependent. After a single dose of 400 mg in NSCLC patients, apparent elimination half-life (t1/2) was 15 hours and at steady state, the t1/2 was 22 hours. However, trough concentrations were similar when steady state was reached.

Special populations

Inter-individual variability

A higher interindividual variability was seen in the NSCLC population compared with healthy subjects. Interindividual variability (%CV) in the population parameter estimates of CL/F and V/F was 48% and 46.9%, respectively.

Pharmacokinetics in target population

The mean plasma concentration-time curves after single dose and at steady state in the NSCLC subjects are shown in Figure 18.

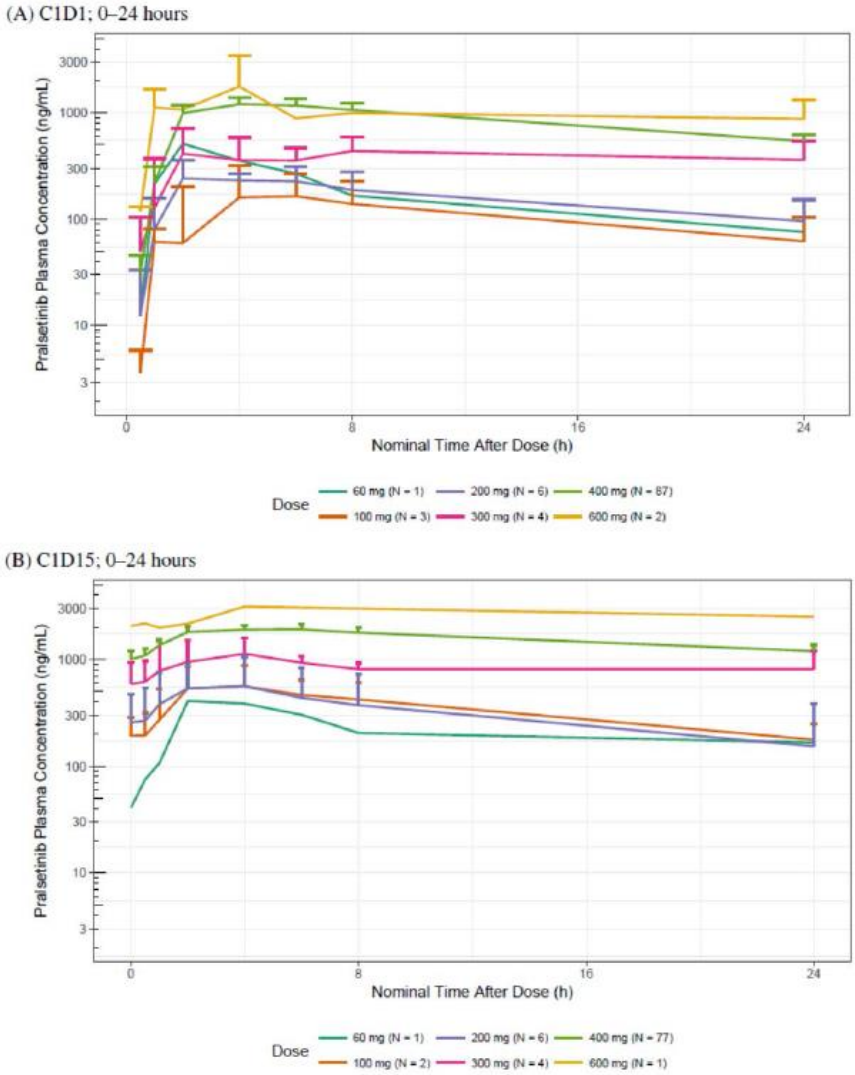

Figure 18. Mean plasma concentration-time profiles of pralsetinib in patients with NSCLC

Abbreviations: C1D1= Cycle 1 Day 1 (single dose); Cycle 1 Day 15 (steady state); N= number of patients with data; NSCLC= non-small cell lung cancer. Source: NCA PK Report BLUE201904

In the patient population (NSCLC subjects) as in healthy volunteers, pralsetinib was rapidly absorbed. The exposure was markedly larger in the NSCLC population compared with healthy volunteers. Clearance was similar in NSCLC patients and healthy subjects and varied from 12-14 L/h.

Renal impairment

Only 6% of pralsetinib is excreted in the urine, and the pop-PK model showed that none of the parameters of kidney function had statistically significant effects on PK parameters. No subjects with severe renal impairment or end-stage renal disease were included in the studies and therefore no data on these patients are available.

Hepatic impairment

Pralsetinib is mainly metabolised in the liver, however, in the pop PK analysis, markers of hepatic impairment were not statistically significant in the model. No subjects with moderate or severe hepatic impairment were included in the studies and therefore no data on these patients are available.

Gender, race, body size, age

No differences between gender regarding PK parameters were observed.

Asian subjects (n=50) had a 7% higher increase in Cmax at steady state, whereas the AUC at steady state was comparable to patients of white, black, other or unknown race (n=304).

In the pop PK analysis, none of the markers of body size were statistically significant in the model after adjusting for other covariates.

Based on the pop PK model, elderly subjects had a lower clearance and thereby a higher exposure to pralsetinib. The exposure increased by 15% in subjects of 80 years compared with subjects of 60 years.

The mean age of subjects included in the model was 49 years with a range of 19 to 87 years. Out of 161 patients, 60 patients were 65 years or above with the majority between 65 and 74 years of age.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	52/161	6/161	2/161

No data in paediatric subjects has been obtained.

Pharmacokinetic interaction studies

Potential effect of pralsetinib on other active substances

In-vitro studies showed that pralsetinib had potential for reversible inhibition of CYP2C8 and CYP2C9, for gut inhibition of CYP3A4/5, for time-dependent inhibition of CYP3A4/5 at clinically relevant concentrations (see section 2.3.3 Pharmacokinetics). The EMA Guideline on investigation of drug interactions recommends *in vivo* studies if *in vivo* inhibition cannot be excluded based on the Ki. The inhibitory potential of pralsetinib (IC_{50}) for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K exceeded the EMA regulatory thresholds (Table 15). However, none of these findings were further investigated *in vivo*.

Table 15. Evaluation of transporter-mediated drug-drug interaction potential for pralsetinib

Transporter	FDA Determination			EMA Determination		
	Equation	Value	Potential Interaction if Value	Equation	Value	Potential Interaction if Value
P-gp	I_{gut} [a] / IC_{50}	8717 (C2BBe1 cells) 304 (MDR1-MDCK cells)	≥ 10	K_i [b] / (0.1 × I_{gut} [a])	0.0006 (C2BBe1 cells), 0.016 (MDR1-MDCK cells)	≤ 1
BCRP	I_{gut} [a] / IC_{50}	1204 (C2BBe1 cells), 649 (MDR1-MDCK cells)	≥ 10	K_i [b] / (0.1 × I_{gut} [a])	0.0042 (C2BBe1 cells), 0.0077 (MDR1-MDCK cells)	≤ 1
OATP1B3	R [c]	1.42	≥ 1.1	K_i [b] / (25 × $f_{u,p}$ × $I_{in,max}$ [d])	0.048	≤ 1
OATP1B1	R [c]	3.2	≥ 1.1	K_i [b] / (25 × $f_{u,p}$ × $I_{in,max}$ [d])	0.009	≤ 1
MATE1	$I_{max,u}$ [e] / IC_{50}	0.193	≥ 0.1	K_i [b] / (50 × $I_{max,u}$ [e])	0.052	≤ 1
MATE2-K	$I_{max,u}$ [e] / IC_{50}	0.154	≥ 0.1	K_i [b] / (50 × $I_{max,u}$ [e])	0.065	≤ 1
OAT1	$I_{max,u}$ [e] / IC_{50}	0.015 [f]	≥ 0.1	K_i [b] / (50 × $I_{max,u}$ [e])	0.65 [f]	≤ 1
OAT3	$I_{max,u}$ [e] / IC_{50}	0.009	≥ 0.1	K_i [b] / (50 × $I_{max,u}$ [e])	1.15	≤ 1
BSEP	Not applicable			K_i [b] / (50 × $I_{max,u}$ [e])	1.35	≤ 1

Abbreviations: BCRP = breast cancer resistance protein; BSEP = bile salt efflux pump; EMA = European Medicines Agency; FDA = Food and Drug Administration; IC50 = half-maximal inhibitory concentration; Ki = inhibition constant; MATE = multidrug and toxin extrusion protein; MDCK = Madin-Darby canine kidney; MDR1 = multidrug-resistant-1 gene; NSCLC = non-small cell lung cancer; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; P-gp = P-glycoprotein.

Note: Cmax = 2830 ng/mL (5.304 µM) (at recommended Phase 2 dose of 400 mg once daily for patients with NSCLC in Study BLU-667-1101).

[a] Igut (molar concentration of pralsetinib in gut) = 2999 µM, calculated by dividing 400 mg by 250 mL and based on molecular weight of 533.6 g/mol; [b] Ki = IC50 / 2; [c] R = 1 + ((fu,pIin,max) / IC50), where fu,p (2.9%) is the unbound fraction in plasma and Iin,max is the estimated maximum plasma inhibitor concentration at the inlet to the liver; [d] Iin,max = Imax, u + [Fa × Fg × Ka × Dose] / Qh, where Fa (fraction of absorbed dose) = 1, Fg (the fraction of absorbed dose escaping gut wall extraction) = 1, Ka (absorption rate constant) = 0.1 min-1, Qh (total hepatic blood flow) = 1.62 L/min, and dose = 400 mg; [e] Imax,u (maximal unbound plasma concentration of the interacting drug at steady state) = 0.154 µM (ie, 2.9% × 5.304 µM); [f] Value estimated using estimated IC50 of 10 µM (Ki = 5 µM) for OAT1.

Source: Calculated from data available in Module 2.6.4 based on *FDA Guidance for Industry: In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, 2020* and *European Medicines Agency: Guideline on Investigation of Drug Interactions, 2012*.

Active substances that may have an effect on pralsetinib

Pralsetinib is a dual substrate of P-gp and BCRP, but not of transporters BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, OAT1, or OAT3 in cell-based assays. *In vitro* studies with recombinant human CYP450 enzymes indicated that Phase I metabolism of pralsetinib is mainly mediated by CYP3A4 (see section 2.3.3 Pharmacokinetics). A clinical drug-drug interaction study was conducted to investigate the effects of a strong inhibitor of CYP3A and P-gp (itraconazole) and a strong inducer of

CYP3A and P-gp (rifampin), on the single-dose PK of pralsetinib (Study BLU-667-0104). The drugs in this study were administered under fasting conditions.

The PK of pralsetinib was evaluated after a single dosage of 200 mg and after concomitant itraconazole 200 mg QD and resulted in exposure increase, from 593.9 to 1089 ng/ml (about 84%) based on Cmax and from 11380 to 40790 h×ng/mL (about 250%) based on AUC0-t, in presence of itraconazole (Figure 19).

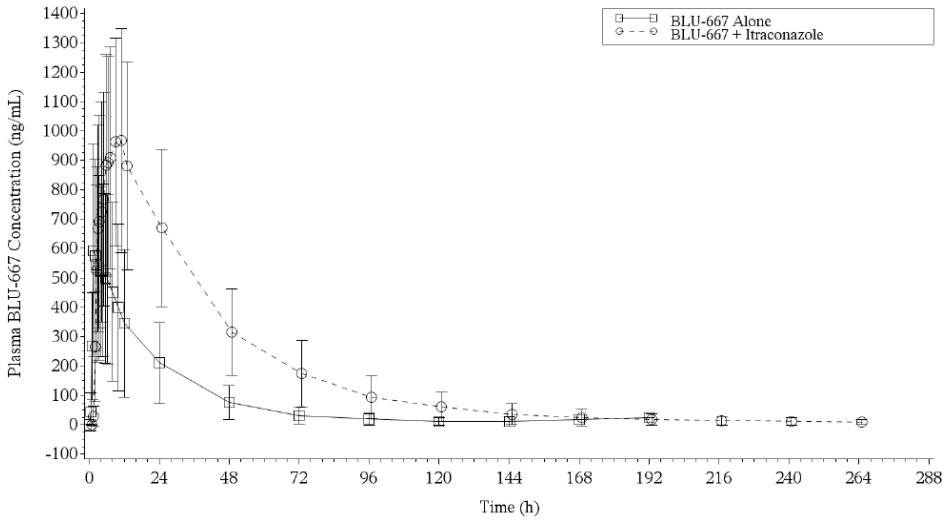

Figure 19. Mean plasma BLU-667 concentration-time profiles following administration of 200 mg BLU-667 with and without coadministration of itraconazole 200mg QD (linear scale) – Part 1 (PK evaluable population)

Note: BLU-667 + Itraconazole is shifted to the right for ease of reading.

The PK of pralsetinib was evaluated after a single dosage of 400 mg and after concomitant rifampin 600 mg QD (Figure 20). The mean exposure of pralsetinib decreased from 1168 to 815.9 ng/ml (about 30%) based on Cmax and from 31100 to 9842 h×ng/mL (about 68%) based on AUC0-t in presence of rifampin. In addition, the mean 6β-hydroxycortisol to free cortisol ratio in urine increased from 5.23 to 25.3-45.2 after concomitant rifampin.

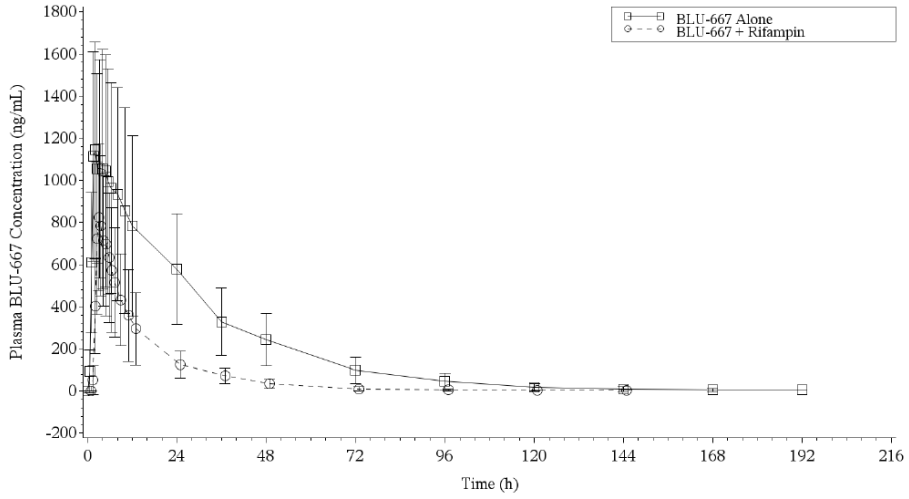

Figure 20. Mean plasma BLU-667 concentration-time profiles following administration of 400 mg BLU-667 with and without coadministration of rifampin 600mg QD (linear scale) – Part 2 (PK evaluable population)

Note: BLU-667 + Rifampin is shifted to the right for ease of reading.

Gastric effect

Pralsetinib is classified as a BCS Class 2 drug substance and the aqueous solubility is strongly pH-dependent. A clinical study of gastric effect with the proton pump inhibitor (PPI) drug esomeprazole resulted in a lower pralsetinib exposure (Cmax and AUC decreased 25% and 15%) after concomitant dosing (Study BLU-667-0105)(Figure 21). The drugs were administered under fasting conditions.

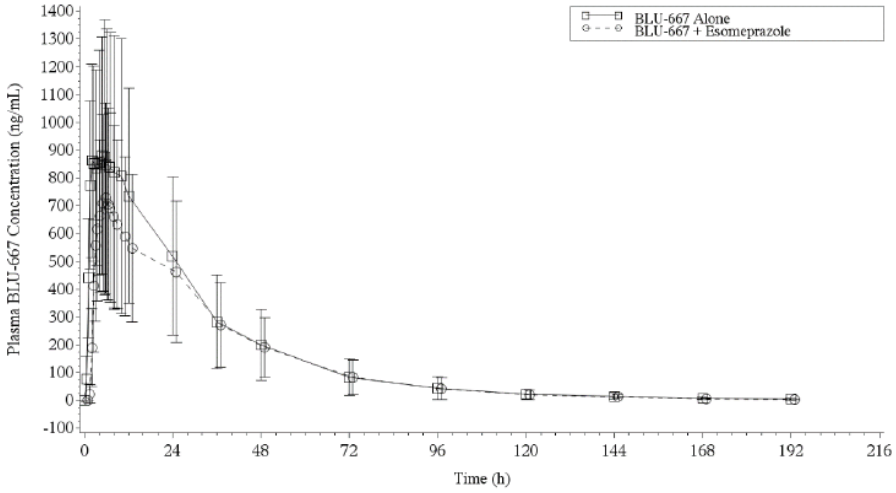

Figure 21. Mean plasma BLU-667 concentration-time profiles following administration of 400 mg BLU-667 with and without coadministration of esomeprazole 40mg QD (linear scale) (PK evaluable population)

Note: BLU-667 + Esomeprazole is shifted to the right for ease of reading.

None of the covariates PPI use (N=27), H2RA use (N=14) and antacid use (N=8) were found to be significant in the final Pop PK model.

2.3.3. Pharmacodynamics

Pharmacodynamics were evaluated in the study of NSCLC patients (study 1101), which is described in detail in section 2.5 Clinical efficacy.

Mechanism of action

The mechanism of action of pralsetinib is based on the evidence of non-clinical studies, PK and PK/pharmacodynamic modelling, no human mechanistic data have been provided.

Primary and Secondary pharmacology

Primary pharmacology

Pralsetinib is a tyrosine kinase inhibitor that targets RET fusions and mutations, including V804 gatekeeper mutations associated with resistance to other therapies. In the pharmacodynamic analysis, changes in dual specificity phosphatase 6 (DUSP6) and sprout receptor tyrosine kinase signaling antagonist 4 (SPRY4) mRNAs were analysed in tumour tissue for different doses of pralsetinib in order to analyse whether the RET pathway is targeted (Figure 22).

From tumour tissue, tumour markers were measured pre-treatment and 4 weeks after treatment initiation in 18 out of 62 patients. The relative change was assessed. The 60 mg QD dose group had an increase in DUSP6 and SPRY4, whereas the 200 mg, QD, 300 mg QD, 400 mg QD, 100/100 BID and 200/100 BID were associated with a decrease in DUSP6 and SPRY4. These results are supportive of a dose of at least 200 mg QD, although the samples are very small in each group (2-3 subjects).

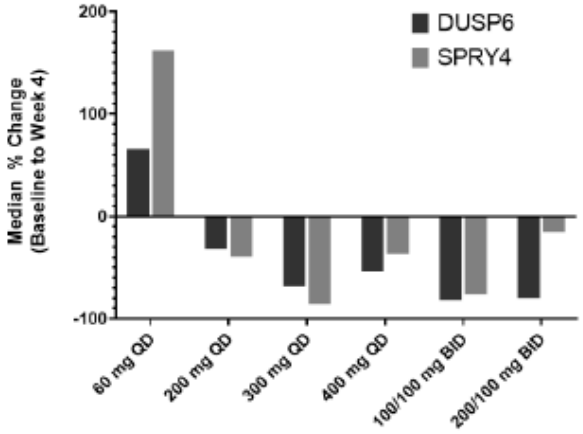

Figure 22. Summary of mitogen-activated protein kinases pathway (dose-escalation patients in safety population)

Abbreviations: BID= twice daily; DUSP6= dual specificity phosphatase 6; QD= once daily; SPRY4= sprout receptor tyrosine kinase signalling antagonist 4. Notes: Baseline is defined as the last assessment prior to first dose of pralsetinib. Samples collected within Week 4 (±2 weeks) were included. Source: Table 14.4.2.1.1.8

Secondary pharmacology

No dedicated QT interval corrected for heart rate (QTc) study was conducted, and a secondary analysis of study 1101 therefore serves as the thorough QTc study for pralsetinib.

In 34 patients, continuous 12-lead ECG recordings were obtained and plasma samples were taken. At steady state, the mean change in QTc was 5.6 ms compared with baseline. Mean change in QTc varied between 4.9 ms and 7.7 ms at all timepoints, and a QTc prolonging effect cannot be ruled out.

Based on Figure 23, there seems to be an exposure response relationship. The higher concentration the greater change in QTc especially for concentrations above 3000 ng/ml. Even though the median Ctrough at 400 mg dose is 1150 ng/ml, a large interindividual variation in exposure is evident, and concentrations above 3000 ng/ml could be expected in some patients.

This is reflected in the SmPC with a relevant warning in section 4.4 and potential interaction with other QTc prolongating medicinal products in section 4.5.

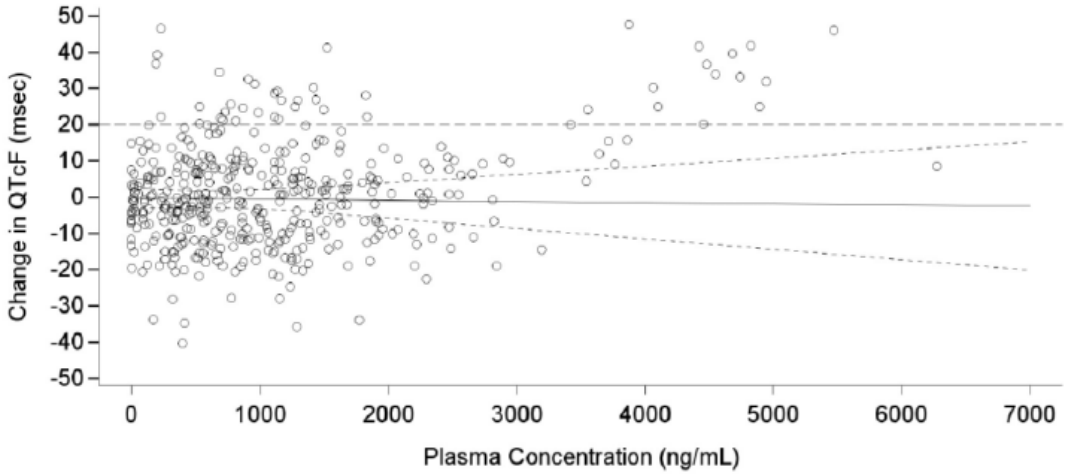

Figure 23. Observed pralsetinib concentration in plasma versus change in QTcF from baseline and 2-sided 90% confidence intervals of the slope

Abbreviations: CI= confidence interval; QTcF= QT corrected for heart rate by the Fridericia method. Note: Regression line (90% CI), intercept= 19.9 slope= -0.0003 (2-sided 90% CI: -0.0030, 0.0024, p = 0.841) for regression of change in QTcF on pralsetinib plasma concentration are calculated from a linear mixed-effects model with baseline value and plasma concentration as continuous covariates, time as a categorical factor, and random intercept and slope per subject. Source: BLU-667-1101, Cardiac Safety Report, Figure 17.

The overall NSCLC safety population treated with pralsetinib with a starting dose of 400 mg QD (n=281) from the ARROW study was included in the investigation of body weight and QT prolongation. 15 patients experienced an AE of QT prolongation. A boxplot of body-weight versus QT prolongation for this patient population did not indicate any link between baseline body weight and QT prolongation.

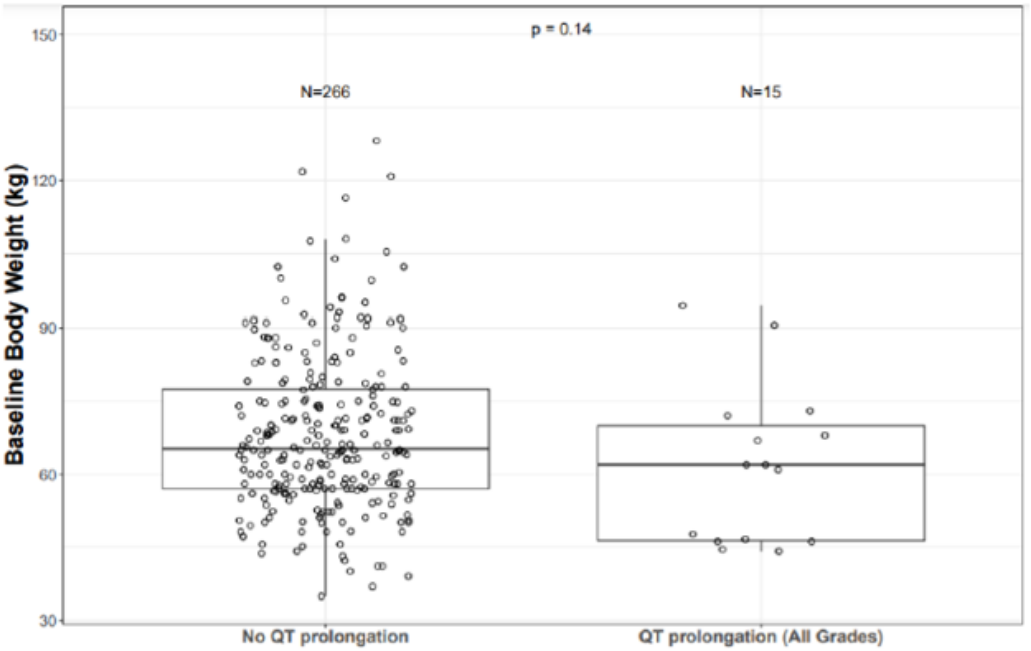

Figure 24. Box plots of body weight by QT prolongation

Relationship between plasma concentration and effect

A number of E-R analyses were conducted. The following outcomes were assessed: Progression free survival, duration of response, best overall response, clinical benefit response, disease control response, systemic tumour kinetics and CNS metastases. None of the analysis showed evidence of an association between exposure and response, besides the analysis of duration of response when stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status. The lack of E-R relationship in the efficacy analysis is indicative of a high degree of receptor occupancy at low exposure levels.

With regards to safety parameters, there was a statistically significant association between exposure and grade 3+pneumonia (Figure 25 and Figure 26) and grade 3+ anaemia and. Furthermore, there were indications of a decrease in haemoglobin and absolute neutrophil count and minor increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with increasing exposure to pralsetinib.

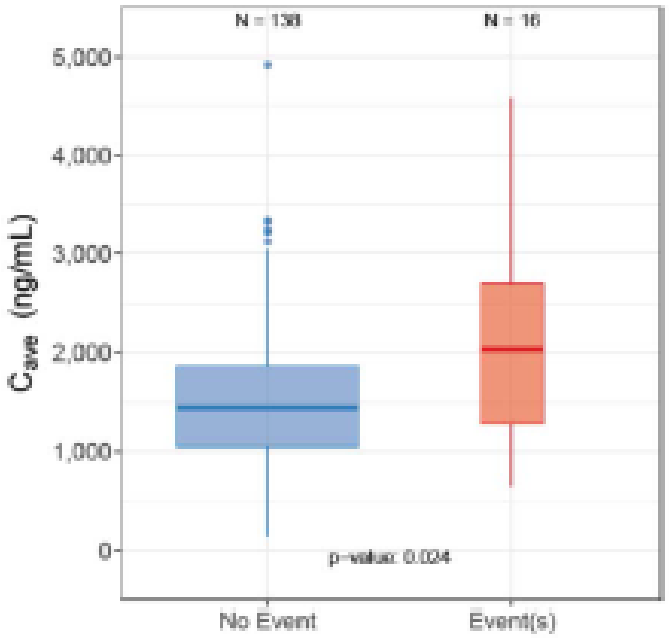

Figure 25. Boxplots of grade 3+ pneumonia adverse events versus pralsetinib Cave (Patients with NSCLC, E-R safety population)

Abbreviations: C_{ave}= Average plasma concentration; E-R= exposure-response; N= number of patients with data; NSCLC= non-small cell lung cancer. Note: The solid horizontal lines and box heights represent the median, and 25th to 75th percentiles, respectively. Dots are the outlier data (≥ 1.5 * interquartile range). Number above each box specifies the number of patients per group. P-value from Wilcoxon rank sum test. The width of the box plots is proportional to the square root of the number of observations in that box. Source: E-R Report BLUE201905, Figure 22.

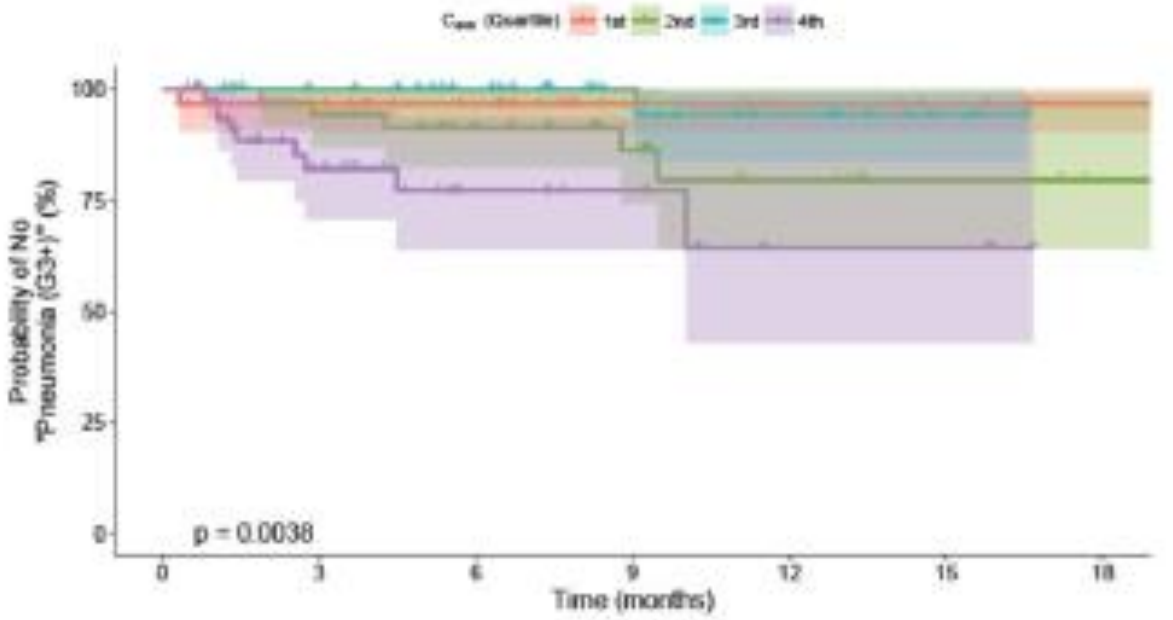

Figure 26. Time to grade 3+ pneumonia adverse events versus pralsetinib Cave quartiles (Patients with NSCLC, E-R safety population)

Abbreviations: C_{ave}= Average plasma concentration; E-R= exposure-response; G3+= Grade 3+; NSCLC= non-small cell lung cancer. Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence interval, and p-value is derived from a log-rank test. Plots truncated at 18 months. Source: E-R report BLUE201905, Figure 23

A scatterplot of change from baseline haemoglobin value versus C_{ave} is provided in Figure 27. A clear trend was apparent, with a reduction in change from baseline haemoglobin value as C_{ave} increased. Similar trends were also evident between change from baseline haemoglobin value and steady state exposure metrics on C1D15 (E-R Report BLUE201905). A 25% reduction in baseline haemoglobin and 30% increase in ALT is expected in NSCLC patients receiving 400 mg of pralsetinib, according to the observed C_{ave} at C1D15.

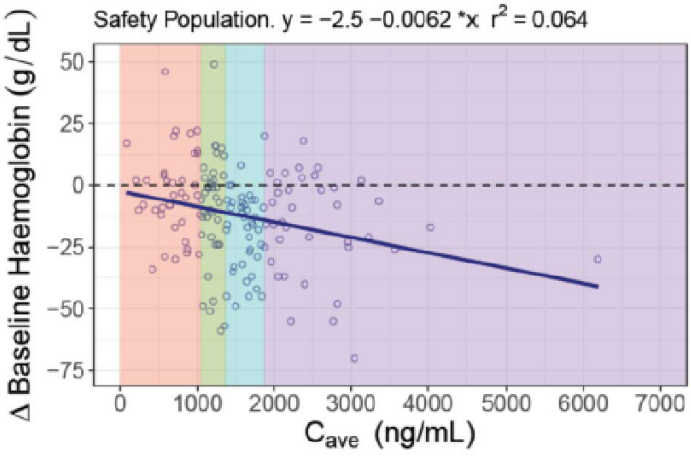

Figure 27. Scatterplot of change from baseline haemoglobin value versus pralsetinib C_{ave} (patients with NSCLC, E-R safety population)

Abbreviations: Δ= change; C_{ave}= average plasma concentration; E-R= exposure-response; NSCLC= non-small cell lung cancer. Note: Open circles= observations, solid line= linear trend. Source: E-R report BLUE201905, Figure 35.

2.3.4. Discussion on clinical pharmacology

Bioanalysis and models

The bioanalysis of pralsetinib is well documented and overall acceptable. The Pop PK of pralsetinib was described by a 1-compartment linear model with several absorption transit compartments depending on the capsule manufacturing process.

The significant covariates included in the final model were Asian race on V/F, NSCLC patients on F, age on CL/F, concomitant CYP3A4 weak inducer use on F, NSCLC patients administered capsule Process I on F, and capsule Process III on the absorption transit rate for HV. The effects of CYP3A4 weak inducer and Capsule Process 1 on pralsetinib exposure were considered not clinically relevant. The expected reduction of CL/F due to age seems plausible. The reduction (26%) in the V/F in Asian population could be related to a lower body weight in the Asian population.

Plots of exposure versus weight in NSCLC patients at steady-state (C1D15) showed a clear relation between weight and pralsetinib exposure. An effect of weight have been included in the Pop PK model. Subgroup analyses investigating the relation between body weight and relevant safety and efficacy measures including QTcF did not indicate any relations. The pvcVPCs showed the model could adequately capture the trend of observations in both HV and patients.

Pop PK simulations indicated that about 90% and 40% of NSCLC patients would maintain adequate brain exposure based on Cmax and Ctrough, respectively, during the dosing interval of 400 mg QD. E-R relations were explored by means of graphical analysis and time-dependent Cox proportional hazard models.

ADME

Gavreto is for oral use. Patients should swallow the hard capsules whole with a glass of water, on an empty stomach. Pralsetinib was rapidly absorbed with a Tmax of 2-4 hours following single doses of pralsetinib 60 mg to 600 mg (0.15 to 1.5 times the approved recommended dose). The absorption differed substantially when pralsetinib was taken after 10 hours of fasting and with a high fat meal. No information was provided regarding food effects for the 400 mg dose level. However, the food effect is expected to be similar for the highest dose level (400 mg) as observed in the 200 mg dose level. In the phase II study, pralsetinib was administered 2 hours after and 1 hour before food intake, which is the recommended administration in the SmPC(see section 4.2 and 5.2 of the SmPC). This method of administration was not examined in the food effect study, but a simulation-based analysis revealed no clinically relevant changes in exposure when pralsetinib is administered after at least 2 hours of fasting and 1 hour before the next meal and when administered after 10 hours of fasting (data not shown).

Distribution, metabolism and elimination were well described. The volume of distribution was estimated to 228 L after a single dose and 268 L at steady state, indicating extensive distribution from plasma into tissues, pralsetinib was mainly metabolised by CYP3A4 and to a lesser extent by CYP2D6 and CYP1A2, and was mainly excreted with faeces. However, the mean total recovery of administered radioactivity in urine and faeces was only 78.6%. The mean plasma elimination half-life of pralsetinib was 14.7 hours following a single dose of 400 mg (the recommended dose) pralsetinib and 22.2 hours following multiple doses of 400 mg pralsetinib. As metabolites account for 5% or less of TRA, their PK has not been evaluated and no additional information is provided.

Pharmacokinetics were both measured in healthy volunteers and NSCLC subjects. In NSCLC subjects, the exposure to pralsetinib was higher than in healthy volunteers, and the interindividual variability was higher. The lack of fasting in the NSCLC population is likely to have explained the higher interindividual variability in the population. Due to a mean T½ of 15 hours after single dose and 22 hours at steady state, a dosing interval of 24 hours is chosen.

Special populations

Pharmacokinetics in special populations were primarily evaluated in the pop PK model. Consistent with the minor excretion in the urine, renal clearance had no effect on PK in the pop PK model. Hence no dose adjustment is recommended in patients with mild or moderate renal impairment.

No subjects with severe renal impairment or end-stage renal disease. Since pralsetinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment or end-stage renal disease.

Markers of hepatic impairment did not have any impact on PK in the pop PK model. Therefore, no dose adjustment is recommended in the SmPC for patients with mild hepatic impairment.

No subjects with moderate or severe hepatic impairment were included in the studies and therefore no data on these patients are available and have been included in the pop PK model, use in these patients is not recommended. This is adequately reflected in section 4.2 in the SmPC. The applicant will conduct study GP43163 to characterise the pharmacokinetics of pralsetinib in patients with hepatic impairment (category 3 study in the RMP).

With regards to race, Asian subjects had a 7% higher Cmax than non-Asian subjects, but AUC at steady state was similar across races. The higher Cmax is not considered clinically relevant. Low weight patients experience markedly higher Cmax exposures than median weight or obese patients. This can be accepted if there is no increased risk for safety events for this patient subgroup.

Based on the pop PK model, elderly subjects had a lower clearance and thereby a higher exposure to pralsetinib than younger subjects. As such, patients of 80 years had a 15 % higher exposure compared with patients of 60 years, which is not considered clinically relevant and no dose adjustment is recommended for patients aged 65 years and above.

No studies have been conducted in the paediatric population, which is considered acceptable.

Interactions

Pralsetinib is mainly metabolised by CYP3A4, with minor contributions from CYP2D6 and CYP1A2 while UGT1A4 is the major enzyme responsible for formation of the N-glucuronide of pralsetinib. Cell-based transporter studies indicated Pralsetinib is also a dual substrate of transporters P-gp/BCRP.

Pralsetinib was a perpetrator of drug-drug interactions (DDI) *in vitro* and none of these findings were further investigated *in vivo*.

Co-administration of pralsetinib can alter the exposure of sensitive substrates of CYP enzymes (CYP3A4, CYP2C9 and CYP2C8) and transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1 and MATE2-K). Substrate drugs of these CYP enzymes and transporters with narrow therapeutic index (including, but not limited to cyclosporine, paclitaxel and warfarin) should be avoided.

The applicant is recommended to conduct clinical interaction studies to evaluate the effect of repeat doses of pralsetinib on the PK of sensitive substrates of CYP3A4, CYP2C8 and CYP2C9, and of transporter substrates of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE-1 and MATE-2K.

Pralsetinib as a victim of DDI were investigated in vivo with itraconazole (strong CYP3A and P-gp inhibitor) and with rifampin (strong CYP3A and P-gp inducer). Co administration of 200 mg pralsetinib once daily with itraconazole 200 mg once daily (a strong CYP3A4 and P- gp inhibitor) increased pralsetinib Cmax by 84% and AUC0-∞ by 251%, compared to pralsetinib administered alone. Therefore, co administration of pralsetinib with strong CYP3A4 inhibitors or combined P gp and strong CYP3A4 inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges) should be avoided

because of the potential increased incidence and severity of adverse reactions of pralsetinib. If co administration with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors cannot be avoided, the dose of pralsetinib should be decreased (see sections 4.2, 4.4 and 4.5 of the SmPC).

Table 16: Recommended dose modifications for Gavreto for co-administration with strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inhibitors

Current Gavreto dose	Recommended Gavreto dose
400 mg orally once daily	200 mg orally once daily
300 mg orally once daily	200 mg orally once daily
200 mg orally once daily	100 mg orally once daily

Co administration of 400 mg pralsetinib as a single dose with rifampin 600 mg once daily (a strong CYP3A4 inducer) decreased pralsetinib Cmax by 30% and AUC0-∞ by 68%. Based on a population PK analysis, CYP3A4 weak inducers decreased pralsetinib exposures, but were not clinically significant in patients with NSCLC. Therefore, co administration of pralsetinib with strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort [Hypericum perforatum]) should be avoided because of the potential decreased efficacy of pralsetinib. If co administration cannot be avoided, the dose of pralsetinib should be increased to double the current pralsetinib dose starting on Day 7 of co administration of pralsetinib with the strong CYP3A4 inducer. After the strong CYP3A4 inducer has been discontinued for at least 14 days, the pralsetinib dose that was taken prior to the use of the inducer should be resumed (see sections 4.2, 4.4 and 4.5 of the SmPC).

The applicant will conduct a DDI study (study GP43162) to evaluate the effect of a P-gp inhibitor on the PK of pralsetinib and to inform appropriate dosing strategies for safe coadministration of pralsetinib with P-gp inhibitors (category 3 study in the RMP).

The applicant is recommended to assess the impact of BCRP inhibition, weak or moderate CYP3A4 inhibition with or without p-gp inhibition, and moderate CYP3A4 induction using PBPK modelling.

Pralsetinib is classified as a BCS Class 2 drug substance and the aqueous solubility is strongly pH-dependent. The effect of concomitant administration of a PPI drug, esomeprazole, was not clinically relevant.

Pharmacodynamics

The pharmacodynamics of pralsetinib are well described. In the primary pharmacology study, there was a decrease in the tumour markers DUSP6 and SPRY4 after treatment with doses of at least 200 mg QD.

In the E-R analysis there was no clear association between exposure and response with regards to efficacy. The lack of E-R relationship is indicative of a high degree of receptor occupancy at low exposure levels.

In order to support the starting dose of 400 mg QD, some explorative analyses were performed (data not shown). The analyses indicate that patients who started on a dose of 400 mg QD and maintained this dose had the greatest and most sustained percentage reduction in tumour size over time compared with patients, who were not adherent, had their dose reduced, or started at a lower dose. This finding should, however, be interpreted with caution, due to the fact that this finding is likely to be highly confounded by disease severity.

Systemic tumour size over time data were available at different dose levels in several patients (data not shown). A model-based analysis showed that differences in percent change from baseline in tumour size by dose reductions and dose interruptions were negligible among the different dose regimens evaluated.

With regards to safety parameters, there was an E-R relationship for grade 3+ anaemia and grade 3+ pneumonia. A 25% reduction in baseline haemoglobin and 30% increase in ALT is expected in NSCLC patients receiving 400 mg of pralsetinib, according to the observed Cave at C1D15.

There was a median change in QTc just above 5 ms and a clear exposure-response relationship for concentrations above 3000 ng/ml. The QTc prolongating effect is reflected in the SmPC in section 4.2, 4.4, 4.5 and 4.8.

2.3.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics and pharmacodynamics were well described.

2.3.6. Clinical efficacy

The primary evidence of efficacy of pralsetinib comes from the pivotal ARROW study (BLU-667-1101), an ongoing phase I/II, open-label, first-in-human, multi-cohort, single-arm trial in patients with advanced, unresectable RET-altered solid tumours. A tabular overview of this study is depicted in (Table 17).

Table 17. Tabular overview of ARROW (BLU-667-1101)

Study ID/ Status	**# Study Centres/ Countries**	**Study Objective(s)**	**Study Design**	**Populations**	**Dose/Dosing Regimen**	**# Patients/ Subjects**
BLU-667-1101 (ARROW) NCT03037385 EudraCT 2016-004390-41 Phase I: complete Phase II: ongoing; data cut-off date of 6 November 2020.	80 centres/ 14 countries: Belgium, China France, Germany, Hong Kong, Italy, Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, UK, USA	*Primary objectives:* Phase I: Determine the MTD/RP2D and safety Phase II: Efficacy and safety Primary efficacy endpoint is ORR	Phase I/II, open- label, multicentre, dose-escalation, first-in-human study with expansion into Phase II at the MTD/RP2D	Patients ≥ 18 years with advanced a, unresectable, RET-altered NSCLC, MTC, or other RET altered solid tumours	Phase I: BOIN dose-escalation design of BLU-667 capsules administered orally with a target toxicity rate for the MTD of 30%. Cohorts of 3-6 patients (1-3 patients for the first 3 dose levels) were enrolled until 12 patients were treated and evaluable for DLT at 1 dose level Phase II: BLU-667 capsules at 400 mg QD (MTD/RP2D)	647 patients overall, 585 received 400 mg QD, of which 233 patients had RET-fusion positive NSCLC (including 75 who were treatment-naïve and 136 who previously received platinum-based chemo-therapy)

Abbreviations: BOIN= Bayesian optimal interval; DLT= Dose-limiting toxicity; MTC= medullary thyroid cancer; MTD= Maximum tolerated dose; NSCLC= non-small cell lung cancer; ORR= overall response rate; QD= once daily; RET= rearranged during transfection; RPD2D= Recommended Phase 2 dose

2.3.7. Dose response study

Dose-response and exposure-response regarding efficacy and safety from the ARROW study have already been depicted and discussed in section 2.4.3 Pharmacodynamics.

2.3.8. Main study

ARROW (study BLU-667-1101)

The study design consists of a dose escalation phase (phase I) to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of pralsetinib and an ongoing dose expansion phase (phase II) to assess clinical efficacy of pralsetinib in specific tumour types and treatment settings across 9 cohorts, and further define safety and tolerability at the RP2D, *i.e.,* 400 mg QD. Figure 28 depicts the study schematic of ARROW.

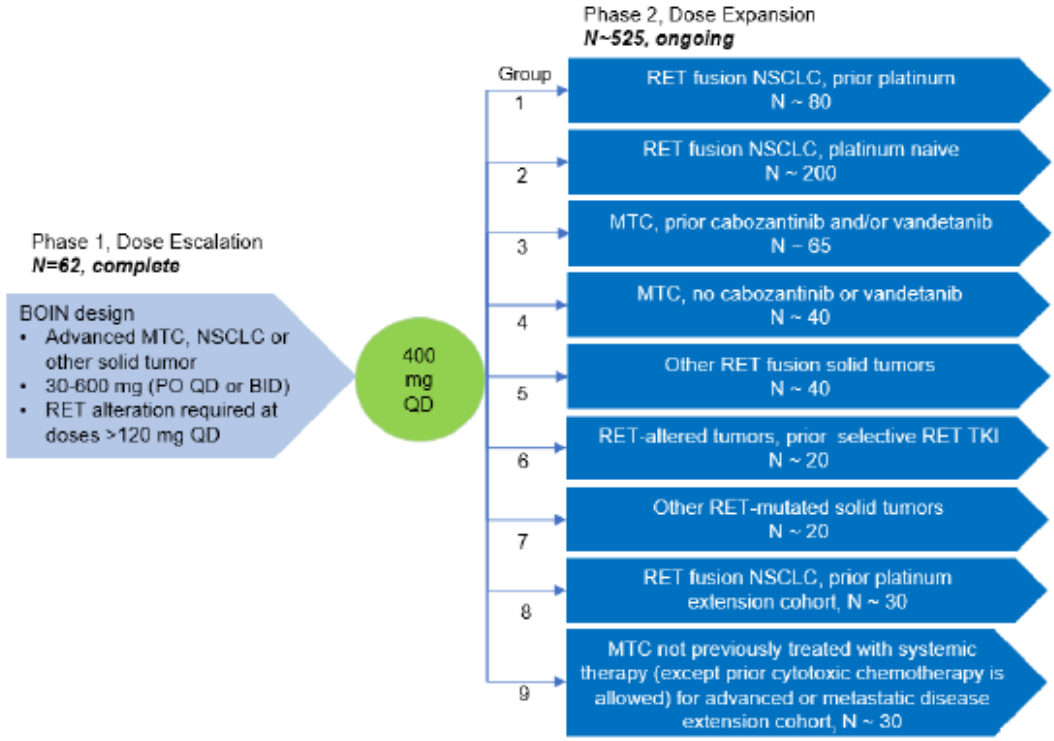

Figure 28. ARROW study schematic

Abbreviations: BOIN: Bayesian optimal interval; MKI = multikinase inhibitor; MTD = Maximum tolerated dose; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; RET = rearranged during transfection; TKI = Tyrosine kinase inhibitor. Note: Ongoing Groups 8 and 9 (NSCLC and MTC patients in centres in China only), introduced with Protocol Amendment 8 (20 December 2018), also contribute data in the safety analysis, but not in the efficacy analysis (they started enrolment after 11 July 2019).

Methods

Study Participants

Approximately 587 patients will be enrolled in the study, including 62 in Phase I (dose escalation, completed) and approximately 525 in Phase II (dose expansion, ongoing) across 80 centres from 14 countries: Belgium, China, France, Germany, Hong Kong, Italy, Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, UK and USA.

Main inclusion criteria (patients from phase I and Groups 1 and 2 from phase II)

- Patient is ≥ 18 years of age and provides informed consent.
- Phase I – Pathologically documented, definitively diagnosed non-resectable advanced solid tumour. All patients treated at doses > 120 mg per day must have MTC, or a RET-altered solid tumour per local assessment of tumour tissue and/or blood. Phase I enrichment patients must have MTC or a RET-altered solid tumour per local assessment of tumour tissue and/or blood.
- Phase II – All patients (with the exception of Groups 3, 4 and 9) must have an oncogenic RET fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumour, as determined by local testing of tumour or circulating tumour nucleic acid in blood (Next Generation Sequencing, fluorescence in situ hybridization, other).
    - Group 1 – patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion previously treated with a platinum-based chemotherapy.
    - Group 2 – patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug.
- Patients must have non-resectable disease. For Phase I only, patients must have progressed following standard therapy or have not adequately responded to standard therapy, or the patient must be intolerant to, or the Investigator has determined that treatment with standard therapy is not appropriate, or there must be no accepted standard therapy for their disease.
- Dose expansion (Phase II) patients in groups 1, 2, 3, 4, 6, 8, and 9 must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Patient agrees to provide tumour tissue (archived, if available or a fresh biopsy) for RET status confirmation and is willing to consider an on-treatment tumour biopsy, if considered safe and medically feasible by the treating Investigator.
- Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.

Main exclusion criteria

- Patient's cancer has a known primary driver alteration other than RET. For example, NSCLC with a targetable mutation in EGFR, ALK, ROS1, or BRAF.
- Inadequate haematologic and/or end-organ function.
- QTcF > 470 msec or personal/familial history of prolonged QT syndrome or Torsades de pointes.
- Significant, uncontrolled cardiovascular disease.

- CNS metastases associated with progressive neurological symptoms or requiring increasing doses of corticosteroids to control the CNS disease.
- Clinically symptomatic ILD or interstitial pneumonitis, including radiation pneumonitis.
- Patient received the following anticancer therapy:
    - Any systemic anticancer therapy (except for immunotherapy or other antibody therapies) and all forms of radiotherapy, within 14 days or 5 half-lives prior to the first dose of study drug. BLU-667 may be started within these washout periods if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.
    - Any immunotherapy or other antibody therapy within 28 days prior to the first dose of study drug (immune related toxicities must have resolved to < Grade 2 prior to starting BLU-667).
- Previous treatment with a selective RET inhibitor such as LOXO-292.
- History of another primary malignancy that has been diagnosed or required therapy (except maintenance anti-hormonal therapy) within the past year.
- Pregnancy, breastfeeding, or unwillingness to employ contraception.

Treatments

Dose and mode of administration: In Phase I, patients received pralsetinib orally in a QD schedule at doses of 30, 60, 100, 200, 300, 400, and 600 mg, and in a BID schedule at doses of 100/100 mg and 200/100 mg. In Phase II, all patients received pralsetinib orally in a QD schedule at a dose of 400 mg.

Duration of treatment: A treatment cycle is 28 days in duration. There was no predefined maximum duration of treatment. Reasons for discontinuation of pralsetinib included disease progression, toxicity, noncompliance, pregnancy, withdrawal of consent, death, or closure of the study by the Sponsor. Patients with progressive disease (PD) could remain on treatment if in the opinion of the Investigator the patient has benefited from the pralsetinib therapy, and it was clearly in the best medical interest of the patient to remain on treatment.

Modification of dose or treatment schedule (phase II): Pralsetinib dose reductions by 100 mg were permitted in case of ≥Grade 3 AEs, but not below 100 mg QD (total dose). If a patient required dose reduction below such dose levels, study treatment was to be discontinued. Doses could be interrupted for study-drug related toxicities for up to 28 days (4 weeks). In general, if a study drug-related toxicity did not resolve to ≤ Grade 2 or has not returned to baseline after dose interruption for more than 28 days, the patient would be discontinued from study treatment. AEs of pneumonitis, hyperphosphatemia or hypertension had specific advice for dose modification.

Objectives

Primary objectives

1. To determine the ORR by RECIST v1.1 by disease type, and/or RET-altered status (including patients treated at MTD/RP2D in Phase I), and/or prior treatment status specified in enrolment group definition, if appropriate.
2. To further define the safety and tolerability of pralsetinib.

Secondary objectives

1. To assess additional measures of clinical benefit including DOR, clinical benefit rate (CBR), disease control rate (DCR), PFS, and OS in all patients by disease type and/or RET-altered status, and/or prior treatment status explained in enrolment group definition, if appropriate. Patients treated at MTD/RP2D in Phase I will be pooled with Phase II patients for this analysis.
2. To assess baseline RET gene status in plasma and/or tumour tissue and correlate with measures of antineoplastic activity including, but not limited to ORR, CBR, DOR, and DCR in all patients, including patients treated at MTD/RP2D in Phase I, by disease type, and/or RET-altered status if applicable, and/or prior specified treatment status if appropriate.
3. To characterize the PK profile of pralsetinib and correlate drug exposure with safety assessments, including changes in ECG intervals, and efficacy.
4. To characterize the pharmacodynamics of pralsetinib, including, but not limited to, changes in blood calcitonin and carcinoembryonic antigen in MTC patients only.

Exploratory objectives

1. To identify potential new blood and tumour tissue biomarkers (*e.g.,* DNA, RNA, and/or protein markers) of pharmacodynamic activity, antineoplastic activity, and/or toxicity.
2. To assess changes in quality of life (QoL) questionnaire.
3. To explore disease-related symptoms, as measured by bowel movement history (MTC patients only).

Outcomes/endpoints

Primary endpoint

Overall response rate (ORR): defined as the proportion of patients with a confirmed response (complete reponse (CR) or partial response (PR) for at least two assessments with at least 28 days apart and no PD in between) before PD and/or other anticancer therapy. Each patient's best overall response (BOR) will be derived based on RECIST v1.1.

*Frequency of imaging: disease response assessment by CT or MRI was performed at screening and on D1 of every other cycle, starting with C3, *i.e.,* Q8W.

Key secondary endpoints

- Duration of response (DOR): defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurs first.
- Clinical Benefit Rate (CBR): defined as the rate of CR or PR, or stable disease (SD) that has been lasting at least 16 weeks from the first dose date.
- Disease Control Rate (DCR): defined as the proportion of patients with a confirmed CR/PR, or SD, per RECIST v1.1.
- Progression free survival (PFS): defined as the time from the first dose of BLU-667 to the date of first documented disease progression or death due to any cause, whichever occurs first.
- Overall survival (OS): defined as the time from the first dose of BLU-667 to the date of death due to any causes.

Sample size

For the NSCLC patients included in the CSR, the sample size calculation was prospectively defined as:

- Group 1: approximately 80 RET-fusion NSCLC patients who previously received treatment with a platinum-based chemotherapy will provide > 95% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.23 versus the alternative ORR=0.5.
- Group 2: The sample size of approximately 170 treatment naïve (1st line) RET-fusion NSCLC patients will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.48 versus the alternative ORR=0.61.

Randomisation and blinding (masking)

BLU-667-1101 is a phase I/II, open-label, single arm study. Therefore, randomisation and blinding are not applicable.

Statistical methods

Analysis populations

- Safety Population: All patients who were exposed to ≥ 1 dose of pralsetinib, regardless of starting dose or cancer diagnosis on or before 06 November 2020. The Safety Population will be the primary population for safety analysis unless otherwise specified.
- Efficacy Population: NSCLC patients in the safety population who were dosed on or before 22 May 2020. The efficacy population was the primary population for efficacy analysis unless otherwise specified and corresponds to the "intent to treat" population. Patients initially treated with MTD/RP2D will be pooled with Phase II patients.
- Response-evaluable Population: NSCLC efficacy population patients who had measurable (target) disease per RECIST v1.1 at baseline as per blinded independent central review (BICR), ≥ 1 evaluable post-baseline disease response assessment performed as per BICR, and had no major protocol violations that would impact the interpretation of the key endpoints of the study. The response-evaluable population was used for the primary efficacy endpoint as a sensitivity analysis for ORR, CBR, and DCR.

  The major protocol deviations leading to exclusion from the response-evaluable population were:
  - Patient had incomplete baseline imaging.
  - Patient was in Group 1, 2, 5, 6, or 7 and does not have evidence of a RET mutation or fusion.
  - Patient had another known primary driver alteration other than RET identified by central ctDNA/tumour assay.

Primary endpoint

ORR and its two-sided 95% CI, which is based on the exact binomial distribution (Clopper-Pearson), was presented. The BOR was summarized by count and frequency for each category: CR, PR, SD, PD, or not evaluable (NE). Patients without disease assessments were imputed with NE as their BOR.

Secondary endpoints

PFS was analysed using Kaplan-Meier methods, the estimated median with two-sided 95% CI and 25th and 75th percentiles were provided. The confidence interval calculation was based on identity (*i.e.,* linear) transformation. PFS at specific time-points (*e.g.,* 3-, 6-, 9-, 12-, 18-, 24-, 30-month *etc.* every 6-month after 12-month) was computed, along with the standard errors using Greenwood's formula (Klen, 2003). PFS was also displayed with Kaplan-Meier (K-M) plots.

DOR was analysed using K-M methods and included the estimated median with two-sided 95% CI and 25th and 75th percentiles. DOR at specific time-points (*e.g.,* 3-, 6-, 9-, 12-, 18-, 24-, 30-month *etc*.) was computed, along with the standard errors using Greenwood's formula (Klen, 2003). Additionally, the proportion of patients with DOR of at least 3, 6, 9, 12, 18, 24, and 30 months were summarized regardless of censoring status. DOR was also displayed with K-M plots.

CBR was analysed and summarized using the same methods as ORR.

OS was analysed and summarized in the same manner as for PFS based on Safety Population. Patients who are still alive or lost to follow-up will be censored at the last known alive date. The last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cut-off date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive.

Table 18. Duration of response (DOR) and progression free survival (PFS) censoring rules

Situation	Date of Progression or Censoring	FDA Censoring Rules	EMA Censoring Rules
No baseline assessments and alive after 2 scheduled assessments (at least 128 days)	Date of first dose of treatment	Censored	Censored
Progression documented between scheduled visits	Date of radiological assessment showing progression	Event	Event
No progression	Date of last radiological assessment with evidence of no progression (or first dose date if no assessment)	Censored	Censored
New antineoplastic/ non-protocol treatment started prior to progression	Date of last radiological assessment with evidence of no progression prior to the start of new antineoplastic treatment	Censored	Event at date of disease progression/death
Death before the second scheduled post-baseline assessment if the first scheduled post-baseline assessment is not PD (defined as 128 days after first dose)	Date of death	Event	Event
Death between scheduled assessments	Date of death	Event	Event
Death or progression after missing two or more consecutively scheduled disease assessments (2 more missed scheduled assessments defined by at least x[1] days)	Date of last radiological assessment with evidence of no progression prior to death/progression	Censored	Event at date of disease progression/death

[1] x= 128 days before EOT visit; x=197 days if the death or progression date is after EOT.

EMA, European Medicine Agency; FDA, Food and Drug Administration (US).

Multiplicity Adjustment

No multiplicity adjustment is planned in this study.

Changes from the planned analysis in protocol

Efficacy Population is not used in this statistical analysis plan (SAP) and analysis since Safety Population is applied for overall population and each pre-specified subgroup. The definition for efficacy population for each pre-specified subgroup is the same as the definition based on Safety Population.

NSCLC patients tested with ODxTT test is added as an ODxTT sub-population in this SAP. RET-fusion positive NSCLC with measurable (target) lesions in CNS/brain patients, including brainstem and cerebellum, and without radiotherapy and radiosurgery 2 months before study drug, will be included into CNS metastases sub-population.

Patients are grouped based on different grouping rules respectively. For example, the grouped starting dose will be based on patients' starting treatment dose.

CNS metastases activity analysis is added as an exploratory analysis. The exploratory analysis on medical history, prior or concomitant medication, and time to event for pneumonitis, pneumonia, and hypertension are added, respectively.

Treatment-emergent adverse event (TEAE), related TEAE, serious adverse event (SAE), and related SAE will be analysed by 1) prior PD-1/PD-L1 status for RET-fusion NSCLC patients treated at 400 mg QD, 2) by selected subgroups, RET-fusion NSCLC, MTC, others, and all Safety Population treated at 400 mg QD.

Changes from SAP version 1.0.

The definition for Efficacy Population is added to the SAP. The Efficacy Population is defined as a subset of the Safety Population who were dosed on or before 22 May 2020.This modification was based on feedback received from FDA. Specifically, to allow sufficient follow up time from initial response among responders.

CNS metastases activity analysis is using only lesions in CNS/brain. The CNS ORR which is based on CNS/brain lesions will be provided. However, the analysis for PFS and DOR which are based on CNS/brain lesions are removed.

The analysis of DOR across RET-altered status, and tumour types, *i.e.,* RET-fusion NSCLC, RET-fusion papillary thyroid cancer (PTC), MTC, and others, are added as a supportive analysis.

Three adverse events of special interest (AESI) categories, pneumonia AESI, pneumonitis AESI, and tumour lysis syndrome AESI are added. Additional analysis for the AESIs are defined.

One grouped term neutropenia, which include neutropenia, neutrophil count decreased, is also added. The analysis for grouped neutropenia will follow the same analysis method for AESIs. The exploratory time to hevent analysis for a single preferred term hypertension will also be provided.

The summary analysis of demographics, medical history, prior and concomitant medication, prior anticancer therapies, dose modification will be provided for the AESIs.

The laboratory parameter creatinine will be graded with NCI CTCAE version 5.0 to correct the grading error for this specific laboratory test used in CTCAE version 4.03.

Results

The applicant has submitted efficacy results from 233 RET fusion-positive NSCLC patients from both phase I (dose escalation) and II (Groups 1, 2 and 8) whose treatment at the proposed starting dose of pralsetinib of 400 mg QD started on or before 22 May 2020. From these, 158 have received previous treatment (136 with platinum chemotherapy and 22 with non-platinum systemic treatment), while 75 were treatment-naïve. The efficacy dataset includes all data reported from these patients up to a cut-off of 6 November 2020. This cut-off was chosen to allow sufficient follow-up time from initial response among responders.

Participant flow

Table 19Patient Disposition (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment: Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Platinum Treatment: No Prior Systemic Treatment (N=75) n (%)
Discontinued from Treatment	123 (52.8)	86 (54.4)	76 (55.9)	10 (45.5)	37 (49.3)
Continuing on Treatment	110 (47.2)	72 (45.6)	60 (44.1)	12 (54.5)	38 (50.7)
Discontinued from Study	102 (43.8)	74 (46.8)	66 (48.5)	8 (36.4)	28 (37.3)
Continuing Study Follow-up	131 (56.2)	84 (53.2)	70 (51.5)	14 (63.6)	47 (62.7)
Reasons for Discontinuation of Treatment[a]					
Disease Progression	74 (31.8)	51 (32.3)	43 (31.6)	8 (36.4)	23 (30.7)
Adverse Event(s)	34 (14.6)	26 (16.5)	24 (17.6)	2 (9.1)	8 (10.7)
Related	17 (7.3)	12 (7.6)	11 (8.1)	1 (4.5)	5 (6.7)
Withdrew Consent	10 (4.3)	6 (3.8)	6 (4.4)	0	4 (5.3)
Investigator's Decision	3 (1.3)	2 (1.3)	2 (1.5)	0	1 (1.3)
Administrative/other	2 (<1)	1 (<1)	1 (<1)	0	1 (1.3)
Reasons for Discontinuation of Study[b]					
Disease Progression	25 (10.7)	14 (8.9)	13 (9.6)	1 (4.5)	11 (14.7)
Adverse Event(s)	2 (<1)	2 (1.3)	2 (1.5)	0	0
Related	1 (<1)	1 (<1)	1 (<1)	0	0
Death	55 (23.6)	43 (27.2)	38 (27.9)	5 (22.7)	12 (16.0)
Lost to Follow-up	2 (<1)	1 (<1)	1 (<1)	0	1 (1.3)
Withdrew Consent	16 (6.9)	12 (7.6)	10 (7.4)	2 (9.1)	4 (5.3)
Initiation of another antineoplastic therapy	2 (<1)	2 (1.3)	2 (1.5)	0	0

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection. Notes: [a] No patients discontinued treatment due to death, loss to follow-up, protocol deviation, pregnancy, administrative/other, or sponsor decision. [b] No patients discontinued study follow-up due to protocol deviation, pregnancy, investigator's decision, or sponsor decision. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.1.2.1.4.2

Recruitment

The first patient was enrolled on 17 March 2017 and the last patient enrolled for the efficacy dataset was on 22 May 2020, with a data cut-off date of 6 November 2020 (cut-off for interim analysis: 18 November 2019 data cut-off with 11 July 2019 enrolment cut-off and 22 May 2020 data cut-off with 11 Jul 2019 enrolment cut-off).

Conduct of the study

Among all 233 patients in the efficacy population, median follow-up is 17.1 months, and 75.5% of patients are censored.

Table 20: Protocol deviations (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population) – (Data cut-off date 6 November 2020)

Category Sub-Category	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
Patients with at Least One Important/Major Deviation	41(17.6)	26(16.5)	20(14.7)	6(27.3)	15(20.0)
Important	39(16.7)	25(15.8)	20(14.7)	5(22.7)	14(18.7)
Study Conduct/Procedures, Study Assessment	13(5.6)	11(7.0)	8(5.9)	3(13.6)	2(2.7)
Study Conduct/Procedures, Screening	7(3.0)	4(2.5)	3(2.2)	1(4.5)	3(4.0)
Safety, Reporting/Follow-Up	5(2.1)	5(3.2)	4(2.9)	1(4.5)	0
Study Conduct/Procedures	4(1.7)	2(1.3)	2(1.5)	0	2(2.7)
Study Conduct/Procedures, Study Restrictions/Withdrawal Criteria	4(1.7)	3(1.9)	2(1.5)	1(4.5)	1(1.3)
Study Conduct/Procedures, Sample Collection	2(<1)	0	0	0	2(2.7)
BLU-667-1101-10-1207-003	1(<1)	0	0	0	1(1.3)
Informed Consent, Presence/Absence	1(<1)	0	0	0	1(1.3)
Informed Consent, Version	1(<1)	0	0	0	1(1.3)
Investigational Product, Dispensing/Accountability	1(<1)	0	0	0	1(1.3)
Other	1(<1)	1(<1)	1(<1)	0	0
Other, Other	1(<1)	1(<1)	1(<1)	0	0
Safety, Recording	1(<1)	1(<1)	1(<1)	0	0
Study Conduct/Procedures, Dose Formulation/Dose Administration	1(<1)	1(<1)	1(<1)	0	0
Major	4(1.7)	3(1.9)	2(1.5)	1(4.5)	1(1.3)
Medical Review 1	3(1.3)	3(1.9)	2(1.5)	1(4.5)	0
Medical Review 1, Medical Review 2	1(<1)	0	0	0	1(1.3)

Source: Listing 16.2.7.1.1

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Note: Medical Review 1 is from medical monitor review for patients excluded from Response Evaluation Population.
Medical Review 1/Medical Review 2 is from medical monitor review for patients excluded from both Response Evaluation Population and RET altered Measurable Disease Population.

Reasons for screen failures for 61 patients were provided (not shown in this report). It is likely that there were more patients who did not undergo 'formal' screening since RET-testing after 'pre-screening' did not yield favourable results for participation.

A total of 41 patients in the efficacy population of NSCLC had at least one major protocol deviation. Most major deviations are procedural and it is likely they would not have a significant impact on efficacy or safety, although a minority might have compromised optimal response assessment.

Baseline data

Table 21: Patient Demographics (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment	
				Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
Age (years)					
n	233	158	136	22	75
Mean (StdDev)	59.2 (12.20)	58.6 (11.39)	58.1 (11.58)	61.4 (9.93)	60.6 (13.74)
Median	60.0	59.5	59.0	60.5	63.0
Min, Max	26, 87	26, 85	26, 85	47, 84	30, 87
Age Group (years) (n (%))					
<65	145 (62.2)	104 (65.8)	90 (66.2)	14 (63.6)	41 (54.7)
>=65	88 (37.8)	54 (34.2)	46 (33.8)	8 (36.4)	34 (45.3)
Sex (n (%))					
Female	122 (52.4)	86 (54.4)	71 (52.2)	15 (68.2)	36 (48.0)
Male	111 (47.6)	72 (45.6)	65 (47.8)	7 (31.8)	39 (52.0)
Ethnicity (n (%))					
Hispanic or Latino	9 (3.9)	6 (3.8)	5 (3.7)	1 (4.5)	3 (4.0)
Not Hispanic or Latino	201 (86.3)	133 (84.2)	113 (83.1)	20 (90.9)	68 (90.7)
Not Reported	6 (2.6)	6 (3.8)	6 (4.4)	0	0
Unknown	17 (7.3)	13 (8.2)	12 (8.8)	1 (4.5)	4 (5.3)
Race (n (%))					
American Indian or Alaska Native	0	0	0	0	0
Asian	92 (39.5)	75 (47.5)	70 (51.5)	5 (22.7)	17 (22.7)
Black or African American	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	2 (0.9)	1 (0.6)	0	1 (4.5)	1 (1.3)
White	121 (51.9)	69 (43.7)	55 (40.4)	14 (63.6)	52 (69.3)
Unknown	16 (6.9)	11 (7.0)	9 (6.6)	2 (9.1)	5 (6.7)
Other	2 (0.9)	2 (1.3)	2 (1.5)	0	0
Race Group (n (%))					
Asian	92 (39.5)	75 (47.5)	70 (51.5)	5 (22.7)	17 (22.7)
Non-Asian	125 (53.6)	72 (45.6)	57 (41.9)	15 (68.2)	53 (70.7)
Unknown	16 (6.9)	11 (7.0)	9 (6.6)	2 (9.1)	5 (6.7)
Region (n (%))					
US	62 (26.6)	40 (25.3)	32 (23.5)	8 (36.4)	22 (29.3)
Europe	85 (36.5)	45 (28.5)	36 (26.5)	9 (40.9)	40 (53.3)
Asia	86 (36.9)	73 (46.2)	68 (50.0)	5 (22.7)	13 (17.3)
Height (cm)					
n	231	157	135	22	74
Mean (StdDev)	166.37 (9.692)	165.78 (9.562)	165.80 (9.360)	165.60 (10.961)	167.63 (9.910)
Median	165.10	164.50	165.00	163.05	167.25
Min, Max	145.0, 190.5	145.0, 190.5	145.0, 188.0	148.0, 190.5	145.1, 185.0

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection; StdDev= standard deviation. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.1.3.1.4.2

Table 22Baseline Disease Characteristics (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment	
				Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
ECOG Performance Status[a]					
0	78 (33.5)	47 (29.7)	37 (27.2)	10 (45.5)	31 (41.3)
1	149 (63.9)	106 (67.1)	94 (69.1)	12 (54.5)	43 (57.3)
2	6 (2.6)	5 (3.2)	5 (3.7)	0	1 (1.3)
Histology Type					
Adenocarcinoma	224 (96.1)	150 (94.9)	131 (96.3)	19 (86.4)	74 (98.7)
Squamous	3 (1.3)	2 (1.3)	1 (<1)	1 (4.5)	1 (1.3)
Undifferentiated	1 (<1)	1 (<1)	1 (<1)	0	0
Other	5 (2.1)	5 (3.2)	3 (2.2)	2 (9.1)	0
Target/Non-Target Lesion Location[b]					
Adrenal	25 (10.7)	17 (10.8)	12 (8.8)	5 (22.7)	8 (10.7)
Bone	86 (36.9)	66 (41.8)	56 (41.2)	10 (45.5)	20 (26.7)
CNS (Brain)	64 (27.5)	45 (28.5)	38 (27.9)	7 (31.8)	19 (25.3)
Hilar Adenopathy	32 (13.7)	16 (10.1)	10 (7.4)	6 (27.3)	16 (21.3)
Liver	52 (22.3)	39 (24.7)	33 (24.3)	6 (27.3)	13 (17.3)
Lung	195 (83.7)	132 (83.5)	110 (80.9)	22 (100)	63 (84.0)
Mediastinal Adenopathy	92 (39.5)	53 (33.5)	39 (28.7)	14 (63.6)	39 (52.0)
Pleural	49 (21.0)	32 (20.3)	26 (19.1)	6 (27.3)	17 (22.7)
Thoracic Adenopathy	25 (10.7)	12 (7.6)	10 (7.4)	2 (9.1)	13 (17.3)
History of CNS/Brain Metastases	87 (37.3)	62 (39.2)	54 (39.7)	8 (36.4)	25 (33.3)
TNM Stage at Screening					
Stage IIB[c]	1 (<1)	0	0	0	1 (1.3)
Stage III	5 (2.1)	4 (2.5)	4 (2.9)	0	1 (1.3)
Stage III	0	0	0	0	0
Stage IIIA	1 (<1)	1 (<1)	1 (<1)	0	0
Stage IIIB	3 (1.3)	2 (1.3)	2 (1.5)	0	1 (1.3)
Stage IIIC	1 (<1)	1 (<1)	1 (<1)	0	0
Stage IV	227 (97.4)	154 (97.5)	132 (97.1)	22 (100)	73 (97.3)
Stage IV	109 (46.8)	64 (40.5)	50 (36.8)	14 (63.6)	45 (60.0)
Stage IVA	40 (17.2)	27 (17.1)	24 (17.6)	3 (13.6)	13 (17.3)
Stage IVB	72 (30.9)	58 (36.7)	55 (40.4)	3 (13.6)	14 (18.7)
Stage IVC	6 (2.6)	5 (3.2)	3 (2.2)	2 (9.1)	1 (1.3)
Smoking History					
Never Smoked	145 (62.2)	104 (65.8)	86 (63.2)	18 (81.8)	41 (54.7)
Former	78 (33.5)	50 (31.6)	47 (34.6)	3 (13.6)	28 (37.3)
Current	6 (2.6)	2 (1.3)	1 (<1)	1 (4.5)	4 (5.3)
Unknown	4 (1.7)	2 (1.3)	2 (1.5)	0	2 (2.7)
RET Fusion Partner					
KIF5B	164 (70.4)	114 (72.2)	98 (72.1)	16 (72.7)	50 (66.7)
CCDC6	41 (17.6)	28 (17.7)	24 (17.6)	4 (18.2)	13 (17.3)
NCOA4	1 (<1)	0	0	0	1 (1.3)
Other[d]	27 (11.6)	16 (10.1)	14 (10.3)	2 (9.1)	11 (14.7)

Abbreviations: CNS= central nervous system; ECOG= eastern cooperative oncology group; NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection. Notes: [a] Patients with a baseline ECOG performance status score of 2 were allocated up until protocol amendment 4.1; [b] Target/non-target lesion location was based on central image data. Selected lesion locations for this table are based on occurrence in >10% overall; [c] Patient had recurrent NSCLC and was considered unfit for surgery based on age and clinical considerations; [d] "Other" includes 20 patients with unknown fusion partner, as well as 7 with know fusion partners of AFF2, EML4, TRIM24, ZBTB5, CCDC186, ANKRD25, KIAA1468. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.1.4.1.4.2

RET fusions were detected in 79.4% of patients using next generation sequencing (NGS) (42.9% tumour samples; 15.9% blood or plasma samples, 20.6% unknown), 18.0% using FISH, and 2.6% using other methods.

Table 23. Prior Antineoplastic Therapies (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

				No Prior Platinum Treatment	
	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
Number of Prior Line of Therapy					
Mean (StdDev)	1.4 (1.54)	2.1 (1.43)	2.3 (1.48)	1.1 (0.29)	0.0 (0)
Median	1.0	2.0	2.0	1.0	0.0
Min, Max	0, 8	1, 8	1, 8	1, 2	0, 0
Prior Systemic Therapies					
Chemotherapy	138 (59.2)	138 (87.3)	136 (100)	2 (9.1)	0
Platinum-based Chemotherapy	136 (58.4)	136 (86.1)	136 (100)	0	0
PD-1/PD-L1 Inhibitors	69 (29.6)	69 (43.7)	55 (40.4)	14 (63.6)	0
Multikinase Inhibitor(s)	44 (18.9)	44 (27.8)	38 (27.9)	6 (27.3)	0
Prior Radiation Therapy	90 (38.6)	74 (46.8)	65 (47.8)	9 (40.9)	16 (21.3)
Prior Cancer Related Surgeries or Procedures	116 (49.8)	82 (51.9)	70 (51.5)	12 (54.5)	34 (45.3)

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection.
Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.1.6.1.4.2

Only 66% (84 out of 128 available samples from the original efficacy dataset N=132, data cut-off 18 November 2019) of centrally-tested pre-treatment ctDNA samples were concordant with local testing techniques that had determined RET positivity. However, this might be attributed –at least in part– to low sensitivity of ctDNA testing, which is conversely highly specific.

Numbers analysed

The safety population includes all patients treated with pralsetinib at 400 mg QD up to data cut-off 6 November 2020 (see section 2.6 Clinical safety). The efficacy population includes those who had started treatment on or before 22 May 2020 (enrolment cut-off date), which allows for sufficient follow-up to assess response up to data cut-off date on 6 November 2020.

Table 24. Analysis Populations (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD)

Patient Group	Efficacy Population - n (%)	Safety Population - n (%)
RET-fusion NSCLC	**233 (100)**	**281 (100)**
Prior systemic treatment	158 (67.8)	165 (58.7)
Prior platinum treatment	136 (58.4)	141 (50.2)
No prior platinum treatment	97 (41.6)	140 (49.8)
Prior non-platinum systemic treatment	22 (9.4)	24 (8.5)
No prior systemic treatment	75 (32.2)	116 (41.3)

Abbreviations: NSCLC = non-small cell lung cancer; QD = once daily; RET = rearranged during transfection.

Note: Percentages are based on the number of patients in each population.

Outcomes and estimation

Primary efficacy endpoint – ORR

Table 25. Summary of Best Overall Response (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment: Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Platinum Treatment: No Prior Systemic Treatment (N=75) n (%)
Overall Response Rate (ORR)[a]	150 (64.4)	96 (60.8)	80 (58.8)	16 (72.7)	54 (72.0)
95% CI	(57.9, 70.5)	(52.7, 68.4)	(50.1, 67.2)	(49.8, 89.3)	(60.4, 81.8)
Best Overall Response					
Complete Response (CR)	11 (4.7)	7 (4.4)	7 (5.1)	0	4 (5.3)
Partial Response (PR)	139 (59.7)	89 (56.3)	73 (53.7)	16 (72.7)	50 (66.7)
Stable Disease (SD)	61 (26.2)	47 (29.7)	43 (31.6)	4 (18.2)	14 (18.7)
Progressive Disease (PD)	13 (5.6)	8 (5.1)	6 (4.4)	2 (9.1)	5 (6.7)
Not Evaluable (NE)	9 (3.9)	7 (4.4)	7 (5.1)	0	2 (2.7)
Clinical Benefit Rate (CBR)[b]	178 (76.4)	118 (74.7)	101 (74.3)	17 (77.3)	60 (80.0)
95% CI	(70.4, 81.7)	(67.2, 81.3)	(66.1, 81.4)	(54.6, 92.2)	(69.2, 88.4)
Disease Control Rate (DCR)[c]	211 (90.6)	143 (90.5)	123 (90.4)	20 (90.9)	68 (90.7)
95% CI	(86.1, 94.0)	(84.8, 94.6)	(84.2, 94.8)	(70.8, 98.9)	(81.7, 96.2)

Abbreviations: CI= confidence interval; NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection. Notes: [a] ORR= The proportion of patients with best overall response of confirmed CR or PR, defined as at least two assessments of CR or PR with at least 28 days apart and no PD in between. A single timepoint of CR o PR is categorised as best overall response of SD. [b] CBR: The proportion of patients with confirmed CR/PR or SD lasting >= 16 weeks (i.e., 4 cycles if 28 days in one cycle) from first dose date. [c] DCR: The proportion of patients with best overall response CR or PR or SD. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.1.1.4.2

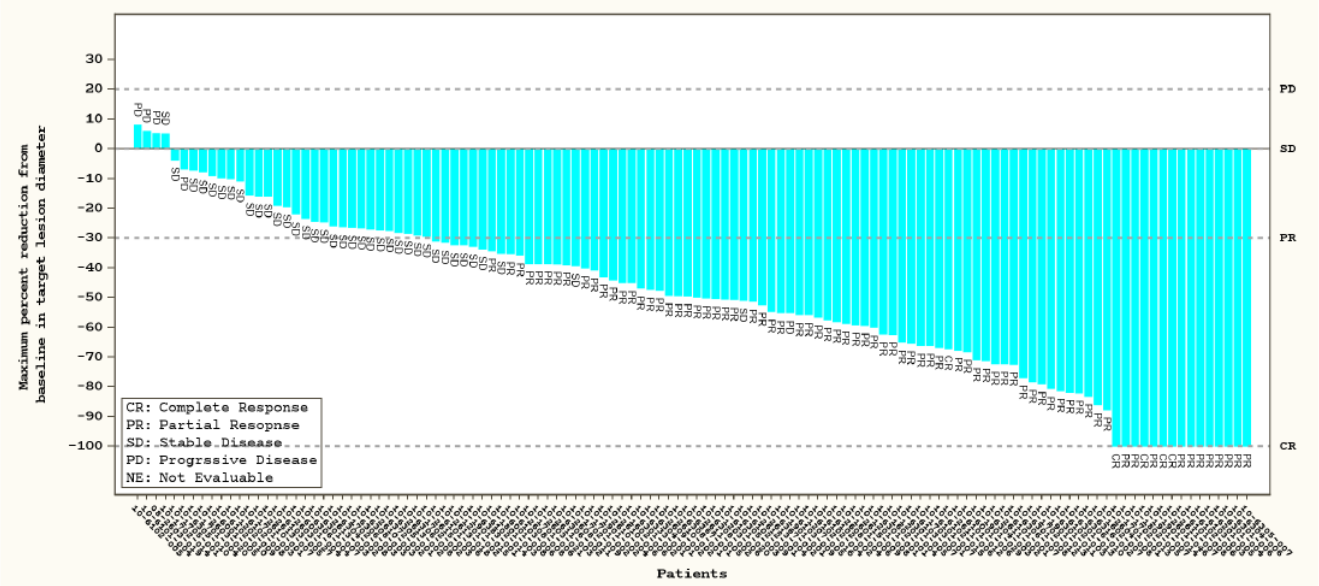

Figure 29. Annotated Waterfall Plot (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Prior Platinum, Efficacy Population)

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.2.1.4.2.1

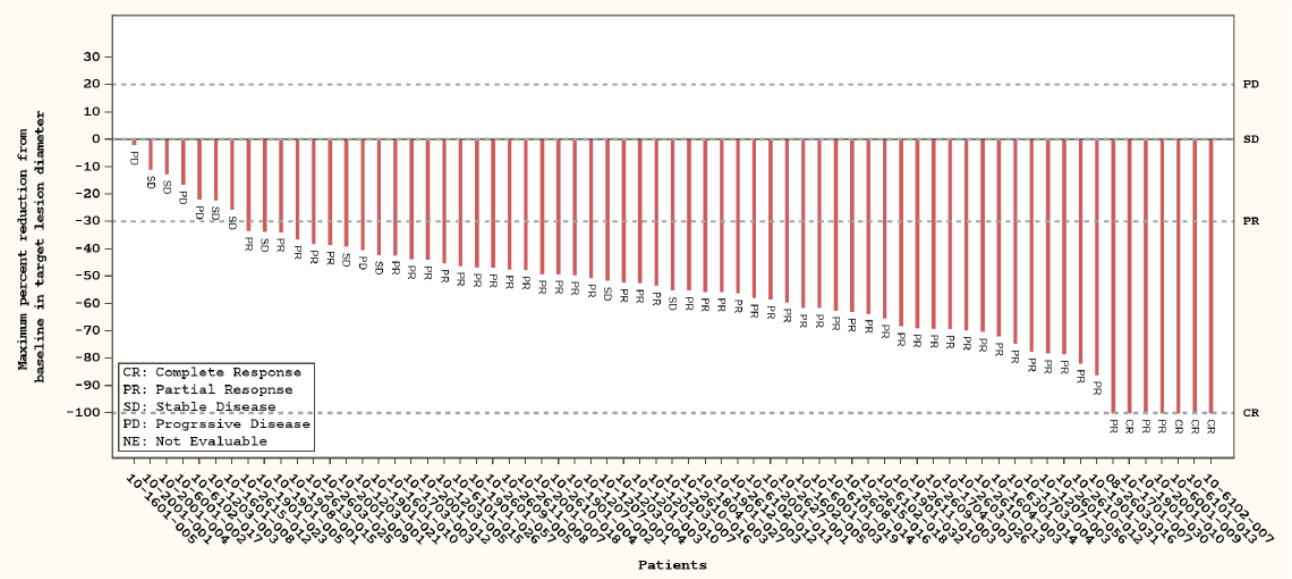

Figure 30. Annotated Waterfall Plot (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Systemic Treatment-Naïve, Efficacy Population)

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.2.1.4.2.1

Secondary efficacy endpoints

Table 33. Summary of Time to and Duration of Response (Confirmed Response Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

				No Prior Platinum Treatment	
	Overall (N=150)	Prior Systemic Treatment (N=96)	Prior Platinum Treatment (N=80)	Prior non-Platinum Systemic Treatment (N=16)	No Prior Systemic Treatment (N=54)
Time to First Response (months)					
Mean (StdDev)	2.48 (1.656)	2.52 (1.816)	2.62 (1.936)	2.05 (0.934)	2.41 (1.338)
Median	1.84	1.84	1.84	1.81	1.81
Min, Max	0.9, 11.4	1.3, 11.4	1.3, 11.4	1.6, 5.5	0.9, 6.1
Patients with Event, n (%)	49 (32.7)	35 (36.5)	30 (37.5)	5 (31.3)	14 (25.9)
Patients Censored, n (%)	101 (67.3)	61 (63.5)	50 (62.5)	11 (68.8)	40 (74.1)
Discontinued from Study	7 (4.7)	3 (3.1)	3 (3.8)	- (-, -)	4 (7.4)
K-M Estimated DOR (months)					
Median (95% CI)	22.3 (14.7, -)	22.3 (15.1, -)	22.3 (15.1, -)	- (9.2, -)	- (9.0, -)
(At Risk, Censored, Events)	(6, 96, 48)	(6, 56, 34)	(6, 45, 29)	(0, 11, 5)[a]	(0, 40, 14)[a]
25th, 75th percentiles	8.7, -	8.8, -	8.8, -	9.2, -	7.4, -
K-M Estimated DOR Rate (95% CI)					
3 months	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
6 months	84.3 (78.1, 90.5)	84.4 (76.8, 91.9)	82.6 (74.0, 91.2)	93.3 (80.7, 100.0)	83.8 (72.8, 94.8)
9 months	73.2 (65.3, 81.2)	74.5 (65.2, 83.7)	73.7 (63.5, 83.9)	78.3 (56.5, 100.0)	69.9 (54.3, 85.5)
12 months	63.8 (54.5, 73.0)	66.9 (56.4, 77.3)	68.4 (57.3, 79.5)	55.9 (25.4, 86.5)	53.9 (33.9, 74.0)
18 months	52.9 (42.2, 63.6)	54.4 (42.5, 66.4)	53.7 (40.7, 66.8)	55.9 (25.4, 86.5)	53.9 (33.9, 74.0)
24 months	44.1 (26.0, 62.2)	45.4 (26.3, 64.4)	44.8 (25.4, 64.1)	- (-, -)	- (-, -)
DOR Rate, n (%)[b]					
<6 months	48 (32.0)	24 (25.0)	21 (26.3)	3 (18.8)	24 (44.4)
<3 months	8 (5.3)	4 (4.2)	4 (5.0)	0	4 (7.4)
>=3 months to <6 months	40 (26.7)	20 (20.8)	17 (21.3)	3 (18.8)	20 (37.0)
>=6 months	102 (68.0)	72 (75.0)	59 (73.8)	13 (81.3)	30 (55.6)
>=9 months	67 (44.7)	53 (55.2)	45 (56.3)	8 (50.0)	14 (25.9)
>=12 months	48 (32.0)	41 (42.7)	36 (45.0)	5 (31.3)	7 (13.0)
>=18 months	26 (17.3)	25 (26.0)	20 (25.0)	5 (31.3)	1 (1.9)
>=24 months	2 (1.3)	2 (2.1)	2 (2.5)	0	0

Abbreviations: CI = confidence interval; DOR= Duration of response; K-M= Kaplan-Meier; NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection; StdDev= standard deviation. Notes: [a] Number of patients at risk, censored, and events at database snapshot; median duration of response is not yet reached if '-' is displayed. [b] Observed duration of response. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.3.1-2.4.2

Table 34. Summary of Progression-Free Survival (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

				No Prior Platinum Treatment	
	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
Patients with Event, n (%)[a]	102 (43.8)	75 (47.5)	65 (47.8)	10 (45.5)	27 (36.0)
Progressive Disease (PD)	77 (33.0)	55 (34.8)	48 (35.3)	7 (31.8)	22 (29.3)
Death without PD before the 1st Scheduled Assessment	8 (3.4)	5 (3.2)	5 (3.7)	0	3 (4.0)
Death without PD before the 2nd Scheduled Assessment	11 (4.7)	8 (5.1)	7 (5.1)	1 (4.5)	3 (4.0)
Death without PD after 2nd and between Scheduled Assessments	14 (6.0)	12 (7.6)	10 (7.4)	2 (9.1)	2 (2.7)
Patients Censored, n (%)[a]	131 (56.2)	83 (52.5)	71 (52.2)	12 (54.5)	48 (64.0)
No Documented PD	131 (56.2)	83 (52.5)	71 (52.2)	12 (54.5)	48 (64.0)
PFS Follow-up K-M Estimates (Months)					
Median (95% CI)	12.9 (11.1, 17.5)	18.4 (13.1, 19.8)	18.4 (13.2, 19.8)	20.2 (9.3, 23.8)	9.2 (8.6, 11.0)
K-M Estimated PFS (Months)					
Median (95% CI)	16.4 (11.0, 24.1)	16.4 (10.7, 24.1)	16.5 (10.5, 24.1)	12.8 (9.1, -)	13.0 (9.1, -)
(At Risk, Censored, Events)	(50, 89, 94)	(45, 46, 67)	(39, 39, 58)	(6, 7, 9)	(11, 38, 26)
25th, 75th percentiles	6.1, -	5.8, -	5.8, -	7.1, -	7.3, -
K-M Estimated PFS Rate (95% CI)					
3 months	90.7 (86.9, 94.5)	90.8 (86.1, 95.4)	90.8 (85.8, 95.7)	90.7 (78.4, 100.0)	90.5 (83.8, 97.2)
6 months	75.1 (69.3, 80.9)	72.7 (65.5, 79.9)	72.1 (64.2, 80.0)	76.1 (57.7, 94.4)	80.2 (70.9, 89.6)
9 months	64.7 (58.2, 71.2)	62.5 (54.6, 70.5)	61.2 (52.6, 69.8)	71.0 (51.4, 90.6)	69.5 (58.1, 80.9)
12 months	56.0 (48.9, 63.1)	56.3 (48.0, 64.5)	56.7 (47.9, 65.6)	52.1 (28.5, 75.7)	52.6 (37.7, 67.5)
18 months	46.7 (38.8, 54.7)	46.5 (37.5, 55.5)	46.7 (37.1, 56.4)	43.4 (18.4, 68.5)	47.8 (31.6, 64.1)
24 months	42.1 (33.2, 51.0)	41.6 (31.8, 51.3)	41.0 (30.3, 51.6)	43.4 (18.4, 68.5)	47.8 (31.6, 64.1)
PFS Rate, n (%)[b]					
<6 months	82 (35.2)	57 (36.1)	50 (36.8)	7 (31.8)	25 (33.3)
<3 months	34 (14.6)	24 (15.2)	21 (15.4)	3 (13.6)	10 (13.3)
>=3 months to <6 months	48 (20.6)	33 (20.9)	29 (21.3)	4 (18.2)	15 (20.0)
>=6 months	151 (64.8)	101 (63.9)	86 (63.2)	15 (68.2)	50 (66.7)
>=9 months	117 (50.2)	86 (54.4)	73 (53.7)	13 (59.1)	31 (41.3)
>=12 months	70 (30.0)	56 (35.4)	50 (36.8)	6 (27.3)	14 (18.7)
>=18 months	45 (19.3)	41 (25.9)	36 (26.5)	5 (22.7)	4 (5.3)
>=24 months	11 (4.7)	10 (6.3)	8 (5.9)	2 (9.1)	1 (1.3)

Abbreviations: CI = confidence interval; K-M = Kaplan-Meier; NSCLC = non-small cell lung cancer; PFS = progression-free survival; QD = once daily; RET= rearranged during transfection. Note: [a] No patients had missing baseline assessment, new anticancer/non-protocol treatment, or a progression event after missing >= 2 consecutively scheduled disease assessments; [b] Observed PFS. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.2.1-2.4.2.

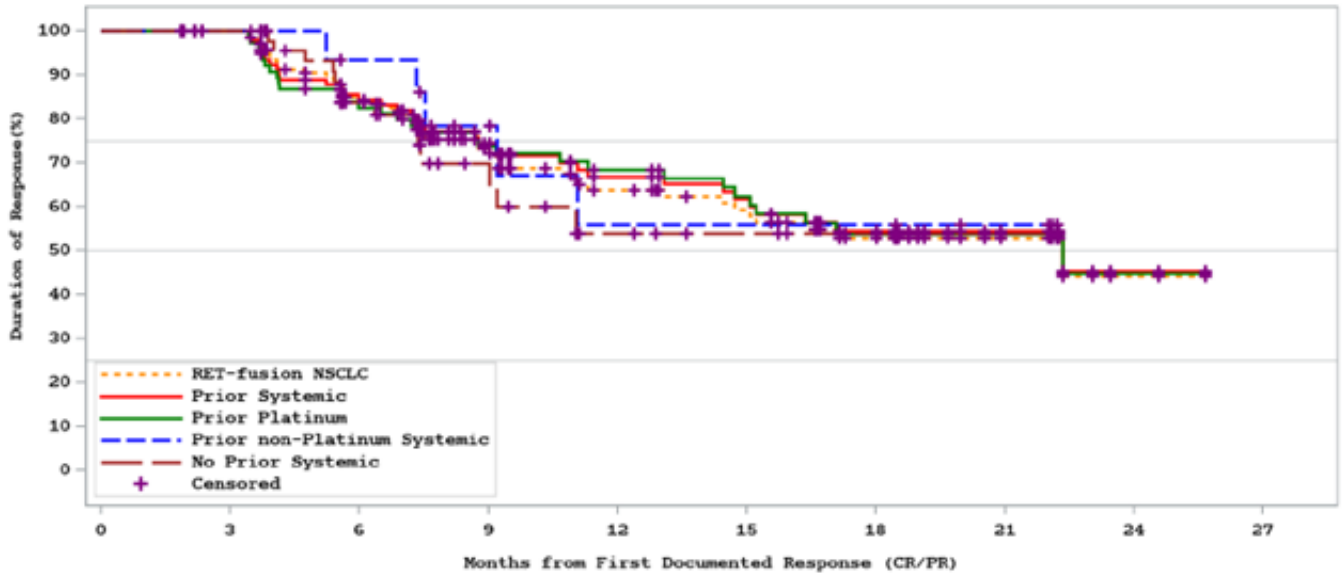

Figure 31. Kaplan-Meier Survival Curves of Duration of Response (Confirmed Response Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection;

Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.4.1-2.4.2

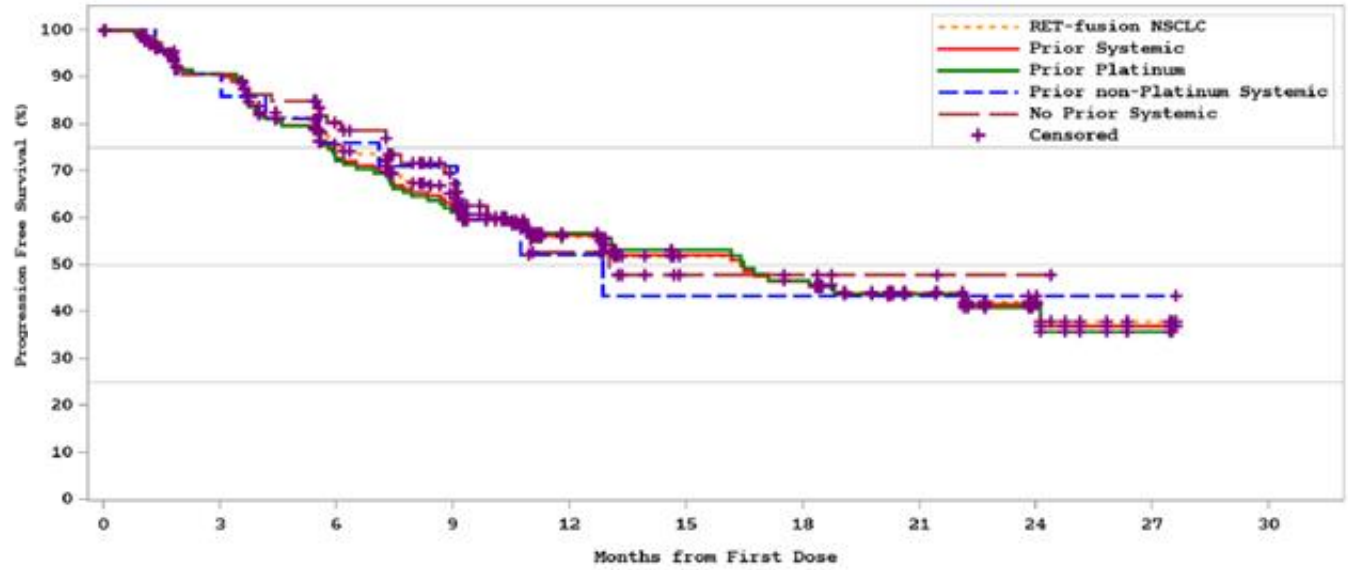

Figure 32. Kaplan-Meier Survival Curves of Progression-Free Survival (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

Abbreviations: NSCLC= non-small cell lung cancer; QD= once daily; RET= rearranged during transfection;

Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.3.1-2.4.2

Table 26. Summary of Overall Survival (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Efficacy Population)

	Overall (N=233) n (%)	Prior Systemic Treatment (N=158) n (%)	Prior Platinum Treatment (N=136) n (%)	No Prior Platinum Treatment	
				Prior non-Platinum Systemic Treatment (N=22) n (%)	No Prior Systemic Treatment (N=75) n (%)
Deaths, n (%)	57 (24.5)	45 (28.5)	40 (29.4)	5 (22.7)	12 (16.0)
Censored, n (%)	176 (75.5)	113 (71.5)	96 (70.6)	17 (77.3)	63 (84.0)
Alive	158 (67.8)	100 (63.3)	85 (62.5)	15 (68.2)	58 (77.3)
Lost to Follow-up	2 (<1)	1 (<1)	1 (<1)	0	1 (1.3)
Withdrawal of Consent	16 (6.9)	12 (7.6)	10 (7.4)	2 (9.1)	4 (5.3)
Overall Follow-up Time K-M Estimates (Months)					
Median (95% CI)	17.1 (13.7, 19.6)	20.1 (19.0, 21.5)	20.1 (19.4, 21.5)	16.6 (10.7, 24.7)	12.8 (11.1, 15.0)
25th, 75th percentiles	11.3, 22.1	12.3, 24.7	12.5, 23.9	10.7, 24.7	9.5, 18.5
K-M Estimates OS (months)					
Median (95% CI)	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
(At Risk, Censored, Events)	(0, 176, 57)	(0, 113, 45)	(0, 96, 40)	(0, 17, 5)	(0, 63, 12)
25th, 75th percentiles	12.8, -	9.0, -	9.0, -	9.1, -	14.9, -
K-M Estimates OS Rate (95% CI)					
3 months	96.0 (93.5, 98.6)	96.1 (93.0, 99.2)	95.4 (91.9, 99.0)	100.0 (100.0, 100.0)	96.0 (91.6, 100.0)
6 months	87.6 (83.2, 92.0)	85.6 (79.9, 91.3)	84.9 (78.6, 91.2)	90.5 (77.9, 100.0)	91.7 (85.4, 98.1)
9 months	80.9 (75.5, 86.2)	75.8 (68.6, 82.9)	75.3 (67.5, 83.0)	79.2 (60.8, 97.5)	91.7 (85.4, 98.1)
12 months	76.0 (69.9, 82.0)	72.5 (64.9, 80.0)	72.4 (64.3, 80.5)	73.1 (52.6, 93.5)	82.3 (71.9, 92.8)
18 months	69.8 (62.5, 77.1)	67.4 (58.9, 75.9)	66.7 (57.5, 75.9)	73.1 (52.6, 93.5)	74.0 (59.3, 88.6)
24 months	66.0 (57.9, 74.1)	63.2 (54.0, 72.4)	61.9 (51.9, 71.9)	73.1 (52.6, 93.5)	74.0 (59.3, 88.6)
OS Rate, n (%)[a]					
<6 months	53 (22.7)	41 (25.9)	35 (25.7)	6 (27.3)	12 (16.0)
<3 months	22 (9.4)	16 (10.1)	15 (11.0)	1 (4.5)	6 (8.0)
>=3 months to <6 months	31 (13.3)	25 (15.8)	20 (14.7)	5 (22.7)	6 (8.0)
>=6 months	180 (77.3)	117 (74.1)	101 (74.3)	16 (72.7)	63 (84.0)
>=9 months	144 (61.8)	97 (61.4)	84 (61.8)	13 (59.1)	47 (62.7)
>=12 months	100 (42.9)	76 (48.1)	67 (49.3)	9 (40.9)	24 (32.0)
>=18 months	57 (24.5)	49 (31.0)	43 (31.6)	6 (27.3)	8 (10.7)
>=24 months	20 (8.6)	18 (11.4)	14 (10.3)	4 (18.2)	2 (2.7)

Abbreviations: CI = confidence interval; K-M = Kaplan-Meier; NSCLC = non-small cell lung cancer; OS = overall survival; QD = once daily; RET= rearranged during transfection. Note: [a] Observed OS. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.4.1.4.2.

Ancillary analyses

Subgroup analyses – ORR

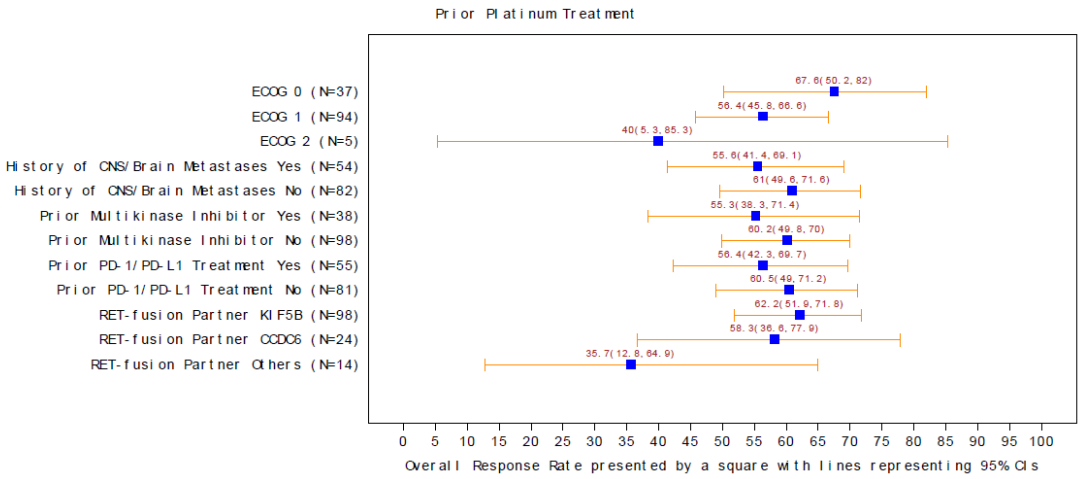

Figure 33. Forest Plot of ORR (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Prior Platinum, Efficacy Population)

Abbreviations: CNS= central nervous system; ECOG= eastern cooperative oncology group; NSCLC = non-small cell lung cancer; ORR = overall response rate; QD = once daily; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.1.1.4.2.1

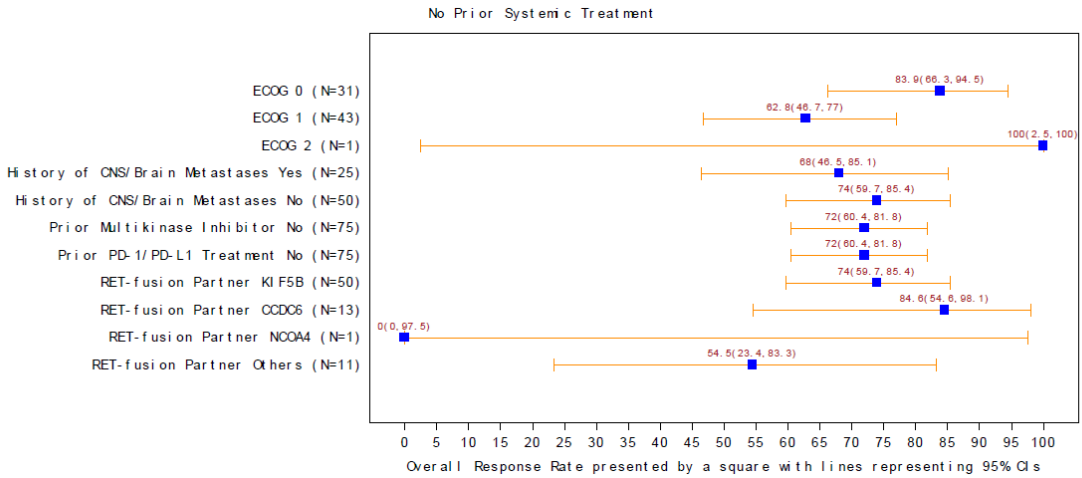

Figure 34. Forest Plot of ORR (Patients with RET Fusion-Positive NSCLC Treated at 400 mg QD, Systemic Treatment-Naïve, Efficacy Population)

Abbreviations: CNS= central nervous system; ECOG= eastern cooperative oncology group; NSCLC = non-small cell lung cancer; ORR = overall response rate; QD = once daily; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Figure 15.2.1.1.4.2.1

BICR response rates were: ORR= 67.7% (95% CI: 59.9, 74.8) in 164 patients with a KIF5B fusion partner; and ORR= 68.3% (95% CI: 51.9, 81.9) in 41 patients with a CCDC6 fusion partner.

Table 27. ORR by Gender

	Female			Male		
	RET fusion NSCLC n (%)	Treatment Naïve n (%)	Prior Platinum Treatment n (%)	RET fusion NSCLC n (%)	Treatment Naïve n (%)	Prior Platinum Treatment n (%)
Efficacy Pop., N	122	36	71	111	39	65
ORR (n/N) (95% CI)	68.0 (83/122) (59.0, 76.2)	75.0 (27/36) (57.8, 87.9)	64.8 (46/71) (52.5, 75.8)	60.4 (67/111) (50.6, 69.5)	69.2 (27/39) (52.4, 83.0)	52.3 (34/65) (39.5, 64.9)

Abbreviations: CI = confidence interval; NSCLC = non-small cell lung cancer; ORR = overall response rate; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.1.1.4.2a, Table 14.2.1.1.5.2a

Table 28. ORR by Age Group

	Age < 65 years			Age ≥ 65 years		
	RET fusion NSCLC n (%)	Treatment Naïve n (%)	Prior Platinum Treatment n (%)	RET fusion NSCLC n (%)	Treatment Naïve n (%)	Prior Platinum Treatment n (%)
Efficacy Pop., N	145	41	90	88	34	46
ORR (n/N) (95% CI)	69.0 (100/145) (60.8, 76.4)	85.4 (35/41) (70.8, 94.4)	62.2 (56/90) (51.4, 72.2)	56.8 (50/88) (45.8, 67.3)	55.9 (19/34) (37.9, 72.8)	52.2 (24/46) (36.9, 67.1)

Abbreviations: CI = confidence interval; NSCLC = non-small cell lung cancer; ORR = overall response rate; RET= rearranged during transfection. Data cut-off date: 06 November 2020. Enrolment cut-off date: 22 May 2020. Source: Table 14.2.1.1.4.2b, Table 14.2.1.1.5.2b

Intracranial ORR

Table 29: Summary of CNS Best Response Rate, Central Radiology Assessment per RECIST v1.1 Response Evaluable Population - RET-fusion NSCLC CNS Metastases Patients Treated at 400 mg QD (Data cutoff date: 06 NOV 2020)

				No Prior Platinum Treatment	
	Overall (N=10) n (%)	Prior Systemic Treatment (N=10) n (%)	Prior Platinum Treatment (N=9) n (%)	Prior non-Platinum Systemic Treatment (N=1) n (%)	No Prior Systemic Treatment (N=0) n (%)
Best Overall Response					
Complete Response (CR)	3 (30.0)	3 (30.0)	2 (22.2)	1 (100)	
Partial Response (PR)	4 (40.0)	4 (40.0)	4 (44.4)	0	
Stable Disease (SD)	3 (30.0)	3 (30.0)	3 (33.3)	0	
Progressive Disease (PD)	0	0	0	0	
Not Evaluable (NE)	0	0	0	0	
Overall Response Rate (ORR) (Confirmed CR or PR) [1]	7 (70.0)	7 (70.0)	6 (66.7)	1 (100)	
95% CI [2]	(34.8, 93.3)	(34.8, 93.3)	(29.9, 92.5)	(2.5, 100)	
Clinical Benefit Rate (CBR) (Confirmed CR or PR or SD>=16 Weeks) [3]	8 (80.0)	8 (80.0)	7 (77.8)	1 (100)	
95% CI [2]	(44.4, 97.5)	(44.4, 97.5)	(40.0, 97.2)	(2.5, 100)	
Disease Control Rate (DCR) (CR or PR or SD) [4]	10 (100)	10 (100)	9 (100)	1 (100)	
95% CI [2]	(69.2, 100)	(69.2, 100)	(66.4, 100)	(2.5, 100)	

Source: Listing 16.3.4.1.2
Notes: CNS best response is based on target/non-target/new lesion(s) assessment in CNS/brain, including brainstem and cerebellum.
Confirmed CR or PR defined as at least two assessments of CR or PR with at least 28 days apart and no PD in between.
One time PR will be categorized as SD.Response evaluable population for CNS metastasis patients is defined as CNS metastasis population who have at least evaluable post-baseline disease response assessment performed on CNS/brain lesions and have experienced no major protocol violations.
[1] ORR: The proportion of patients with best overall response of confirmed CR or PR.
[2] Two-side 95% confidence interval (CI) based on exact binomial distribution using Clopper-Pearson method.
[3] CBR: The proportion of patients with confirmed CR/PR or SD lasting >=16 weeks (i.e.4 cycles if 28 days in one cycle) from first dose date.
[4] DCR: The proportion of patients with best overall response CR or PR or SD.

Sensitivity analyses – measurable disease population (MDP):

The MDP includes 216 NSCLC patients in the efficacy population with documented evidence of a targetable RET fusion by either local or central testing, and measurable (target) disease at baseline per BICR. Although study eligibility required measurable disease at baseline by investigator assessment, this was not confirmed upon BICR review in all cases, and patients who are not assessed with measurable disease are not eligible for a Partial Response assessment by RECIST 1.1. Sixteen patients were excluded from the MDP because they did not have measurable disease at baseline per BICR and 1 patient was excluded due to inconclusive evidence of RET fusion. Of these, 68 were treatment-naïve while 126 patients had previously received platinum-based chemotherapy. The other 22 patients had received prior therapy other than platinum-based chemotherapy.

Table 30 Highlights of Efficacy Results (Initial MAA, D120 Response to Questions, D180 Response to Questions)

	All RET Fusion-Positive NSCLC			Treatment-Naïve			Prior Platinum Treatment		
Submission	Initial MAA	D120 RtQ	**D180 RtQ**	Initial MAA	D120 RtQ	**D180 RtQ**	Initial MAA	D120 RtQ	**D180 RtQ**
Data Cut-off	18 Nov 19	22 May 20	**6 Nov 20**	18 Nov 19	22 May 20	**6 Nov 20**	18 Nov 19	22 May 20	**6 Nov 20**
Enrolment Cut	11 Jul 19		**22 May 20**	11 Jul 19		**22 May 20**	11 Jul 19		**22 May 20**
MDP, N	Not reported	125	**216**	Not reported	27	**68**	Not reported	87	**126**
ORR (n/N) (95% CI)	Not reported	62% (77/125) (52, 70)	**69% (148/216) (62, 75)**	Not reported	70% (19/27) (50, 86)	**79% (54/68) (68, 88)**	Not reported	59% (51/87) (48, 69)	**62% (78/126) (53, 70)**
mDOR, mos (95% CI)	Not reported	17.1 (13.1, -)	**22.3 (15.1, -)**	Not reported	9.0 (6.3, -)	**NR (9.0, -)**	Not reported	NR (15.2, -)	**22.3 (15.1, -)**
Efficacy Pop., N	132	132	**233**	29	29	**75**	92	92	**136**
ORR (n/N) (95% CI)	57% (75/132) (48, 65)	59% (78/132) (50, 68)	**64% (150/233) (58, 71)**	66% (19/29) (46, 82)	66% (19/29) (46, 82)	**72% (54/75) (60, 82)**	53% (49/92) (43, 64)	57% (52/92) (46, 67)	**59% (80/136) (50, 67)**
mDOR, mos (95% CI)	NR (11.3, -)	17.1 (13.1, -)	**22.3 (14.7, -)**	7.4 (6.3, -)	9.0 (6.3, -)	**NR (9.0, -)**	NR (11.3, -)	NR (15.2, -)	**22.3 (15.1, -)**
mPFS, mos (95% CI)	12.7 (9.1, -)	13.1 (8.8, 22.1)	**16.4 (11.0, 24.1)**	9.9 (5.6, -)	9.1 (6.1, 13.0)	**13.0 (9.1, -)**	13.1 (7.7, -)	17.1 (8.3, 22.1)	**16.5 (10.5, 24.1)**
mOS, mos (95% CI)	NR (- , -)	NR (- , -)	**NR (- , -)**	NR (- , -)	NR (14.9, -)	**NR (- , -)**	NR (- , -)	NR (18.2, -)	**NR (- , -)**

Abbreviations: CI= confidence interval; mDOR= median duration of response; MAA= marketing authorisation application; MDP= RET-altered measurable disease population; mos= months; mOS= median overall survival; mPFS= median progression-free survival; NR: not reached; ORR= overall response rate; pop= population; RtQ= response to questions. Results based on independent central review.

Summary of main study

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

Table 31. Summary of efficacy for trial ARROW

Title: A phase 1/2 study of the highly-selective RET inhibitor, BLU-667, in patients with thyroid cancer, NSCLC, and other advanced solid tumours		
Study identifier	ARROW, study BLU-667-1101 (EudraCT 2016-004390-41; NCT03037385)	
Design	Multicentre, multi-cohort, single arm, open-label, study consisting of a dose-escalation part (Phase 1) and an expansion part (Phase 2)	
	Duration of main phase:	Not applicable
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Group 1 of phase 2: The sample size of approximately 80 RET-fusion NSCLC patients who previously received treatment with a platinum-based chemotherapy will provide > 95% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.23 versus the alternative ORR=0.5. Group 2 of phase 2: The sample size of approximately 170 treatment naïve (1st line) RET-fusion NSCLC patients will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.48 versus the alternative ORR=0.61.	
Treatment groups	Patients with advanced RET fusion-positive NSCLC	Pralsetinib 400 mg QD n=233[a]

Endpoints and definitions	Primary efficacy endpoint	ORR-BICR	Proportion of patients achieving with a confirmed response of complete response (CR) or partial response (PR) per RECIST v1.1 by blinded independent central review (BICR)
	Secondary efficacy endpoints	DOR-BICR	Time from first documentation of response per RECIST v1.1 by BICR until progressive disease (PD) or death
		PFS-BICR	Time from first dose until PD per RECIST v1.1 by BICR or death of any cause
		OS	Time from first dose until death of any cause
Clinical cut-off	06-NOV-2020		
Database lock	*Not reported*		
Results and Analysis			
Analysis description	Updated analysis at D180 response to questions		
Analysis population and time point description	The Efficacy Population includes all patients RET fusion-positive NSCLC who started treatment with pralsetinib at 400 mg QD on or before 22-MAY-2020.[a]		
Descriptive statistics and estimate variability	Treatment group	RET fusion-positive NSCLC	
	Number of subjects	233	
	ORR (n)	64.4% 150	
	95% CI[b]	57.9%, 70.5%	
	Median DOR in 150 responders, months[c]	22.3	
	95% CI[c]	14.7, not reached	
	Median PFS, months[c]	16.4	
	95% CI[c]	11.0, 24.1	
	Median OS, months[c]	Not reached	
	95% CI[c]	Not reached, not reached	
Effect estimate per comparison	Not applicable, single arm trial		
Notes	[a] The efficacy dataset included patients from phases 1 and 2 of the trial, as long as they had started treatment on or before 22-MAY-2020. [b] Exact 2-sided 95% CI based on exact binomial distribution (Clopper-Pearson). [c] Kaplan Meier estimate, observed values are not yet evaluable.		

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

Not applicable.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	NA	NA	NA
Non Controlled trials	66/233 (28%)	19/233 (8%)	3/233 (1%)

In vitro biomarker test for patient selection for efficacy

A listing of the tests used to identify the patients with NSCLC that harboured RET fusions in the ARROW trial was provided (not shown in this report). In line with this, a table with available validation

information of the diverse tests used for local diagnostic of RET-fusion positivity across sites was presented. Adequate validated tests with CE-mark to identify patients with NSCLC harbouring RET fusions are available across Europe.

A systematic literature review outlined poor responses from patients with RET-fusion positive NSCLC treated with chemotherapy or immune-checkpoint inhibition.

Supportive studies

Efficacy analyses in PTC, MTC and other advanced solid tumours from ARROW:

Table 32. Summary of Best Response Rate by Investigator Assessment per RECIST v1.1 in Patients Treated at 400 mg QD (Efficacy Population)

Parameter	RET-fusion PTC N = 11	RET mutation MTC N = 92	Others [c] N = 23
ORR (confirmed CR or PR), n (%) [a]	7 (63.6)	45 (48.9)	4 (17.4)
95% CI	(30.8, 89.1)	(38.3, 59.6)	(5.0, 38.8)
CR, n (%)	0	2 (2.2)	0
PR, n (%)	7 (63.6)	43 (46.7)	4 (17.4)
SD, n (%)	4 (36.4)	42 (45.7)	13 (56.5)
PD, n (%)	0	2 (2.2)	5 (21.7)
Not evaluable, n (%)	0	3 (3.3)	1 (4.3)
CBR (confirmed CR or PR or SD ≥ 16 weeks), n (%) [b]	10 (90.9)	75 (81.5)	12 (52.2)
95% CI	(58.7, 99.8)	(72.1, 88.9)	(30.6, 73.2)

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PTC = papillary thyroid cancer; QD = once daily; RET = rearranged during transfection. Notes: [a] The proportion of patients with best overall response of confirmed CR or PR. [b] The proportion of patients with confirmed CR or PR or SD lasting for ≥ 4 cycles (ie, 16 weeks if 28 days in 1 cycle) from first dose date. [c] The group "Others" includes patients with RET-fusion other tumor (3 patients with colon tumor, 2 patients with pancreas tumor), RET mutation other than MTC (2 patients with small-cell lung cancer, 2 patients with colon cancer and 1 patient each with adenoid cystic carcinoma of trachea, breast, pancreas, salivary gland, or thymus), and no/unknown RET-altered other solid tumor (9 patients with MTC). Source: CSR BLU-667-1101, Table 14.2.1.2.4.7.

2.3.9. Discussion on clinical efficacy

Clinical data to support the conditional marketing authorisation (CMA) for pralsetinib as monotherapy for patients with advanced RET fusion-positive NSCLC in a line-agnostic setting come from the pivotal phase I/II, open-label, multi-cohort, single-arm ARROW study.

Design and conduct of clinical studies

The applicant received Scientific Advice from CHMP in April 2019. The main purposes for that advice were to consult on the possibility of CMA for the 2L NSCLC cohort (based on preliminary efficacy and safety data) and discussing the design of the confirmatory trial in 1L. The CHMP pointed out an important concern: several options are currently available for treatment in the post-platinum 2L setting of unselected NSCLC patients (*e.g.* immune checkpoint inhibitors, chemotherapy +/- ramucirumab), and hence, outstanding ORR and DOR results from pralsetinib for the intended population (RET-fusion positive) would be necessary in order to consider a CMA.

The ARROW study included a dose-escalation phase I to determine the MTD and RP2D of pralsetinib, followed by a phase II expansion with diverse RET-altered cancer cohorts, among them NSCLC (1L/2L), MTC, and other tumours. The cohorts of interest for the proposed indication included patients with RET-fusion positive NSCLC in the 1L (treatment-naïve) or ⩾2L (prior platinum) settings, from either phase I or II of the trial, as long as they had been treated at the RP2D (400 mg QD).

The cut-off for the initially submitted efficacy dataset was 18 November 2019, but only patients with sufficient follow-up, defined as those who had started treatment on or before 11 July 2019, had been included. Therefore, an updated efficacy dataset with data cut-off on 06 November 2020 including all patients that started treatment on or before the 22 May 2020 was submitted during the procedure.

Despite multiple modifications along protocol amendments, inclusion and exclusion criteria reflect the NSCLC population intended for treatment with pralsetinib.

The overall primary and secondary objectives from the extension phase (II) of ARROW are considered appropriate to ascertain the efficacy and safety of pralsetinib. ORR and DOR, as assessed by BICR, are acceptable measures of anti-tumour activity for tyrosine kinase inhibitors (TKIs) in a phase I/II trial.

Up to the last data cut-off date (06 November 2020), 281 patients with advanced, RET fusion-positive NSCLC from either phase I or II had been treated. From these, 233 fulfilled the efficacy dataset requirement to allow for appropriate response assessment, *i.e.* having started treatment on or before 22 May 2020. The updated disposition table shows that 32% of patients discontinued treatment because of PD and 15% because of AEs.

Efficacy data and additional analyses

At data cut-off 06 November 2020, with an estimated median follow-up time of 17.1 months, 150 out of the 233 patients from the efficacy dataset had achieved confirmed response by BICR, attaining a BOR of 64.4% (95% CI 57.9, 70.5). From these 233 patients, 11 exhibited a confirmed CR, 139 confirmed PR, 61 had SD ad 13 PD as best response, whereas the remaining 9 patients were non-evaluable. Responses were fast (median time to response (TTR) 1.84 months) and durable (DOR ≥ 6 months in 68% of responders), but observed median DOR, PFS or OS have not been reached yet. The K-M estimates for mDOR (22.3 months) and mPFS (16.4 months) are nevertheless encouraging.

The forest plot of ORR suggests that pralsetinib exerted benefits across most important subgroups (ECOG PS status, CNS metastases at enrolment, prior treatments). No clinically relevant difference in efficacy was seen in patients with a KIF5B or CCDC6 fusion partner although the response rate was slightly lower in patients whose tumours exhibited other RET-fusion partners. BICR response rates were: ORR= 67.7% (95% CI: 59.9, 74.8) in 164 patients with a KIF5B fusion partner; and ORR= 68.3% (95% CI: 51.9, 81.9) in 41 patients with a CCDC6 fusion partner; and ORR= 39.3% (95% CI:21.5, 59.4) in 28 patients with other RET-fusion partners. The intracranial ORR assessed by BICR was 70.0% (95% CI: 34.8, 93.3) in 10 response evaluable patients with brain metastases at baseline, including 3 patients with a complete response. All patients had target brain lesion shrinkage with pralsetinib treatment.

Importantly, the ORR benefit of pralsetinib for the intended population was observed regardless of line of treatment, with slightly higher ORR in the treatment-naïve population (n=75, ORR 72.0%), even when this subgroup has a lower K-M estimate of median PFS (13.0 months) than the prior-platinum subpopulation (16.5 months). This slight difference could be impacted by the fact that prior to protocol amendment 9 (issued in July 2019), eligibility for the treatment-naïve subpopulation required that they were not candidates for standard platinum therapy, hence likely to exhibit a worse baseline prognosis.

The unmet medical need in the applied indication is recognized. Major therapeutic advantage (MTA) of pralsetinib can be considered demonstrated regardless of line of therapy in the RET fusion-positive NSCLC population. This is based on a differential safety profile, the convenience of oral administration, and the provision of a treatment alternative with a novel mechanism of action in the context of a reported high rate of durable responses that leads to the expectation that pralsetinib would be at least similarly active to first line available chemotherapy, immunotherapy or immunochemotherapy options. Of note, the observed response rate and duration of response of pralsetinib is expected to address the unmet medical need in previously treated patients to a similar extent to selpercatinib, i.e. the first RET inhibitor conditionally approved in Europe for the treatment of RET-fusion positive NSCLC following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Additional expert consultation

The following input of the SAG-Oncology has been requested:

"While the activity of Gavreto in terms of ORR in the first line treatment, is higher than what is seen for chemo-immunotherapy, there is uncertainty about the impact on time-dependent endpoints, including OS. Furthermore, it is inherent to single arm trials, that patient selection might impact the magnitude of ORR. Given that available treatment options have demonstrated a clinically relevant OS gain, the CHMP is seeking the opinion of the SAG -Oncology on whether Gavreto would be a reasonable treatment option also in patients with RET+ NSCLC that have not previously been treated for advanced disease."

On the meeting of the 7th of September 2021, the conclusions of the SAG-O were as follows:

The SAG agreed with the complexity of the evaluation of treatment effect given the non-randomized comparative data presented.

However, the SAG agreed that pralsetinib was associated with very high antitumour activity. In general, in this setting including first-line treatment, response rates in the order of about two thirds of patients or more would be considered a level of activity that is sufficiently high to assume an effect also on important clinical endpoints like PFS. Unfortunately, due to short follow-up duration of response data were not available to support this conclusion although available results are encouraging.

Although the reported overall response rate from the pooled cohorts may be an over-estimation of the true activity in a broader population, in this population the effect was considered very high such that selection bias would not be a major concern.

The majority of the SAG agreed that based on the totality of data and particularly the high response rate, activity on brain disease, mechanistic rationale, experience with other TKIs, that pralsetinib represents a reasonable treatment option in 1st line RET+ NSCLC.

It is understood that the uncertainty in terms of clinically relevant effects (overall survival, progression-free survival, health-related quality of life) in first-line would need to be further addressed. The results presented in terms of the clinical endpoint progression-free survival showing and advantage of pralsetinib over alternative options in indirect comparisons are difficult to assess given the non-randomized controlled design of such analyses.

Concerning alternative treatment options, comprehensive efficacy evaluations in RET+ patients are lacking. In general, it is not easy to establish what is the level of efficacy of conventional regimens in this subpopulation. A number of publications were presented showing seemingly lower activity of chemo-immunotherapies in patients with oncogenic drivers such as EGFR/ALK and seemingly also RET. Thus, the SAG agreed that available treatment options are also associated with considerable uncertainties in this population.

In terms of clinical decisions, pralsetinib as a targeted therapy with high activity, including on brain metastases, and a well-characterised toxicity profile, can be considered as a reasonable option alongside available alternatives which are also associated with important uncertainties in this rare population. Availability of highly active targeted agents is important in this disease with poor prognosis despite available options and despite the current uncertainties associated with pralsetinib.

Concerning the fact that comprehensive clinical data are currently not available, it is considered that the benefits of availability of this additional treatment with its expected clinical benefits outweigh the risks if such benefits are not confirmed also taking into account the seemingly modest effect of available options in this population.

One expert disagreed and considered the data presented, especially given the lack of a randomized trial, are insufficient to conclude that this is a reasonable option.

All experts agreed that there are important uncertainties that need to be addressed about efficacy in terms of longer follow-up of duration of response and, more importantly, confirmation of an effect on important clinical endpoints like PFS, overall survival, or health-related quality of life, and to better characterise the effect in distinct subgroups like elderly/frail patients or patients with poor performance status. A phase III trial is ongoing and claimed to address many of these aspects.

Additional efficacy data needed in the context of a conditional MA

The main limitations in relation to the efficacy of pralsetinib are related to the uncontrolled nature of the pivotal evidence which hampers the assessment of the time-to-event endpoints and the limited number of patients included.

The applicant will submit the results of a further follow up of efficacy from evaluable patients from the ongoing pivotal ARROW study (BLU-667-1101, phase I/II) in RET fusion-positive NSCLC patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy). In addition, the applicant will conduct and submit the results from the confirmatory phase III AcceleRET study (BLU-667-2303), an open-label, randomized, controlled multicentre phase III study in RET fusion-positive NSCLC patients. This study is designed to assess the efficacy of pralsetinib as compared to Investigator's choice platinum-based chemotherapy regimen for patients with metastatic NSCLC harbouring an oncogenic RET fusion and who have not received prior systemic therapy.

Results from both studies are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA.

2.3.10. Conclusions on the clinical efficacy

Efficacy in terms of the primary endpoint ORR and key-secondary endpoint DOR from the efficacy dataset of the ARROW study (N=233) with updated cut-off of 06 November 2020 is consistent with the results provided in the original submission (data cut-off 18 November 2019). Albeit the intrinsic limitations of single arm studies and the challenges to compare the reported results with historical controls and the literature, bearing in mind that oncogenic RET fusions are rare and identified in only 1-2% of NSCLC patients, the currently available data are deemed to support the efficacy of pralsetinib regardless of treatment line in patients with advanced RET-fusion positive NSCLC.

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

- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of a longer follow-up of efficacy evaluable patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy) of study BLU-667-1101, a Phase 1/2 Study of pralsetinib in patients with thyroid cancer, NSCLC and other advanced solid tumours. The CSR should be submitted by 31 December 2022.
- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of study BLU-667-2303, a randomized, open-label, Phase 3 Study of pralsetinib versus standard of care for first line treatment of RET fusion-positive, metastatic NSCLC. The CSR should be submitted by 31 December 2026.

2.4. Clinical safety

The initial safety review of pralsetinib was based on Study BLU-667-1101 (ARROW) with data cut-off on 18 November 2019, focusing on 354 patients (any tumour) that had received the RP2D of 400 mg QD and from these, 179 patients with NSCLC. The safety database was updated twice, with a data cut-off on 22 May 2020 (471 patients with any tumour, 233 with NSCLC) and on 06 November 2020 (528 with any tumour and 281 with NSCLC).

Patient exposure

Table 33. Summary of Study Drug Exposure

Parameter	Treated at 400 mg QD (06 November 2020 Data Cut-off)		Treated at 400 mg QD (22 May 2020 Data Cut-off)	
	RET Fusion-Positive NSCLC N=281	Overall Safety Population N=528	RET Fusion-Positive NSCLC N=233	Overall Safety Population N=471
Exposure (months)				
Median (min, max)	7.89 (0.3, 28.4)	9.46 (0.1, 33.9)	6.34 (0.1, 23.8)	6.67 (<1, 28.4)
Relative dose intensity (%) [1]				
Median (min, max)	92.1 (27, 100)	91.1 (21, 100)	95.0 (30, 100)	93.5 (23, 100)

Abbreviations: mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. [1] Relative dose intensity: dose intensity/planned dose intensity * 100. Planned dose intensity is based on initial assigned daily dose.

Adverse events

Table 34. Summary of Adverse Events from 06 November 2020 vs 22 May 2020 Data Cut-off

Parameters	RET Fusion-Positive NSCLC Patients at 400 mg QD		Overall Safety Population at 400 mg QD	
	N=281 n (%) (06 Nov 20)	N=233 n (%) (22 May 20)	N=528 n (%) (06 Nov 20)	N=471 n (%) (22 May 20)
Patients with any AE	279 (99.3)	230 (98.7)	525 (99.4)	468 (99.4)
Patients with ≥ Grade 3 AE	212 (75.4)	155 (66.5)	406 (76.9)	333 (70.7)
Patients with treatment related AE	264 (94.0)	216 (92.7)	493 (93.4)	437 (92.8)
Patients with ≥ Grade 3 treatment related AE	155 (55.2)	111 (47.6)	291 (55.1)	233 (49.5)
Patients with SAE	166 (59.1)	129 (55.4)	288 (54.5)	235 (49.9)
Patients with ≥ Grade 3 SAE	137 (48.8)	103 (44.2)	249 (47.2)	200 (42.5)
Patients with treatment related SAE	69 (24.6)	55 (23.6)	108 (20.5)	89 (18.9)
Interruption of treatment due to AE	190 (67.6)	148 (63.5)	363 (68.8)	307 (65.2)
Dose reduction due to AE	126 (44.8)	92 (39.5)	239 (45.3)	189 (40.1)
Discontinuation of treatment	55 (19.6)	43 (18.5)	91 (17.2)	68 (14.4)
Disease progression	10 (3.6)	8 (3.4)	15 (2.8)	11 (2.3)
Deaths due to AE	35 (12.5)	24 (10.3)	66 (12.5)	47 (10.0)
Deaths related to pralsetinib	2 (<1)	0	6 (1.1)	4 (< 1)

Abbreviations: AE= adverse event; mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. SAE= serious adverse event.

Common AEs

Table 35. Adverse Events with ≥ 10%* Incidence by Preferred Term from 06 November 2020 vs 22 May 2020 Data Cut-off

Preferred Term	RET Fusion-Positive NSCLC Patients at 400 mg QD		Overall Safety Population at 400 mg QD	
	N=281 n (%) (06 Nov 20)	N=233 n (%) (22 May 20)	N=528 n (%) (06 Nov 20)	N=471 n (%) (22 May 20)
Patients with any AE	**279 (99.3)**	**230 (98.7)**	**525 (99.4)**	**468 (99.4)**
Anaemia	129 (45.9)	94 (40.3)	241 (45.6)	185 (39.3)
AST increased	126 (44.8)	101 (43.3)	243 (46.0)	208 (44.2)
Constipation	118 (42.0)	90 (38.6)	221 (41.9)	183 (38.9)
Hypertension	96 (34.2)	73 (31.3)	172 (32.6)	144 (30.6)
Alanine aminotransferase increased	92 (32.7)	68 (29.2)	179 (33.9)	148 (31.4)
Neutrophil count decreased	81 (28.8)	51 (21.9)	128 (24.2)	94 (20.0)
Pyrexia	72 (25.6)	52 (22.3)	133(25.2)	105 (22.3)
White blood cell count decreased	72 (25.6)	46 (19.7)	142 (26.9)	109 (23.1)
Diarrhoea	70 (24.9)	55 (23.6)	155 (29.4)	136 (28.9)
Fatigue	67 (23.8)	55 (23.6)	132 (25.0)	103 (21.9)
Cough	65 (23.1)	53 (22.7)	114 (21.6)	99 (21.0)
Blood creatinine increased	62 (22.1)	50 (21.5)	118 (22.3)	100 (21.2)
Neutropenia	61 (21.7)	51 (21.9)	116 (22.0)	102 (21.7)
Blood creatine phosphokinase increased	53 (18.9)	29 (12.4)	86 (16.3)	56 (11.9)
Dry mouth	47 (16.7)	39 (16.7)	84 (15.9)	70 (14.9)
Dyspnoea	47 (16.7)	34 (14.6)	89 (16.9)	72 (15.3)
Pneumonia	44 (15.7)	33 (14.2)	75 (14.2)	56 (11.9)
Dysgeusia	42 (14.9)	35 (15.0)	81 (15.3)	72 (15.3)
Oedema peripheral	42 (14.9)	33 (14.2)	82 (15.5)	68 (14.4)
Nausea	42 (14.9)	29 (12.4)	84 (15.9)	67 (14.2)
Asthenia	39 (13.9)	31 (13.3)	73 (13.8)	63 (13.4)
Back pain	38 (13.5)	32 (13.7)	60 (11.4)	51 (10.8)
Dizziness	38 (13.5)	29 (12.4)	70 (13.3)	58 (12.3)
Decreased appetite	38 (13.5)	26 (11.2)	80 (15.2)	59 (12.5)
Urinary tract infection	38 (13.5)	28 (12.0)	67 (12.7)	53 (11.3)
Hypokalaemia	38 (13.5)	23 (9.9)	69 (13.1)	49 (10.4)
Hypoalbuminemia	37 (13.2)	25 (10.7)	61 (11.6)	42 (8.9)
Hypophosphataemia	35 (12.5)	25 (10.7)	55 (10.4)	43 (9.1)
Blood alkaline phosphate increased	35 (12.5)	27 (11.6)	55 (10.4)	45 (9.6)
Hypocalcaemia	34 (12.1)	23 (9.9)	109 (20.6)	80 (17.0)
Headache	34 (12.1)	26 (11.2)	82 (15.5)	67 (14.2)
Platelet count decreased	33 (11.7)	17 (7.3)	58 (11.0)	39 (8.3)
Hyperphosphataemia	32 (11.4)	27 (11.6)	94 (17.8)	86 (18.3)
Pneumonitis	32 (11.4)	27 (11.6)	55 (10.4)	47 (10)
Vomiting	32 (11.4)	25 (10.7)	65 (12.3)	51 (10.8)
Hyponatraemia	30 (10.7)	18 (7.7)	54 (10.2)	37 (7.9)
Leukopenia	30 (10.7)	22 (9.4)	49 (9.3)	42 (8.9)

Abbreviations: AE= adverse event; mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. Note: AEs were coded using MedDRA 19.1. * 'Adverse events with ≥10% cut-off' is based n RET-fusion positive NSCLC patients treated at 400 mg QD as of 06 Nov 2020

G≥3 AEs

Table 36. Grade 3/4/5 Adverse Events in ≥1% of Patients by Preferred Term Regardless of Causality. Safety Population -All Patients Treated at 400mg QD. Data Cut-off 06 November 2020)

Preferred Term	RET fusion-positive NSCLC Patients (N=281) n (%)	All Patients (N=528) n (%)
Patients with Grade 3/4/5 AE	212 (75.4)	406 (76.9)
Anaemia	46 (16.4)	91 (17.2)
Hypertension	45 (16.0)	85 (16.1)
Neutropenia	30 (10.7)	59 (11.2)
Neutrophil count decreased	36 (12.8)	51 (9.7)
Pneumonia	27 (9.6)	49 (9.3)
Disease progression	21 (7.5)	41 (7.8)
Lymphocyte count decreased	14 (5.0)	38 (7.2)
Lymphopenia	17 (6.0)	37 (7.0)
Blood creatine phosphokinase increased	19 (6.8)	34 (6.4)
White blood cell count decreased	15 (5.3)	32 (6.1)
Aspartate aminotransferase increased	15 (5.3)	30 (5.7)
Hypophosphataemia	20 (7.1)	29 (5.5)
Alanine aminotransferase increased	9 (3.2)	22 (4.2)
Hyponatraemia	12 (4.3)	22 (4.2)
Urinary tract infection	9 (3.2)	20 (3.8)
Hypocalcaemia	3 (1.1)	19 (3.6)
Hypokalaemia	9 (3.2)	17 (3.2)
Platelet count decreased	8 (2.8)	16 (3.0)
Pneumonitis	6 (2.1)	16 (3.0)
Diarrhoea	5 (1.8)	15 (2.8)
Sepsis	8 (2.8)	15 (2.8)
Dyspnoea	8 (2.8)	13 (2.5)
Fatigue	6 (2.1)	12 (2.3)
Leukopenia	8 (2.8)	12 (2.3)
Pulmonary embolism	9 (3.2)	12 (2.3)
Asthenia	2 (<1)	11 (2.1)
Thrombocytopenia	8 (2.8)	11 (2.1)
Pleural effusion	5 (1.8)	9 (1.7)
Syncope	3 (1.1)	9 (1.7)
Corona virus infection	1 (<1)	8 (1.5)
Hypotension	3 (1.1)	7 (1.3)
Blood alkaline phosphatase increased	4 (1.4)	6 (1.1)
Hyperkalaemia	4 (1.4)	6 (1.1)
Pyrexia	1 (<1)	6 (1.1)
Stomatitis	5 (1.8)	6 (1.1)
Vomiting	3 (1.1)	6 (1.1)
Back pain	3 (1.1)	5 (<1)
Febrile neutropenia	4 (1.4)	5 (<1)
Gamma-glutamyltransferase increased	3 (1.1)	5 (<1)
General physical health deterioration	3 (1.1)	5 (<1)
Intervertebral disc protrusion	4 (1.4)	5 (<1)
Muscular weakness	3 (1.1)	5 (<1)
Hypoxia	4 (1.4)	4 (<1)
Lipase increased	3 (1.1)	4 (<1)
Colitis	3 (1.1)	3 (<1)
Lung infection	3 (1.1)	3 (<1)
Mental status changes	3 (1.1)	3 (<1)

Abbreviations: AE= adverse event; mg = milligram; NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection.

Adverse drug reactions (ADRs)

Table 37. Adverse Reactions Reported in all Patients Treated with Pralsetinib in the ARROW Trial (n=528). Data Cut-off 06 November 2020

System organ class / Adverse reactions	Frequency category	All grades %	Grades 3-4 %
Infections and infestations			
Pneumonia[1]	Very common	17.4	10.2
Urinary tract infection		12.7	3.8
Blood and lymphatic system disorders			
Anaemia[2]	Very common	47.2	17.6
Neutropenia[3]		43.9	20.1
Leukopenia[4]		35.4	8.3
Lymphopenia[5]		22.3	14.2
Thrombocytopenia[6]		18.8	4.7
Metabolism and nutrition disorders			
Hypocalcaemia	Very common	20.6	3.6
Hyperphosphataemia		17.8	0.2
Hypoalbuminaemia		11.6	-
Hypophosphataemia		10.4	5.5
Hyponatraemia		10.2	4.2
Nervous system disorders			
Taste disorder[7]	Very common	15.9	-
Headache[8]		15.7	0.4
Vascular disorders			
Hypertension[9]	Very common	33.0	16.1
Haemorrhage[10]		18.8	3.0
Respiratory, thoracic and mediastinal disorders			
Cough[11]	Very common	23.7	0.6
Dyspnoea		16.9	2.1
Pneumonitis[12]		11.6	3.0
Gastrointestinal disorders			
Constipation	Very common	41.9	0.6
Diarrhoea		29.4	2.8
Dry mouth		15.9	-
Nausea		15.9	0.2
Abdominal pain[13]		15.3	1.3
Vomiting		12.3	1.1
Stomatitis[14]	Common	6.8	1.3
Hepatobiliary disorders			
Aspartate aminotransferase increased*	Very common	46.0	5.7
Alanine aminotransferase increased*		33.9	4.2
Hyperbilirubinaemia[15]		13.4	1.3
Skin and subcutaneous tissue disorders			
Rash[16]	Very common	17.2	-
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[17]	Very common	39.8	2.1
Blood creatine phosphokinase increased		16.3	6.4
General disorders and administration site conditions			

Fatigue[18]	Very common	37.3	4.0
Oedema[19]		28.2	0.2
Pyrexia		25.2	1.1
Cardiac disorders			
QT prolongation[20]	Common	5.1	0.4
Renal and urinary disorders			
Blood creatinine increased	Very common	22.3	0.4
Investigations			
Blood alkaline phosphatase increased	Very common	10.4	1.1

[1] includes pneumonia, pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, atypical pneumonia, lung infection, pneumonia bacterial, pneumonia haemophilus, pneumonia influenzal, pneumonia streptococcal, pneumonia moraxella, pneumonia staphylococcal, pneumonia pseudomonal, atypical mycobacterial pneumonia, pneumonia legionella

[2] includes anaemia, haematocrit decreased, red blood cell count decreased, haemoglobin decreased, aplastic anaemia

[3] includes neutrophil count decreased, neutropenia

[4] includes white blood cell count decreased, leukopenia

[5] includes lymphopenia, lymphocyte count decreased

[6] includes thrombocytopenia, platelet count decreased

[7] includes ageusia, dysgeusia

[8] includes headache, tension headache

[9] includes hypertension, blood pressure increased

[10] includes 39 preferred terms from the SMQ Haemorrhage (excl laboratory terms) narrow, with the exclusion of terms related to invasive drug administration, terms related to rupture, disseminated intravascular coagulopathy, terms related to traumatic haemorrhages, and haemorrhagic terms related to pregnancy, birth or neonatal

[11] includes cough, productive cough

[12] includes pneumonitis, interstitial lung disease

[13] includes abdominal pain, abdominal pain upper

[14] includes stomatitis, aphthous ulcer

[15] includes blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, blood bilirubin unconjugated increased

[16] includes rash, rash maculo-papular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pustular, rash macular, rash erythematous

[17] includes musculoskeletal chest pain, myalgia, arthralgia, pain in extremity, neck pain, musculoskeletal pain, back pain, bone pain, spinal pain, musculoskeletal stiffness

[18] includes asthenia, fatigue

[19] includes oedema, swelling face, peripheral swelling, oedema peripheral, face oedema, periorbital oedema, eyelid oedema, generalised oedema, swelling, localised oedema

[20] includes electrocardiogram QT prolonged, long QT syndrome

[*] additionally, 3.0% transaminases increased were reported (0.6% Grades 3-4)

Infections were commonly experienced by 57.2% of 528 patients during the median treatment time of 9.5 months. Most frequently (>10%), the preferred terms of pneumonia and urinary tract infection were reported (14.2% and 12.7%, respectively). The majority of infections were mild (Grade 1 or 2) and resolved; severe infection (Grade ≥3) occurred in 23.5% patients (with fatal events reported for 1.9%). Infections reported as serious occurred for 24.2% of patients. The most common (>2%) serious infection preferred term was pneumonia (9.8%), followed by urinary tract infection (3.4%) and sepsis (2.8%). The majority of patients experiencing sepsis had concurrent pneumonia or urinary tract infection reported. Dose interruption due to infection occurred for 19.5% of patients (mainly due to the preferred terms of pneumonia [6.8%] and urinary tract infection [2.7%]). Dose was reduced due to infections in 3.2% of patients (mainly due to the preferred term of pneumonia [1.9%]). Permanent

treatment discontinuation was required by 3.4% of patients due to infections (mainly due to the preferred term of pneumonia [1.7%]).

Adverse events of special interest (AESIs)

AESIs (pneumonitis, hypertension and transaminase elevations) by overall occurrence, serious AESIs, and AESIs leading to permanent treatment discontinuation by preferred term for the overall patient population (n=528) and RET fusion-positive advanced NSCLC patients (n=281) are provided in Table 38, Table 39 and Table 40.

Table 38. AESIs by Category and Preferred Term (RET fusion-positive NSCLC and All patients in safety population treated at 400mg QD) (Data Cut-off 06 November 2020)

AESI category Preferred Term	RET fusion-positive NSCLC patients at 400 mg QD N=281	All patients at 400 mg QD N=528
	n (%)	n (%)
Pneumonitis	**36 (12.8%)**	**61 (11.6%)**
Pneumonitis	32 (11.4%)	55 (10.4%)
Interstitial lung disease	4 (1.4%)	6 (1.1%)
Hypertension	**97 (34.5%)**	**174 (33.0%)**
Hypertension	96 (34.2%)	172 (32.6%)
Blood pressure increased	3 (1.1%)	4 (0.8%)
Transaminase elevations	**138 (49.1%)**	**262 (49.6%)**
Aspartate aminotransferase increased	126 (44.8%)	243 (46.0%)
Alanine aminotraserase increased	92 (32.7%)	179 (33.9%)
Transaminases increased	8 (2.8%)	16 (3.0%)
Hypertransaminasaemia	0	1 (0.2%)
Haemorrhage	**55 (19.6%)**	**99 (18.8%)**
Epistaxis	14 (5.0%)	30 (5.7%)
Haematuria	4 (1.4%)	12 (2.3%)
Haemoptysis	11 (3.9%)	11 (2.1%)
Contusion	5 (1.8%)	10 (1.9%)
Haematoma	4 (1.4%)	7 (1.3%)
Astringent therapy	5 (1.8%)	6 (1.1%)
Gingival bleeding	3 (1.1%)	6 (1.1%)
Haematochezia	2 (0.7%)	6 (1.1%)
Blood urine	3 (1.1%)	3 (0.6%)
Ecchymosis	1 (0.4%)	3 (0.6%)
Gastrointestinal haemorrhage	2 (0.7%)	3 (0.6%)
Conjunctival haemorrhage	1 (0.4%)	2 (0.4%)
Haemorrhagic diathesis	0	2 (0.4%)
Haemorrhoidal haemorrhage	0	2 (0.4%)
Melaena	1 (0.4%)	2 (0.4%)
Metrorrhagia	2 (0.7%)	2 (0.4%)
Vaginal haemorrhage	1 (0.4%)	2 (0.4%)
Blood urine present	1 (0.4%)	1 (0.2%)
Cerebellar haemorrhage	1 (0.4%)	1 (0.2%)
Cerebral haematoma	1 (0.4%)	1 (0.2%)
Cerebral microhaemorrhage	1 (0.4%)	1 (0.2%)
Chronic pigmented purpura	0	0
Cystitis haemorrhagic	1 (0.4%)	1 (0.2%)
Haemorrhage intracranial	1 (0.4%)	1 (0.2%)
Haemorrhage urinary tract	1 (0.4%)	1 (0.2%)
Haemorrhagic anaemia	1 (0.4%)	1 (0.2%)
Haematothorax	0	0
Laryngeal haemorrhage	1 (0.4%)	1 (0.2%)
Muscle haemorrhage	1 (0.4%)	1 (0.2%)
Postmenopausal haemorrhage	1 (0.4%)	1 (0.2%)
Purpura	1 (0.4%)	1 (0.2%)
Shock haemorrhagic	1 (0.4%)	1 (0.2%)
Spinal cord haematoma	1 (0.4%)	1 (0.2%)
Subdural haematoma	1 (0.4%)	1 (0.2%)
Upper gastrointestinal haemorrhage	0	1 (0.2%)
QT prolongation	**15 (5.3%)**	**27 (5.1%)**
Electrocardiogram QT prolonged	15 (5.3%)	26 (4.9%)
Long QT syndrome	0	1 (0.2%)

Abbreviations: AESI= adverse event of special interest; ALT= alanine aminotransferase; AST= aspartate aminotransferase; NSCLC= non-small cell lung cancer; QD= once daily. Source: Listing 16.4.1.1.1. Note: [a] Data in SmPC and EU-RMP do not include prehypertension PT as a grouped hypertension term; [b] In the SmPC and EU-RMP,

the term of elevated transaminases (including PTs Aspartate aminotransferase increased, Alanine aminotransferase increased, Transaminases increased, Hypertransaminasaemia) have been used.

Table 39. Serious AESIs by Category and Preferred Term (RET fusion-positive NSCLC and All patients in safety population treated at 400mg QD) (Data Cut-off 06 November 2020)

AESI Category Preferred Term	RET fusion-positive NSCLC Patients at 400 mg QD N=281	All patients at 400 mg QD N=528
	n (%)	n (%)
Pneumonitis	15 (5.3)	28 (5.3)
Pneumonitis	13 (4.6)	24 (4.5)
Interstitial lung disease	2 (<1)	4 (<1)
Hypertension	4 (1.4)	7 (1.3)
Hypertension	4 (1.4)	7 (1.3)
Hepatotoxicity	5 (1.8)	8 (1.5)
AST Increased	3 (1.1)	3 (<1)
ALT Increased	2 (<1)	3 (<1)
Blood bilirubin increased	0	1 (<1)
Transaminases increased	0	1 (<1)
Hepatic enzyme increased	1 (<1)	1 (<1)
Hepatic function abnormal	0	1 (<1)
Liver injury	1 (<1)	1 (<1)
Haemorrhage	3 (1.1)	5 (<1)
Epistaxis	1 (<1)	1 (<1)
Gastrointestinal haemorrhage	1 (<1)	2 (<1)
Haemorrhage intracranial	1 (<1)	1 (<1)
Upper gastrointestinal haemorrhage	0	1 (<1)
QT prolongation	2 (<1)	2 (<1)
Electrocardiogram QT prolonged	2 (<1)	2 (<1)

Abbreviations: AESI= adverse event of special interest; ALT= alanine aminotransferase; AST= aspartate aminotransferase; NSCLC= non-small cell lung cancer; QD= once daily. Source: Listing 16.4.1.1.1

Table 40. AESIs Leading to permanent discontinuation by Category and Preferred Term (RET fusion-positive NSCLC and All patients in safety population treated at 400mg QD) (Data Cut-off 06 November 2020)

AESI Category Preferred Term	RET fusion-positive NSCLC Patients at 400 mg QD N=281	All patients at 400 mg QD N=528
	n (%)	n (%)
Pneumonitis	7 (2.5)	10 (1.9)
Pneumonitis	7 (2.5)	10 (1.9)
Hypertension	1 (<1)	1 (<1)
Hypertension	1 (<1)	1 (<1)
Hepatotoxicity	0	2 (<1)
Transaminases increased	0	2 (<1)
Blood bilirubin increased	0	1 (<1)
Liver injury	1 (<1)	1 (<1)
Haemorrhage	1 (<1)	1 (<1)
Haemorrhage intracranial	1 (<1)	1 (<1)
QT prolongation	0	0

Abbreviations: AESI= adverse event of special interest; NSCLC= non-small cell lung cancer; QD= once daily. Source: Listing 16.4.1.1.2

Transaminases elevations

Increased AST and ALT Grade 3 or 4 occurred in 5.7% and 4.2% of patients respectively. The median time to first onset for increased AST was 2.1 weeks and increased ALT was 3.1 weeks. Serious adverse reactions of increased AST and ALT were reported for 0.6% of all patients and patients with Grades 3 and 4 events, respectively. There were no events Grade ≤2 in severity.

Dose interruption due to increased AST or ALT occurred in 4.4% and 3.4% of patients, respectively and dose reduction in 1.3% for both events. No patients required permanent dose discontinuation. The median time to resolution was 5.3 and 4.1 weeks for increased AST and ALT, respectively.

Pneumonitis/ILD

Among the patients who had pneumonitis/ILD, the median time to onset was 15.6 weeks. Serious adverse reactions of pneumonitis/ILD were reported for 5.3% of patients, including Grade 3 events (2.5%), Grade 4 (0.6%) and one fatal (Grade 5) event (0.2%).

In clinical trials, the majority of the patients with Grade 1 or Grade 2 pneumonitis were able to continue treatment without recurrent pneumonitis/ILD following dose interruption and dose reduction. Dose interruption occurred in 8.9%, dose reduction in 5.3% and permanent dose discontinuation in 1.9% of patients due to ILD/pneumonitis. The median time to resolution was 3.7 weeks.

Hypertension

Grade ≤2 events occurred in 16.9% and Grade 3 in 16.1% of patients. No Grade 4 or Grade 5 events were reported. Among the patients who had hypertension, the median time to onset was 2.1 weeks. Serious adverse reactions of Grade 3 were reported in 1.3% of all patients.

Dose interruption occurred in 7.4% of patients, dose reduction in 4.0% and one patient (0.2%) required permanent dose discontinuation. The median time to resolution was 3.1 weeks.

Haemorrhagic events

Haemorrhagic events occurred in 18.8% of the 528 patients, including Grade 3 events in 2.8% of patients and a Grade 4 or fatal (Grade 5) event each occurred in one patient (0.2%).

Serious adverse reactions of haemorrhage were reported for 3.2% of patients, which included Grades 3 and 4 (0.6%) and one fatal case (0.2%).

Fourteen patients (2.7%) required dose interruption and dose reduction or permanent dose discontinuation due to haemorrhage each occurred in one patient.

Serious adverse event/deaths/other significant events

SAEs

Table 41 Serious Adverse Events Occurring in ⩾ 1%* Patients from 06 Nov 2020 vs 22 May 2020 Data Cut-off

Preferred Term	RET Fusion-Positive NSCLC Patients at 400 mg QD		Overall Safety Population at 400 mg QD	
	N=281 n (%) (06 Nov 20)	N=233 n (%) (22 May 20)	N=528 n (%) (06 Nov 20)	N=471 n (%) (22 May 20)
Patients with SAE	166 (59.1)	129 (55.4)	288 (54.5)	235 (49.9)
Pneumonia	33 (11.7)	25 (10.7)	52 (9.8)	39 (8.3)
Disease progression	21 (7.5)	15 (6.4)	41 (7.8)	30 (6.4)
Pneumonitis	13 (4.6)	11 (4.7)	24 (4.5)	21 (4.5)
Anaemia	9 (3.2)	6 (2.6)	20 (3.8)	14 (3.0)
Sepsis	8 (2.8)	8 (3.4)	15 (2.8)	13 (2.8)
Pyrexia	8 (2.8)	6 (2.6)	12 (2.3)	12 (2.5)
Dyspnoea	6 (2.1)	5 (2.1)	10 (1.9)	7 (1.5)
Urinary tract infection	6 (2.1)	4 (1.7)	18 (3.4)	14 (3.0)
Pleural effusion	6 (2.1)	4 (1.7)	10 (1.9)	7 (1.5)
Neutropenia	5 (1.8)	5 (2.1)	7 (1.3)	7 (1.5)
Seizure	5 (1.8)	4 (1.7)	6 (1.1)	5 (1.1)
Hypertension	4 (1.4)	4 (1.7)	7 (1.3)	6 (1.3)
Pulmonary embolism	4 (1.4)	3 (1.3)	5 (<1)	4(<1)
Back pain	4 (1.4)	3 (1.3)	4 (<1)	3 (<1)
Diarrhoea	3 (1.1)	3 (1.3)	5 (<1)	6 (1.3)
Bacteraemia	3 (1.1)	3 (1.3)	4(<1)	4(<1)
AST increased	3 (1.1)	3 (1.3)	3 (<1)	3 (<1)
Dizziness	3 (1.1)	3 (1.3)	5 (<1)	5 (1.1)
Hyponatraemia	3 (1.1)	2 (<1)	8 (1.5)	6 (1.3)

Abbreviations: AST= aspartate aminotransferase; mg=milligram; NSCLC= non-small cell lung cancer; QD= once daily; RET = rearranged during transfection; SAE= serious adverse event. Note: * Serious adverse events with ≥1% cut-off is based on RET fusion-positive NSCLC patients treated at 400 mg QD as of 06 Nov 2020

Deaths

Among all patients treated with pralsetinib at 400 mg QD, 66 patients (12.5%) died during the study due to an AE (35 patients (12.5%) RET fusion-positive NSCLC patients died due an AE) as presented in Table 42and 6 patients (1.1%) due to a treatment related (investigator assessed) AE (rhabdomyolysis, pneumonia, pneumocystis jirovecii pneumonia, pneumonitis, and death [in 2 patients, unknown cause of death in 1 patient and multifactorial cause in 1 patient]).

Table 42. Deaths Due to AEs Regardless of Causality: Safety Population - All Patients and RET fusion-positive Advanced NSCLC Patients treated at 400 mg QD. (Data Cut-off 06 November 2020**)**

	RET fusion-positive NSCLC Patients (N=281) n (%)	All Patients (N=528) n (%)
Deaths due to AEs	35 (12.5)	66 (12.5)
Disease progression	14 (5.0)	32 (6.1)
Pneumonia	4 (1.4)	5 (<1)
Death	2 (<1)	4 (<1)
Dyspnoea	2 (<1)	2 (<1)
General physical health deterioration	1 (<1)	2 (<1)
Respiratory failure	1 (<1)	2 (<1)
Sepsis	1 (<1)	2 (<1)
Acute myocardial infarction	1 (<1)	1 (<1)
Asthenia	1 (<1)	1 (<1)
Cardio-respiratory arrest	1 (<1)	1 (<1)
Disseminated intravascular coagulation	1 (<1)	1 (<1)
Embolism	1 (<1)	1 (<1)
Haemorrhage intracranial	1 (<1)	1 (<1)
Multiple organ dysfunction syndrome	1 (<1)	1 (<1)
Pneumonia cytomegaloviral	1 (<1)	1 (<1)
Rhabdomyolysis	1 (<1)	1 (<1)
Urosepsis	1 (<1)	1 (<1)
Pneumonia aspiration	0	2 (<1)
Acute respiratory failure	0	1 (<1)
Asphyxia	0	1 (<1)
Jugular vein thrombosis	0	1 (<1)
Pneumocystis jirovecii pneumonia	0	1 (<1)
Pneumonitis	0	1 (<1)

Abbreviations: AE= adverse event; NSCLC= non-small cell lung cancer; QD= once daily.

Laboratory findings

Table 43. Serum Chemistry and Haematology, Shift from Baseline to Worst on Treatment (Grade 3 and Grade 4) in the RET Fusion-Positive NSCLC Patients and Overall Safety Population Treated at 400 mg QD. (Data cut-off 22 May 2020)

Parameter (unit)	Treated at 400 mg QD			
	RET Fusion-Positive NSCLC Patients (N=233)		Overall Safety Population (N=471)	
	Grade 3 (n %)	Grade 4 (n %)	Grade 3 (n %)	Grade 4 (n %)
Decreased Albumin	0	0	4 (<1)	0
Decreased Calcium Corrected	2 (<1)	0	15 (3.2)	9 (1.9)
Decreased Hemoglobin	24 (10.3)	0	54 (11.5)	0
Decreased Leukocytes	18 (7.7)	2 (<1)	44 (9.3)	2 (<1)
Decreased Lymphocytes	36 (15.5)	15 (6.4)	86 (18.3)	28 (5.9)
Decreased Magnesium	0	0	1 (<1)	1 (<1)
Decreased Neutrophils	31 (13.3)	14 (6.0)	69 (14.6)	19 (4.0)
Decreased Phosphate	26 (11.2)	1 (<1)	48 (10.2)	2 (<1)
Decreased Platelets	5 (2.1)	4 (1.7)	9 (1.9)	12 (2.5)
Decreased Sodium	14 (6.0)	2 (<1)	20 (4.2)	2 (<1)
Increased Activated Partial Thromboplastin Time	1 (<1)	0	1(<1)	0
Increased Alanine Aminotransferase	6 (2.6)	1 (<1)	18(3.8)	4 (<1)
Increased Alkaline Phosphatase	4 (1.7)	0	9(1.9)	0
Increased Aspartate Aminotransferase	4 (1.7)	2 (<1)	18 (3.8)	6 (1.3)
Increased Bilirubin	2 (<1)	0	7 (1.5)	0
Increased Creatinine	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Increased Potassium	1 (<1)	0	3 (<1)	0
Increased Prothrombin Intl. Normalized Ratio	1 (<1)	0	2 (<1)	0

Abbreviations: mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. Source: Listings 16.4.2.1.1, 16.4.2.1.3

Despite incidence and severity of hepatotoxicity, there are no cases that potentially fulfil Hy's law definition criteria.

ECG changes

All patients treated at 400 mg QD (N=528): A total of 45 events in 41 patients (7.8%) were identified (22 patients with RET fusion-positive NSCLC, 17 patients with thyroid cancer and 1 patient each with prostate and sweat gland cancer). Serious AEs were observed in 5 patients (<1%) and non-serious AEs in 37 patients (7.0%) (of which 1 patient experienced both a serious and non-serious AE). The events included ECG QT prolonged (29 events in 26 patients), syncope (15 events in 14 patients), and long QT syndrome (1 event in 1 patient). Of the 41 patients, 23 patients (4.4%) experienced Grade 1 events, 7 patients (1.3%) experienced Grade 2 events, and 11 patients (2.1%) experienced Grade 3 events; no Grade 4 or Grade 5 events were reported. Six patients (1.1%) reported events that led to temporary interruption of study drug treatment (3 events led to a restart of study drug at a reduced dose). No events resulted in permanent discontinuation of study drug.

QT prolongation occurred in 5.1% of 528 patients with NSCLC or other solid tumours. In 2 patients (0.4%) the event was assessed as serious. The majority of patients experienced non-severe events – i.e. Grade 1, in 21 (4.0%) and Grade 2, in 4 patients (0.8%). Two patients (0.4%) experienced Grade 3 events of Electrocardiogram QT prolonged, which both resolved. Three patients (0.6%) had an event that remained unresolved by time of data cut-off. Dose reductions or interruptions were required by two Electrocardiogram QT prolonged patients, each.

RET Fusion-positive Advanced NSCLC Patients Treated at 400 mg QD (N=281): A total of 25 events in 22 patients (7.8%) were identified in RET fusion-positive advanced NSCLC patients. Serious

AEs were observed in 3 patients (1.1%) and non-serious AEs in 20 patients (6.8%). The events included ECG QT prolonged (18 events in 15 patients) and syncope (7 events in 7 patients). Of the 22 patients, 14 patients (5.0%) experienced Grade 1 events, 4 patients (1.4%) experienced Grade 2 events, and 4 patients (1.4%) experienced Grade 3 events (only 1 patient with Grade 3 AE of ECG QT prolonged); no Grade 4 or Grade 5 events were reported. Nineteen patients (3.6%) reported events that resulted in no change in study drug dosing. Three patients (<1%) reported events that led to temporary interruption of study drug treatment. These three patients restarted at a reduced pralsetinib dose without recurrence of the event. All events were reported as resolved. The Investigator assessed the events as related to study drug for 13 patients (4.3%) and not related for 10 patients (3.9%) (of which 1 patient experienced both a related and unrelated event of ECG QT prolonged).

Table 44. Adverse Events Related to ECG by Preferred Term Safety Population - All Patients Treated at 400mg QD. (Data Cut-off 06 November 2020)

Preferred Term	RET fusion-positive NSCLC Patients (N=281) n (%)
Patients with AE	22 (7.8)
Electrocardiogram QT prolonged	15 (5.3)
Syncope	7 (2.5)
Long QT syndrome	0

Abbreviations: AE= Adverse event; ECG= electrocardiogram; NSCLC= non-small cell lung cancer; QD= once daily

Safety in special populations

Age

Table 45. Summary of Adverse Events in ≥ 10% of patients by Age Group of <65 and ≥65; RET Fusion-Positive NSCLC Patients and Overall Safety Population Treated at 400 mg QD (Data Cut-off 22 May 2020)

Preferred Term	Patients treated at 400mg QD			
	<65		≥65	
	RET Fusion-Positive NSCLC Patients (N=145) n (%)	Overall Safety Population (N=328) n (%)	RET Fusion-Positive NSCLC Patients (N=88) n (%)	Overall Safety Population (N=143) n (%)
Patients with AE	143 (98.6)	326 (99.4)	87 (98.9)	142 (99.3)
Aspartate aminotransferase increased	65 (44.8)	146 (44.5)	36 (40.9)	62 (43.4)
Constipation	55 (37.9)	127 (38.7)	35 (39.8)	56 (39.2)
Anaemia	57 (39.3)	119 (36.3)	37 (42.0)	66 (46.2)
Alanine aminotransferase increased	47 (32.4)	110 (33.5)	21 (23.9)	38 (26.6)
Neutrophil count decreased	40 (27.6)	72 (22.0)	11 (12.5)	22 (15.4)
White blood cell count decreased	34 (23.4)	79 (24.1)	12 (13.6)	30 (21.0)
Cough	34 (23.4)	70 (21.3)	19 (21.6)	29 (20.3)
Blood creatinine increased	34 (23.4)	67 (20.4)	16 (18.2)	33 (23.1)

Neutropenia	33 (22.8)	77 (23.5)	18 (20.5)	25 (17.5)
Diarrhoea	32 (22.1)	89 (27.1)	23 (26.1)	47 (32.9)
Hypertension	32 (22.1)	82 (25.0)	41 (46.6)	62 (43.4)
Pyrexia	32 (22.1)	75 (22.9)	20 (22.7)	30 (21.0)
Fatigue	25 (17.2)	60 (18.3)	30 (34.1)	43 (30.1)
Back pain	23 (15.9)	38 (11.6)	9 (10.2)	13 (9.1)
Dyspnoea	22 (15.2)	45 (13.7)	12 (13.6)	27 (18.9)
Headache	22 (15.2)	52 (15.9)	4 (4.5)	15 (10.5)
Hyperphosphataemia	20 (13.8)	71 (21.6)	7 (8.0)	15 (10.5)
Asthenia	20 (13.8)	45 (13.7)	11 (12.5)	18 (12.6)
Dry mouth	20 (13.8)	41 (12.5)	19 (21.6)	29 (20.3)
Hypoalbuminaemia	20 (13.8)	34 (10.4)	5 (5.7)	8 (5.6)
Pneumonia	19 (13.1)	38 (11.6)	14 (15.9)	18 (12.6)
Nausea	18 (12.4)	49 (14.9)	11 (12.5)	18 (12.6)
Blood creatine phosphokinase increased	18 (12.4)	42 (12.8)	11 (12.5)	14 (9.8)
Pneumonitis	17 (11.7)	31 (9.5)	10 (11.4)	16 (11.2)
Dysgeusia	16 (11.0)	45 (13.7)	19 (21.6)	27 (18.9)
Blood alkaline phosphatase increased	16 (11.0)	31 (9.5)	11 (12.5)	14 (9.8)
Oedema peripheral	15 (10.3)	40 (12.2)	18 (20.5)	28 (19.6)

Abbreviations: AE = adverse event, mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. Source: 14.3.2.1.1.10a

Table 46. Safety Profile of Pralsetinib in Elderly Patients – RET Fusion-Positive NSCLC Patients Treated at 400 mg QD. (Data Cut-off 22 May 2020)

MedDRA Terms	Age <65 (N=145) N (%)	Age 65-74 (N=66) N (%)	Age 75-84 (N=19) N (%)	Age 85+ (N=3) N (%)
Total AEs	143 (98.6)	66 (100)	18 (94.7)	3 (100)
Serious AEs – Total*	76 (52.4)	44 (66.7)	12 (63.1)	1 (33.3)
Fatal*	13 (11.7)	8 (12.1)	3 (15.7)	0
Hospitalization/prolong existing hospitalization*	57 (39.3)	35 (53.0)	8 (42.1)	1 (33.3)
Life-threatening*	3 (2.06)	1 (1.51)	1 (5.2)	0
Disability/incapacity*	0	0	0	0

Other (medically significant) *	2 (0.61)	0	0	0
AE leading to treatment discontinuation	22 (15.2)	16 (24.2)	4 (21.1)	1 (33.3)
SOC- Psychiatric disorders	27 (18.6)	7 (10.6)	3 (15.8)	2 (66.7)
SOC- Nervous system disorders	67 (46.2)	40 (60.6)	11 (57.9)	2 (66.7)
SOC- Accidents and injuries	0	0	0	0
SOC- Cardiac disorders	13 (9.0)	14 (15.9)	10 (15.2)	4 (21.1)
SOC- Vascular disorders	42 (29.0)	36 (54.5)	10 (52.6)	2 (66.7)
PT- Cerebrovascular disorders	0	0	0	0
SOC- Infections and infestations	74 (51.0)	35 (53.0)	9 (47.4)	2 (66.7)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	18 (12.4)	14 (21.2)	6 (31.5)	2 (66.7)
AEs that appear more frequently in older patients (≥10% difference in incidence between <65 and ≥65)				
PT				
Hypertension	32 (22.1)	30 (45.5)	10 (52.6)	1 (33.3)
White blood cell count decreased	34 (23.4)	7 (10.6)	5 (26.3)	0
Fatigue	25 (17.2)	21 (31.8)	7 (36.8)	2 (66.7)
Hypoalbuminaemia	20 (13.8)	3 (4.5)	2 (10.5)	0
Oedema peripheral	15 (10.3)	16 (24.2)	1 (5.3)	1 (33.3)
Dysgeusia	16 (11.0)	13 (19.7)	6 (31.6)	0

Abbreviations: AE, adverse event; MedDRA= Medical dictionary for regulatory activities; PT= Preferred term; SOC= system organ class. Note: If a subject had multiple seriousness criteria reported for a single AE, highest seriousness was used for analysis. *Data on SAEs and serious criteria were obtained from the safety database which has higher number of patients with SAEs compared to the clinical database at the time of the data cut-off date. Percentages are estimated.

Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (87.1% versus 72.3%). Compared with younger patients (<65), more patients of ≥65 years old reported adverse reactions that led to permanent dose discontinuation (25.8% versus 13.4%) (Data cut-off 06 Nov 2020).

Gender

Table 47. Summary of Adverse Events in ≥10% patients by Gender in RET Fusion- Positive NSCLC Patients and Overall Safety Population Treated at 400 mg QD. (Data Cut-off 22 May 2020)

Preferred Term	Patients treated at 400 mg			
	Male		Female	
	RET fusion-positive NSCLC Patients (N=111) N (%)	Overall Safety Population (N=255) N (%)	RET fusion-positive NSCLC Patients (N=122) N (%)	Overall Safety Population (N=216) N (%)
Patients with AE	110 (99.1)	254 (99.6)	120 (98.4)	214 (99.1)
Aspartate aminotransferase increased	45 (40.5)	111 (43.5)	56 (45.9)	97 (44.9)
Constipation	38 (34.2)	92 (36.1)	52 (42.6)	91 (42.1)
Anaemia	35 (31.5)	91 (35.7)	59 (48.4)	94 (43.5)
Hypertension	35 (31.5)	83 (32.5)	38 (31.1)	61 (28.2)
Fatigue	30 (27.0)	56 (22.0)	25 (20.5)	47 (21.8)
Cough	27 (24.3)	54 (21.2)	26 (21.3)	45 (20.8)
Alanine aminotransferase increased	26 (23.4)	72 (28.2)	42 (34.4)	76 (35.2)
Pyrexia	22 (19.8)	54 (21.2)	30 (24.6)	51 (23.6)
Diarrhoea	21 (18.9)	69 (27.1)	34 (27.9)	67 (31.0)
Neutropenia	18 (16.2)	44 (17.3)	33 (27.0)	58 (26.9)
Dry mouth	18 (16.2)	40 (15.7)	15 (12.3)	26 (12.0)
Neutrophil count decreased	17 (15.3)	39 (15.3)	34 (27.9)	55 (25.5)
Dyspnoea	17 (15.3)	41 (16.1)	13 (10.7)	30 (13.9)
Dizziness	17 (15.3)	33 (12.9)	17 (13.9)	31 (14.4)
Pneumonia	17 (15.3)	31 (12.2)	20 (16.4)	31 (14.4)
Back pain	17 (15.3)	26 (10.2)	20 (16.4)	33 (15.3)
White blood cell count decreased	16 (14.4)	50 (19.6)	30 (24.6)	59 (27.3)
Dysgeusia	15 (13.5)	31 (12.2)	17 (13.9)	31 (14.4)
Oedema peripheral	13 (11.7)	37 (14.5)	19 (15.6)	29 (13.4)
Headache	13 (11.7)	37 (14.5)	15 (12.3)	26 (12.0)
Asthenia	12 (10.8)	32 (12.5)	21 (17.2)	30 (13.9)
Decreased appetite	12 (10.8)	34 (13.3)	19 (15.6)	31 (14.4)
Pneumonitis	12 (10.8)	21 (8.2)	12 (9.8)	24 (11.1)

Abbreviations: AE = adverse event, mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. Source: 14.3.1.1.1.10b

Region

Table 48. Summary of Adverse Events in ≥10% patients by Region RET Fusion-Positive NSCLC Patients and Overall Safety Population Treated at 400 mg QD. (Data Cut-off 22 May 2020)

Preferred Term	Patients treated at 400mg					
	USA		Europe		Asia	
	RET fusion-Positive NSCLC (N=62) n (%)	Overall Safety Population (N=153) n (%)	RET fusion-Positive NSCLC (N=85) n (%)	Overall Safety Population (N=171) n (%)	RET fusion-Positive NSCLC (N=86) n (%)	Overall Safety Population (N=147) n (%)
Patients with AE	62 (100)	153 (100)	83 (97.6)	169 (98.8)	85 (98.8)	146(99.3)
Aspartate amino-transferase increased	29 (46.8)	69 (45.1)	24 (28.2)	60 (35.1)	48 (55.8)	79(53.7)
Anaemia	24 (38.7)	64 (41.8)	30 (35.3)	64 (37.4)	40 (46.5)	57(38.8)
Constipation	22 (35.5)	59 (38.6)	33 (38.8)	62 (36.3)	35 (40.7)	62(42.2)
Hypertension	21 (33.9)	56 (36.6)	19 (22.4)	44 (25.7)	33 (38.4)	44(29.9)
Fatigue	21 (33.9)	50 (32.7)	20 (23.5)	35 (20.5)	14 (16.3)	18(12.2)
ALT increased	19 (30.6)	50 (32.7)	19 (22.4)	44 (25.7)	32 (37.2)	55(37.4)
Diarrhoea	18 (29.0)	54 (35.3)	20 (23.5)	47 (27.5)	17 (19.8)	35(23.8)
Dry mouth	17 (27.4)	38 (24.8)	12 (14.1)	20 (11.7)	10 (11.6)	12 (8.2)
Blood creatinine increased	16 (25.8)	40 (26.1)	19 (22.4)	37 (21.6)	15 (17.4)	23(15.6)
Oedema peripheral	16 (25.8)	37 (24.2)	9 (10.6)	18 (10.5)	8 (9.3)	13 (8.8)
Neutropenia	16 (25.8)	30 (19.6)	17 (20.0)	49 (28.7)	18 (20.9)	23 (15.6)
White blood cell count decreased	14 (22.6)	48 (31.4)	9 (10.6)	18 (10.5)	23 (26.7)	43(29.3)
Dizziness	13 (21.0)	34 (22.2)	7 (8.2)	10 (5.8)	9 (10.5)	14 (9.5)
Cough	12 (19.4)	34 (22.2)	20 (23.5)	36 (21.1)	21 (24.4)	29(19.7)
Dysgeusia	11 (17.7)	29 (19.0)	18 (21.2)	33 (19.3)	6 (7.0)	10 (6.8)
Back pain	11 (17.7)	19 (12.4)	11 (12.9)	18 (10.5)	10 (11.6)	14 (9.5)
Muscle spasms	11 (17.7)	13 (8.5)	7 (8.2)	8 (4.7)	0	0
Headache	10 (16.1)	35 (22.9)	12 (14.1)	22 (12.9)	4 (4.7)	10 (6.8)
Pyrexia	10 (16.1)	35 (22.9)	22 (25.9)	45 (26.3)	20 (23.3)	25(17.0)
Nausea	10 (16.1)	30 (19.6)	11 (12.9)	25 (14.6)	8 (9.3)	12 (8.2)
Vomiting	10 (16.1)	23 (15.0)	9 (10.6)	17 (9.9)	6 (7.0)	11 (7.5)
Neutrophil count decreased	9 (14.5)	31 (20.3)	6 (7.1)	9 (5.3)	36 (41.9)	54(36.7)
Urinary tract infection	8 (12.9)	22 (14.4)	12 (14.1)	20 (11.7)	8 (9.3)	11 (7.5)
Lymphocyte count decreased	7 (11.3)	31 (20.3)	2 (2.4)	8 (4.7)	4 (4.7)	7 (4.8)
Hypocalcaemia	7 (11.3)	30 (19.6)	7 (8.2)	22 (12.9)	9 (10.5)	28(19.0)
Upper respiratory tract infection	7 (11.3)	16 (10.5)	2 (2.4)	4 (2.3)	3 (3.5)	7 (4.8)
Pneumonia	7 (11.3)	20 (13.1)	11 (12.9)	14 (8.2)	15 (17.4)	22 (15.0)
Pneumonitis	7 (11.3)	15 (9.8)	7 (8.2)	16 (9.4)	13 (15.1)	16 (10.9)
Rash	7 (11.3)	14 (9.2)	2 (2.4)	7 (4.1)	6 (7.0)	9 (6.1)
Neuropathy peripheral	7 (11.3)	13 (8.5)	1 (1.2)	4 (2.3)	2 (2.3)	2 (1.4)
Hyperphosphataemia	6 (9.7)	26 (17.0)	9 (10.6)	29 (17.0)	12 (14.0)	31(21.1)
Arthralgia	6 (9.7)	24 (15.7)	3 (3.5)	9 (5.3)	0	3 (2.0)

Abdominal pain	6 (9.7)	22 (14.4)	4 (4.7)	9 (5.3)	5 (5.8)	7 (4.8)
Dyspnoea	6 (9.7)	22 (14.4)	14 (16.5)	32 (18.7)	14 (16.3)	18 (12.2)
Dysphagia	6 (9.7)	14 (9.2)	10 (11.8)	15 (8.8)	3 (3.5)	3 (2.0)
Myalgia	5 (8.1)	22 (14.4)	4 (4.7)	18 (10.5)	7 (8.1)	8 (5.4)
Hyponatraemia	5 (8.1)	20 (13.1)	4 (4.7)	6 (3.5)	9 (10.5)	11 (7.5)
Lymphopenia	5 (8.1)	16 (10.5)	12 (14.1)	22 (12.9)	0	1 (<1)
Leukopenia	4 (6.5)	7 (4.6)	14 (16.5)	29 (17.0)	4 (4.7)	6 (4.1)
Erectile dysfunction	4 (6.5)	16 (10.5)	2 (2.4)	7 (4.1)	1 (1.2)	1 (<1)
Asthenia	3 (4.8)	7 (4.6)	24 (28.2)	51 (29.8)	4 (4.7)	5 (3.4)
Chills	3 (4.8)	16 (10.5)	0	5 (2.9)	0	1 (<1)
Musculoskeletal pain	1 (1.6)	3 (2.0)	10 (11.8)	15 (8.8)	7 (8.1)	8 (5.4)
Blood creatine phosphokinase increased	0	3 (2.0)	13 (15.3)	27 (15.8)	16 (18.6)	26(17.7)

Abbreviations: AE = adverse event; mg = milligram; NSCLC = non-small cell lung cancer; QD = once daily; RET = rearranged during transfection. Source: 14.3.2.1.1.10c

Race, G≥3

Table 49. Grade ≥ 3 Adverse Events in ≥2% of patients by Preferred Term by Race RET Fusion-Positive NSCLC Patients and Overall Safety Population Treated at 400 mg QD. (Data Cut-off 22 May 2020)

Preferred Term	Patients treated at 400mg					
	Asian		Non- Asian		Unknown	
	RET fusion-Positive NSCLC Patients (N=92) n (%)	Overall Safety Population (N=159) n (%)	RET fusion-Positive NSCLC (N=125) n (%)	Overall Safety Population (N=283) n (%)	RET fusion-Positive NSCLC (N=16) n (%)	Overall Safety Population (N=29) n (%)
Patients with Grade 3/4/5 AE	67 (72.8)	109 (68.6)	80 (64.0)	204 (72.1)	8 (50.0)	20 (69.0)
Neutrophil count decreased	17 (18.5)	25 (15.7)	0	0	6 (4.8)	9 (3.2)
Anaemia	16 (17.4)	23 (14.5)	17 (13.6)	42 (14.8)	1 (6.3)	3 (10.3)
Hypertension	15 (16.3)	21 (13.2)	20 (16.0)	49 (17.3)	0	2 (6.9)
Neutropenia	15 (16.3)	19 (11.9)	13 (10.4)	32 (11.3)	0	5 (17.2)
Pneumonia	9 (9.8)	13 (8.2)	10 (8.0)	21 (7.4)	1 (6.3)	2 (6.9)
Hypophosphataemia	9 (9.8)	10 (6.3)	6 (4.8)	12 (4.2)	1 (6.3)	1 (3.4)
Disease progression	8 (8.7)	10 (6.3)	7 (5.6)	18 (6.4)	0	2 (6.9)
White blood cell count decreased	6 (6.5)	8 (5.0)	3 (2.4)	11 (3.9)	0	2 (6.9)
AST increased	5 (5.4)	8 (5.0)	7 (5.6)	16 (5.7)	0	1 (3.4)
Thrombocytopenia	5 (5.4)	6 (3.8)	1 (<1)	3 (1.1)	0	1 (3.4)
Platelet count decreased	4 (4.3)	7 (4.4)	0	4 (1.4)	0	1 (3.4)
Hypokalaemia	4 (4.3)	5 (3.1)	2 (1.6)	7 (2.5)	0	0
Hyponatraemia	4 (4.3)	5 (3.1)	4 (3.2)	10 (3.5)	0	0

Blood creatine phosphokinase increased	3 (3.3)	6 (3.8)	3 (2.4)	8 (2.8)	2 (12.5)	7 (24.1)
Vomiting	3 (3.3)	3 (1.9)	0	2 (<1)	0	0
Pneumonitis	3 (3.3)	6 (3.8)	1 (<1)	6 (2.1)	0	1 (3.4)
Diarrhoea	2 (2.2)	6 (3.8)	2 (1.6)	9 (3.2)	0	0
ALT increased	2 (2.2)	5 (3.1)	5 (4.0)	13 (4.6)	1 (6.3)	2 (6.9)
Hypocalcaemia	2 (2.2)	5 (3.1)	1 (<1)	8 (2.8)	0	0
Lymphocyte count decreased	2 (2.2)	5 (3.1)	3 (2.4)	18 (6.4)	0	1 (3.4)
Pleural effusion	2 (2.2)	3 (1.9)	1 (<1)	2 (<1)	1 (6.3)	2 (6.9)
Sepsis	2 (2.2)	3 (1.9)	5 (4.0)	9 (3.2)	1 (6.3)	1 (3.4)
Urinary tract infection	2 (2.2)	3 (1.9)	4 (3.2)	11 (3.9)	0	1 (3.4)
Weight increased	2 (2.2)	3 (1.9)	0	0	0	0
Blood alkaline phosphatase increased	2 (2.2)	2 (1.3)	0	2 (<1)	0	0
Cholecystitis	2 (2.2)	2 (1.3)	0	1 (<1)	0	0
Dehydration	2 (2.2)	2 (1.3)	0	1 (<1)	0	0
Disseminated intravascular coagulation	2 (2.2)	2 (1.3)	0	0	0	0
Dyspnoea	2 (2.2)	2 (1.3)	3 (2.4)	6 (2.1)	1 (6.3)	1 (3.4)
Haemoglobin decreased	2 (2.2)	2 (1.3)	0	1 (<1)	0	0
Leukopenia	2 (2.2)	2 (1.3)	4 (3.2)	7 (2.5)	0	0
Stomatitis	2 (2.2)	2 (1.3)	2 (1.6)	2 (<1)	0	1 (3.4)
Pulmonary embolism	1 (1.1)	1 (<1)	4 (3.2)	7 (2.5)	2 (12.5)	2 (6.9)
Fatigue	1 (1.1)	1 (<1)	3 (2.4)	7 (2.5)	1 (6.3)	2 (6.9)
Back pain	0	0	3 (2.4)	4 (1.4)	0	0
Intervertebral disc protrusion	0	1 (<1)	3 (2.4)	3 (1.1)	0	0

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, mg = milligram, NSCLC = non-small cell lung cancer, QD = once daily, RET = rearranged during transfection. Source: Table 14.3.2.9.1.10d

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

The metabolism of pralsetinib is mediated by CYP3A4. Pralsetinib inhibits CYP2C8, CYP2C9, CYP3A4/5, CYP3A4/5, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K, and induces CYP2C8, CYP2C9, and CYP3A4/5. A clinical assessment should be done for each individual patient depending on the necessity of coadministration of other drugs that might affect or be affected by pralsetinib.

Discontinuation due to adverse events

AEs leading to treatment discontinuation

Table 50. Adverse Events Leading to Treatment Discontinuation (≥1 Patient; Safety Population – All Patients Treated at 400 mg QD. (Data Cut-off 06 November 2020)

Preferred Term	RET fusion-positive NSCLC Patients (N=281) n (%)	All Patients (N=528) n (%)
Patients with AE Leading to Permanent Discontinuation of Treatment Regardless of Causality	55 (19.6)	91 (17.2)
Disease progression	10 (3.6)	15 (2.8)
Pneumonitis	7 (2.5)	10 (1.9)
Pneumonia	7 (2.5)	9 (1.7)
Sepsis	3 (1.1)	4 (<1)
Death	2 (<1)	3 (<1)
Dyspnoea	2 (<1)	2 (<1)
Thrombocytopenia	2 (<1)	2 (<1)
Fatigue	1 (<1)	2 (<1)
Hyponatraemia	1 (<1)	2 (<1)
Neutropenia	1 (<1)	2 (<1)
Pulmonary embolism	1 (<1)	2 (<1)
Respiratory failure	1 (<1)	2 (<1)
Cardio-respiratory arrest	1 (<1)	1 (<1)
Chest pain	1 (<1)	1 (<1)
Clostridium difficile colitis	1 (<1)	1 (<1)
Colitis	1 (<1)	1 (<1)
Constipation	1 (<1)	1 (<1)
Electrolyte imbalance	1 (<1)	1 (<1)
Embolism	1 (<1)	1 (<1)
Gait disturbance	1 (<1)	1 (<1)
General physical health deterioration	1 (<1)	1 (<1)
Haemorrhage intracranial	1 (<1)	1 (<1)
Heart injury	1 (<1)	1 (<1)
Hypertension	1 (<1)	1 (<1)
Hypoxia	1 (<1)	1 (<1)
Lymphocyte count decreased	1 (<1)	1 (<1)
Pancytopenia	1 (<1)	1 (<1)
Pericardial effusion	1 (<1)	1 (<1)
Respiratory distress	1 (<1)	1 (<1)
Rhabdomyolysis	1 (<1)	1 (<1)
Stomatitis	1 (<1)	1 (<1)
Superior vena cava syndrome	1 (<1)	1 (<1)
Therapy cessation	1 (<1)	1 (<1)
Urosepsis	1 (<1)	1 (<1)
Asthenia	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	1 (<1)	2 (<1)
Transaminases increased	0	2 (<1)
Acute respiratory distress syndrome	0	1 (<1)
Acute respiratory failure	0	1 (<1)

Asphyxia	0	1 (<1)
Blood bilirubin increased	0	1 (<1)
Blood calcitonin increased	0	1 (<1)
Bronchopulmonary aspergillosis	0	1 (<1)
Cognitive disorder	0	1 (<1)
Corona virus infection	0	1 (<1)
Deep vein thrombosis	0	1 (<1)
Hydrocephalus	0	1 (<1)
Hypercalcaemia of malignancy	0	1 (<1)
Jugular vein thrombosis	0	1 (<1)
Large intestine perforation	0	1 (<1)
Platelet count decreased	0	1 (<1)
Pneumocystis jirovecii pneumonia	0	1 (<1)
Pneumonia aspiration	0	1 (<1)
Renal failure	0	1 (<1)

Abbreviations: AE= adverse event; NSCLC: non-small cell lung cancer; QD= once daily. Source: Table 14.3.2.21.1.10

AEs leading to dose interruptions

Table 51Adverse Events Leading to Dose Interruption Regardless of Causality by Preferred Term in ≥ 3 Patients; Safety Population – All Patients Treated at 400 mg QD. (Data Cut-off 06 November 2020)

Preferred Term	RET fusion-positive NSCLC Patients (N=281) n (%)	All Patients (N=528) n (%)
Patients with AE Leading to Dose Interruption Regardless of Causality	190 (67.6)	363 (68.8)
Neutrophil count decreased	28 (10.0)	38 (7.2)
Anaemia	27 (9.6)	50 (9.5)
Pneumonitis	27 (9.6)	42 (8.0)
Neutropenia	24 (8.5)	49 (9.3)
Hypertension	24 (8.5)	39 (7.4)
Pneumonia	21 (7.5)	36 (6.8)
Blood creatine phosphokinase increased	16 (5.7)	31 (5.9)
Pyrexia	15 (5.3)	27 (5.1)
White blood cell count decreased	14 (5.0)	24 (4.5)
Aspartate aminotransferase increased	11 (3.9)	23 (4.4)
Fatigue	10 (3.6)	15 (2.8)
Alanine aminotransferase increased	9 (3.2)	18 (3.4)
Diarrhoea	7 (2.5)	20 (3.8)
Thrombocytopenia	7 (2.5)	13 (2.5)
Vomiting	6 (2.1)	13 (2.5)
Lymphopenia	6 (2.1)	11 (2.1)
Platelet count decreased	6 (2.1)	11 (2.1)
Sepsis	6 (2.1)	10 (1.9)
Hypophosphataemia	6 (2.1)	6 (1.1)

Lymphocyte count decreased	5 (1.8)	14 (2.7)
Urinary tract infection	5 (1.8)	14 (2.7)
Dyspnoea	5 (1.8)	11 (2.1)
Stomatitis	5 (1.8)	8 (1.5)
Leukopenia	5 (1.8)	6 (1.1)
Face oedema	4 (1.4)	5 (<1)
Interstitial lung disease	4 (1.4)	5 (<1)
Cough	3 (1.1)	8 (1.5)
Dizziness	3 (1.1)	8 (1.5)
Hyponatraemia	3 (1.1)	7 (1.3)
Hypoxia	3 (1.1)	4 (<1)
Rash	3 (1.1)	4 (<1)
Nausea	3 (1.1)	6 (1.1)
Dehydration	3 (1.1)	3 (<1)
Lipase increased	3 (1.1)	3 (<1)
Muscular weakness	3 (1.1)	3 (<1)
Pleural effusion	3 (1.1)	3 (<1)
Abdominal pain	2 (<1)	8 (1.5)
Corona virus infection	2 (<1)	8 (1.5)
Cholecystitis	2 (<1)	4 (<1)
Decreased appetite	2 (<1)	4 (<1)
Haematoma	2 (<1)	4 (<1)
Oedema peripheral	2 (<1)	4 (<1)
Blood alkaline phosphatase increased	2 (<1)	3 (<1)
Diverticulitis	2 (<1)	3 (<1)
Pulmonary embolism	2 (<1)	3 (<1)
Blood creatinine increased	1 (<1)	6 (1.1)
Ascites	1 (<1)	4 (<1)
Headache	1 (<1)	4 (<1)
Hypokalaemia	1 (<1)	4 (<1)
Hypotension	1 (<1)	4 (<1)
Syncope	1 (<1)	4 (<1)
Acute respiratory failure	1 (<1)	3 (<1)
Constipation	1 (<1)	3 (<1)
Appendicitis	1 (<1)	3 (<1)
Dysphagia	1 (<1)	3 (<1)
Influenza	1 (<1)	3 (<1)
Mucosal inflammation	1 (<1)	3 (<1)
Respiratory failure	1 (<1)	3 (<1)
Upper respiratory tract infection	1 (<1)	3 (<1)
Urinary retention	1 (<1)	3 (<1)
Myalgia	0	5 (<1)
Blood bilirubin increased	0	3 (<1)
Hypercalcaemia	0	3 (<1)
Pyelonephritis	0	3 (<1)
Hypocalcaemia	0	8 (1.5)

Abbreviations: AE= adverse event; NSCLC: non-small cell lung cancer; QD= once daily. Source: Table 14.3.2.23.1.10

AEs leading to dose reductions

Table 52. Adverse Events Leading to Dose Reduction Regardless of Causality by Preferred Term in ≥3 patients; Safety Population – All Patients Treated at 400 mg QD. (Data cut-off 06 November 2020)

Preferred Term	RET fusion-positive NSCLC Patients (N=281) n (%)	All Patients (N=528) n (%)
Patients with AE Leading to Dose Reduction Regardless of Causality	126 (44.8)	239 (45.3)
Anaemia	22 (7.8)	43 (8.1)
Neutropenia	22 (7.8)	42 (8.0)
Neutrophil count decreased	21 (7.5)	34 (6.4)
Pneumonitis	18 (6.4)	27 (5.1)
Hypertension	12 (4.3)	21 (4.0)
Blood creatine phosphokinase increased	10 (3.6)	21 (4.0)
White blood cell count decreased	10 (3.6)	18 (3.4)
Fatigue	10 (3.6)	16 (3.0)
Lymphopenia	7 (2.5)	12 (2.3)
Pneumonia	7 (2.5)	10 (1.9)
Lymphocyte count decreased	5 (1.8)	16 (3.0)
Aspartate aminotransferase increased	4 (1.4)	7 (1.3)
Platelet count decreased	4 (1.4)	7 (1.3)
Decreased appetite	4 (1.4)	6 (1.1)
Hypophosphataemia	4 (1.4)	4 (<1)
Thrombocytopenia	3 (1.1)	6 (1.1)
Leukopenia	3 (1.1)	4 (<1)
Alanine aminotransferase increased	2 (<1)	7 (1.3)
Dysgeusia	2 (<1)	3 (<1)
Muscular weakness	2 (<1)	3 (<1)
Stomatitis	2 (<1)	3 (<1)
Asthenia	1 (<1)	4 (<1)
Diarrhoea	1 (<1)	4 (<1)
Hypocalcaemia	0	3 (<1)

Abbreviations: AE= adverse event; NSCLC: non-small cell lung cancer; QD= once daily. Source: Table 14.3.2.25.1.10

Post marketing experience

Not applicable.

2.4.1. Discussion on clinical safety

Overall safety population (N=528), data cut-off 06 November 2020

Likely on account of its potent RET-inhibitor mechanism of action, the overall summary of adverse events from pralsetinib in the population intended for indication depicts a considerable toxicity burden. As expected, almost every patient presented any type of AEs. Nearly three quarters of patients

presented ≥G3 AEs, and 54.5% had SAEs. As a consequence of such events, 68.8% of patients needed dose interruptions, 45.3% dose reductions and 17.2 % discontinued treatment permanently.

Common AEs: The most frequent AE from pralsetinib is aspartate aminotransferase increased, which occurred in 46.0% of patients. Other common AEs in the NSCLC population are anaemia (45.6%), constipation (41.9%), alanine aminotransferase increase (33.9%), hypertension (32.6%), neutrophil count decreased (24.2%) and diarrhoea (29.4%). Some other frequent AEs, particularly those of respiratory/thoracic/mediastinal nature (e.g. cough, dyspnoea, pneumonia) might also be related to the baseline disease and its risk factors.

≥G3 AEs (incidence 76.9%): The most frequent high-grade AEs are anaemia (17.2%), hypertension (16.1%) and neutropenia (11.2%).

Severe, life-threatening or fatal cases of pneumonitis/ILD have been reported in patients who received pralsetinib in clinical trials. Patients who present with clinically symptomatic pneumonitis or ILD were excluded from clinical trials. Patients should be advised to contact their healthcare provider immediately to report new or worsening respiratory symptoms. Patients who present with acute or worsening of respiratory symptoms indicative of pneumonitis/ILD (e.g., dyspnoea, cough, and fever) should be investigated to exclude other potential causes. If pneumonitis/ILD is considered to be related to pralsetinib, the dose of pralsetinib should be interrupted, reduced or permanently discontinued based on severity of confirmed pneumonitis/ILD (see sections 4.2, 4.4 and 4.8 of the SmPC).

Hypertension was observed in pralsetinib-treated patients in clinical trials. Treatment-related hypertension was most commonly managed with anti-hypertensive medicinal products. Treatment with pralsetinib should not be initiated in patients with uncontrolled hypertension. Pre-existing hypertension should be adequately controlled before starting pralsetinib treatment. Monitoring of blood pressure is recommended after 1 week, at least monthly thereafter and as clinically indicated. Anti-hypertensive therapy should be initiated or adjusted as appropriate. The dose should be interrupted, reduced, or permanently discontinued based on the severity of the hypertension observed during treatment with pralsetinib (see sections 4.2, 4.4 and 4.8 of the SmPC).

Severe cases of transaminase elevations have been reported in patients who received pralsetinib in clinical trials. ALT and AST should be monitored prior to initiating pralsetinib, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Treatment with pralsetinib should be interrupted, reduced or permanently discontinued based on severity of the transaminase elevation observed during treatment with pralsetinib (see sections 4.2, 4.4 and 4.8 of the SmPC).

Severe, including fatal, haemorrhagic events can occur with pralsetinib. In patients with life-threatening or recurrent severe haemorrhage, pralsetinib should be permanently discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

Prolongation of the QT interval has been observed in patients who received Gavreto in clinical trials (see section 4.8). Therefore, before starting Gavreto treatment, patients should have a QTc interval ≤470 ms and serum electrolytes within normal range. Hypokalaemia, hypomagnesaemia, and hypocalcaemia should be corrected both prior and during Gavreto treatment. Electrocardiograms (ECGs) and serum electrolytes should be monitored at the end of the first week and of the first month of Gavreto treatment, then periodically, as clinically indicated, depending also on the presence of other risk factors (e.g. intercurrent diarrhoea, vomiting, nausea, concomitant medications). Pralsetinib should be used with caution in patients with medical history of cardiac arrhythmias or QT interval prolongation, as well as in patients on strong CYP 3A4 inhibitors or on medicinal products known to be associated with QT/QTc prolongation. Gavreto may require interruption, dose modification, or discontinuation (see sections 4.2, 4.4 and 4.8 of the SmPC).

SAEs (incidence 54.5%): Infections (pneumonia 9.8%, sepsis 2.8%, urinary tract infection 3.4%), events of thoracic nature (pneumonitis 4.5%, dyspnoea 1.9%, pleural effusion 1.9%), and myelotoxicity (anaemia 3.8%, neutropenia 1.3%) were the predominant SAEs in patients treated with pralsetinib.

Deaths: 66 out of 528 patients (12.5%) died due to an AE. 32 of these deaths were due to disease progression, dubiously labelled as an AE. From the rest, events of thoracic nature (pneumonia, dyspnoea, respiratory failure) were the most frequent cause of death.

Laboratory shifts: Relating to anaemia incidence, G3 haemoglobin decrease was reported in 11.5% of patients. G3/4 neutropenia occurred in 19% of patients and G3/4 lymphopenia in 24%. G3 hypophosphatemia, although of dubious clinical relevance, occurred in 10% of patients.

Discontinuations/interruptions/reductions: The most frequent AEs that led to permanent treatment discontinuations were pneumonitis (1.9%), pneumonia (1.7%) and sepsis (<1%). Interruptions and/or dose reductions were most frequently due to neutropenia/neutrophil count decreased, anaemia and pneumonitis.

Special populations: AEs that happened more frequently in older patients ($\geqslant$ 65 years) were hypertension, leukopenia and fatigue. The proportion of SAEs was higher in older (65%) than younger (52%) patients (data from NSCLC population). Anaemia, neutropenia and neutrophil count decreased, nausea and vomiting, pneumonitis, UTIs, platelet count decreased and hypoalbuminemia were reported in a higher incidence in females, while blood creatinine increased was reported in a higher incidence for males. These differences did not seem to translate into unbalances in overall AEs, SAEs or discontinuations due to AEs. However, for treatment interruptions and dose reductions, higher percentages were found for females. No clear reason for these differences has been found and no effect in the Pop PK model was found either. Overall, the observed unbalances are not considered relevant enough to consider that pralsetinib tolerability might be different between males and females. The incidence of myelotoxic events was slightly higher in Asian patients.

In study ARROW (N=528), 37.8% of patients were 65 years of age and older. Compared with younger patients (<65), more patients of $\geqslant$65 years old reported adverse reactions that led to permanent dose discontinuation (25.8% versus 13.4%). Of the commonly reported events with higher incidence in elderly patients ($\geqslant$65), hypertension has the greatest difference in comparison with patients <65 years of age. However, hypertension is also expected to occur more frequently in the elderly population. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (87.1% versus 72.3%) (see section 4.8 of the SmPC).

There are no available data from the use of pralsetinib in pregnant women. Studies in animals have shown reproductive toxicity. Based on its mechanism of action and findings in animals, pralsetinib may cause foetal harm when administered to pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving pralsetinib. A highly effective non-hormonal method of contraception is required for female patients during treatment with pralsetinib, because pralsetinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 2 weeks after the final dose. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the final dose of pralsetinib (see section 4.4 and 4.6 of the SmPC).

It should not be used during pregnancy unless the clinical condition of the woman requires treatment with pralsetinib.

It is unknown whether pralsetinib or its metabolites are excreted in human milk. A risk to breast-fed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with

pralsetinib and for at least one week after the final dose.

No clinical data on the effect of pralsetinib on fertility are available. Based on findings from animal studies, male and female fertility may be compromised by treatment with pralsetinib. Both men and women should seek advice on effective fertility preservation before treatment.

Pralsetinib has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or operating machines as patients may experience fatigue while taking pralsetinib (see section 4.7 of the SmPC).

Preferred term 'disease progression'

From a clinical oncology perspective, disease progression is often connected to a lack of efficacy or natural progression of the disease, not being considered as an actual adverse event related to a drug. According to the BLU-667-1101 protocol, the term "disease progression" (which exists in the MedDRA database) was used as a reported AE across the safety database of pralsetinib. This explains why 'disease progression' appears as one of the most frequent AEs (first cause of deaths due to AEs regardless of causality, second most frequent SAE, sixth most frequent high-grade AE) in the tables presented in this assessment report, but not as an adverse drug reaction (causality not established) in section 4.8 of the SmPC.

Impacted safety database:

Methodological differences in the recording of AEs and their outcomes have been identified by the current applicant (Roche) regarding the original submission by the initial applicant (Blueprint Medicines). Both methodologies are scientifically valid, not posing a significant impact on the overall safety profile of pralsetinib. The finding of five additional G5 AEs using Roche's methodology is reasonably justified and none of the cases seems related to study drug.

Safety profile or pralsetinib in 1L vs. ⩾2L patients

For the most part, the overall proportion of AEs [any AEs, high-grade (⩾G3) AEs, SAEs, AESIs, G5 AEs, AEs leading to dose interruption/reduction and AEs leading to permanent treatment discontinuation] seems slightly higher in the sub-population of pretreated patients (n=165) as compared to treatment-naïve patients (n=116).

No cases of overdose have been reported in clinical trials with pralsetinib. The maximum dose of pralsetinib studied clinically is 600 mg orally once daily. Adverse reactions observed at this dose were consistent with the safety profile at 400 mg once daily. There is no known antidote for Gavreto overdose. In the event of suspected overdose, Gavreto should be interrupted and supportive care instituted. Based on the large volume of distribution of pralsetinib and extensive protein binding, dialysis is unlikely to result in significant removal of pralsetinib. (see sections 4.8 and 4.9 of the SmPC).

NSCLC (N=281), data cut-off 06 November 2020

Safety performance of pralsetinib for the NSCLC population is comparable to that described for the larger safety population.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultation

The following input of the SAG-Oncology has been requested:

Is the observed safety profile of Gavreto acceptable in first line?

On the meeting of the 7th of September 2021, the conclusions of the SAG-O were as follows:

The majority of the SAG agreed that the safety profile is well-characterised and acceptable given the high activity and also the toxicity generally associated with alternative treatment options. However, many uncertainties exist including subgroups frail/elderly and longer follow-up (see above).

For ~~a~~ minority of experts the uncertainties in efficacy/safety are too important to conclude on a positive balance of benefits and risks.

Additional safety data needed in the context of a conditional MA

Additional safety data including comparative data will be provided as part of the specific obligations in order to fulfil a CMA. Longer follow-up from the ARROW study will allow a better characterisation of the long-term safety and the randomised phase 3 study AcceleRET will allow a contextualisation of the safety data compared to the control arm.

2.4.2. Conclusions on the clinical safety

Overall safety data of pralsetinib are scarce since the design of the pivotal study ARROW is open-label and single arm, with limited exposure and follow-up. Importantly, however, toxicity does not seem to differ substantially between treatment-naïve and pretreated patients. Hepatotoxicity, hypertension, myelotoxicity and intestinal motility disturbances are the most frequently observed AEs from pralsetinib treatment, which can nonetheless be interrupted and/or reduced to improve tolerability. Transaminase elevations, hypertension, pneumonitis, haemorrhagic events and QTc prolongation are identified as safety concerns for pralsetinib in the RMP. The observed safety findings are clinically manageable.

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

- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of a longer follow-up of efficacy evaluable patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy) of study BLU-667-1101, a Phase 1/2 Study of pralsetinib in patients with thyroid cancer, NSCLC and other advanced solid tumours. The CSR should be submitted by 31 December 2022.
- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of study BLU-667-2303, a randomized, open-label, Phase 3 Study of pralsetinib versus standard of care for first line treatment of RET fusion-positive, metastatic NSCLC. The CSR should be submitted by 31 December 2026.

2.5. Risk Management Plan

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

Safety concerns

Table 53. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Pneumonitis Hypertension Haemorrhage Transaminase Elevations
Important potential risks	Embryo-foetal toxicity Severe infections QT prolongation
Missing information	Use in patients with moderate or severe hepatic impairment Drug-drug interactions

Pharmacovigilance plan

Table 54. On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study GP43162 (DDI Study) A Study to evaluate the effect of repeat doses of a P-gp inhibitor on the pharmacokinetics of pralsetinib and to inform appropriate dosing strategies for safe coadministration of pralsetinib with P-gp inhibitors.	• To assess the impact of coadministration of a P-gp inhibitor on the single-dose PK of pralsetinib. • To assess the safety and tolerability of a single-dose of pralsetinib alone and co administered with a P-gp inhibitor.	Drug-drug interaction	Final protocol submission Trial completion Final report submission	05/2021 12/2021 04/2022
Study GP43163 A Study to Evaluate the Pharmacokinetics of BLU-667 in Healthy and Hepatically Impaired Subjects	• to characterise the pharmacokinetics of pralsetinib in patients with hepatic impairment	Use in patients with severe hepatic impairment	Final study protocol submission Trial completion Final clinical study report	May 2021 March 2024 September 2024

CSR = clinical study report; NSCLC = non-small cell lung cancer; P-gp = P-glycoprotein; RET = rearranged during transfection

Risk minimisation measures

Table 55. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pneumonitis	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Recommendation on dose interruptions, dose reduction and discontinuation in SmPC section 4.2. Recommendation that health care providers advise patients to immediately report new or worsening respiratory symptoms. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None
Hypertension	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Recommendation on dose interruptions, dose reduction and discontinuation in SmPC section 4.2. Advice on monitoring in SmPC sections 4.2 and 4.4. Recommendation to not start treatment in case of uncontrolled hypertension. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None
Haemorrhage	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Recommendation on dose interruptions, dose reduction and discontinuation in SmPC section 4.2. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None

Transaminase Elevations	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 PL sections 2 and 4 Recommendation on dose interruptions and discontinuation in SmPC section 4.2.Advice on monitoring. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** Risk will be assessed through Study GP43163 in Healthy and Hepatically Impaired subjects
Embryo-foetal Toxicity	**Routine risk minimization measures:** SmPC sections 4.4, 4.6 and 5.3 PL section 2 Advice on the use of contraception in SmPC sections 4.4 and 4.6 and section 2 of the PL Advice on treatment avoidance in case of pregnancy. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None
Severe Infections	**Routine risk minimization measures:** SmPC sections 4.2, and 4.8. Recommendation on dose adjustment and discontinuation in SmPC section 4.2. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None
QT Prolongation	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.5, 4.8, and 5.1 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs **Additional pharmacovigilance activities:** None

Use in Patients with Severe Hepatic impairment	**Routine risk minimization measures:** SmPC sections 4.2 and 5.2. Recommendation on dose adjustment in SmPC section 4.2. Advice on treatment avoidance in case of severe hepatic impairment. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** Study GP43163 planned; final protocol submission May 2021
Drug-Drug Interaction	**Routine risk minimization measures:** Sections 4.2, 4.4, 4.5, 5.2, of the SmPC "Dose modification for use with strong cytochrome P-450 (CYP)3A4 inhibitors or combined P- glycoprotein (P-gp) and strong CYP3A4 inhibitors", "Dose modification for use with strong CYP3A4 inducers", "Drug interactions", and "Strong CYP3A4 inhibitors and or combined P-gp and strong CYP3A4 inhibitors" and avoid "Sensitive substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1 and MATE2-K with narrow therapeutic index" provide recommendations on risk management approach. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** Study GP43162 planned; final protocol submission May 2021

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 04.09.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.7. New Active Substance

The applicant compared the structure of pralsetinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers pralsetinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Gavreto (pralsetinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Gavreto (pralsetinib) is as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC).

The aim of treatment is to induce tumour response, as measured by the primary efficacy endpoint ORR.

3.1.2. Available therapies and unmet medical need

Oncogenic RET fusions have been identified in 1-2% of NSCLC. Patient with RET-fusion positive advanced NSCLC are usually treated per NCCN and ESMO guidelines for NSCLC testing negative for ALK/BRAF/EGFR/ROS1 with platinum doublet-based cytotoxic chemotherapy and/or immunotherapy with a checkpoint inhibitor. As of February 2021, selpercatinib (Retsevmo SmPC) is the first RET inhibitor approved in Europe. However, since it holds an indication after immunotherapy and/or platinum-based chemotherapy in patients with advanced RET fusion-positive NSCLC, an unmet medical need still exists.

3.1.3. Main clinical studies

The main efficacy data in support of the claimed indication is based on a single pivotal trial: BLU-667-1101 (ARROW), an ongoing phase I/II, open-label, first-in-human, multi-cohort, single-arm trial in patients with advanced, unresectable RET-altered solid tumours. The study design consists of a dose escalation phase (phase I) to determine the MTD and RP2D of pralsetinib and an ongoing dose expansion phase (phase II) to assess clinical efficacy of pralsetinib in specific tumour types and treatment settings across nine cohorts, and further define safety and tolerability at the RP2D, *i.e.,* 400 mg QD.

The applicant has submitted updated efficacy results from 233 RET fusion-positive NSCLC patients from both phase I (dose escalation) and II (Groups 1 and 2) whose treatment at the proposed starting dose of pralsetinib of 400 mg QD started on or before 22 May 2020, which constitute the population of interest for the pursued indication. The efficacy dataset includes all data reported from these patients up to a cut-off of 06 November 2020.

The primary endpoint of the trial is ORR by BICR based on RECIST v1.1. The secondary endpoints are DOR, PFS and OS.

3.2. Favourable effects

- At data cut-off 06 November 2020, with an estimated median follow-up time of 17.1 months, 150 out of the 233 patients from the efficacy dataset had achieved confirmed response by BICR, attaining a BOR of 64.4% (95% CI 57.9, 70.5). From the group of responders, 11 patients exhibited a confirmed CR.
- The median TTR was 1.8 months and, in 68% of responders, DOR was more than 6 months. However, the observed medians for the time-to-event endpoints (DOR, PFS or OS) have not been

reached yet. The K-M estimates for mDOR (22.3 months) and mPFS (16.4 months) are nevertheless encouraging.

- The forest plot of ORR suggests that pralsetinib exerted benefits across most important subgroups (ECOG PS status, CNS metastases at enrolment, prior treatments), although the ORR in patients whose tumours had other RET-fusion partners was considerably inferior.
- The ORR benefit of pralsetinib for the intended population was observed regardless of line of treatment, with slightly higher ORR in the treatment-naïve population (n=75, ORR 72.0 %).

3.3. Uncertainties and limitations about favourable effects

Data from time-to-event endpoints (PFS, OS) are difficult to interpret in the context of an uncontrolled trial.

The uncontrolled nature of the study is a limitation to interpretation of efficacy results, particularly since historical data from patients with RET fusion-positive NSCLC are scarce. The submission of further follow-up from the pivotal trial (BLU-667-1101) together with the results from an open-label, randomized, controlled multicentre phase III study in RET fusion-positive NSCLC patients (AcceleRET - BLU-667-2303) investigating the efficacy of pralsetinib in patients with metastatic NSCLC harbouring an oncogenic RET fusion and who have not received prior systemic therapy will address these uncertainties.

3.4. Unfavourable effects

- The most frequent AE from pralsetinib is aspartate aminotransferase increased, which occurred in 46% of patients.
- Other common AEs in the NSCLC population are anaemia (46%), constipation (42%), alanine aminotransferase (ALT) (34%), hypertension (33%), diarrhoea (29%), white blood cell count decreased (27%), pyrexia (25%) and fatigue (25%).
- The most common high-grade AEs (incidence 76.9%) from pralsetinib are anaemia, hypertension and neutropenia.
- The most common SAEs (incidence 54.5%) were infections, pneumonitis, dyspnoea, pleural effusion and myelotoxicity.
- 12.5% of patients died from AEs, although almost half of these deaths were reported as progressive disease (as an AE).
- Due to toxicity from pralsetinib, a significant proportion of patients required dose interruptions (68.8%), dose reductions (45.3%) or permanent treatment discontinuation (17.2%).
- The toxicity profile of pralsetinib does not seem to differ substantially between treatment-naïve and pretreated patients.

3.5. Uncertainties and limitations about unfavourable effects

- Long-term safety data are missing. The submission of further follow-up from the pivotal trial (BLU-667-1101) together with the results from an open-label, randomized, controlled multicentre phase III study in RET fusion-positive NSCLC patients (AcceleRET - BLU-667-2303) will address these uncertainties.

3.6. Effects Table

Table 56: Effects Table for pralsetinib in the treatment of patients with advanced RET fusion-positive NSCLC. (Data cut-off 06 November 2020)

Effect	Short Description	Unit	Treatment (monotherapy pralsetinib) N=233			Uncertainties/ Strength of evidence	eferences
Favourable Effects							
			Treatment naïve N=75	**Pre-treated with platinum treatment N=136**	**Pre-treated with non-platinum systemic treatment N=22**		
ORR	PR+CR (RECIST 1.1) by BICR	% 95% CI	72.0% (60.4%, 81.8%)	58.8% (50.1%, 67.2%)	72.7% (49.8%, 89.3%)	Selected and uncontrolled data	CSR, SCE
DOR	Median (K-M estimate)	Months 95% CI	NR (9.0, NR)	22.3 (15.1, NR)	NR (9.2, NR)	Immature and uncontrolled data	CSR, SCE
PFS	Median (K-M estimate)	Months 95% CI	13.0 (9.1, NR)	16.5 (10.5, 24.1)	12.8 (9.1, NR)	Immature and uncontrolled data	CSR, SCE
OS	Median (K-M estimate)	Months 95% CI	NR	NR	NR, NR	Immature and uncontrolled data	CSR, SCE
Unfavourable Effects							
			All patients (n=528)				
≥G3 AEs		%	76.9			Immature data	CSR, SCS
SAEs		%	54.5			Immature data	CSR, SCS
Deaths due to AEs		%	12.5			Immature data	CSR, SCS
AEs leading to permanent discontinuation		%	17.2			Immature data	CSR, SCS
AST increased Gr ≥3		%	46.0 5.7				CSR, SCS
Hypertension Gr ≥3		%	33.0 16.1				CSR, SCS
Pneumonitis/ILD Gr ≥3		%	11.6 3.3				CSR, SCS
QTc prolongation Gr ≥3		%	5.1 0.4				
Haemorrhagic events Gr ≥3		%	18.8 3.2				

Abbreviations: NSCLC= Non-small cell lung cancer; AE= Adverse event; AESI= Adverse event of special interest; SAE= Serious adverse event; ORR= Overall response rate; DOR= Duration of response; PFS= Progression free survival; OS= Overall survival;

PR= partial response; CR= complete response; K-M= Kaplan-Meier; CI= confidence interval; CSR= clinical study report; SCE= summary of clinical efficacy; SCS= summary of clinical safety.

3.7. Benefit-risk assessment and discussion

3.7.1 Importance of favourable and unfavourable effects

The application is based on one single-arm trial, which challenges the interpretation of any potential long-term beneficial effects of pralsetinib in terms of PFS and OS. Nevertheless, this approach may be acceptable for a product intended for a rare population with an unmet medical need, which is indeed the case of patients with advanced RET fusion-positive NSCLC (about 1-2% of all NSCLC).

An ORR of 64.4% from pralsetinib in the targeted population is encouraging and, considering the reported high rate of durable responses, expected to translate into a clinically meaningful benefit.

The main concern for a line-agnostic indication is the uncertainty about the impact on time-dependent endpoints, even if activity in terms of ORR in the first line setting appears higher than what is seen for chemo-immunotherapy in a non-selected population. Although the medians for the time-to-event endpoints (DOR, PFS, OS) have not been reached yet, preliminary results suggest that responses are durable and *KM-estimates* of PFS and OS allow to anticipate lasting benefits from treatment with pralsetinib.

Indirect comparisons of available OS and PFS results of pralsetinib in RET-fusion positive NSCLC against those reported with chemo-immunotherapy in 'all-comer' NSCLC patients treated in studies IMpower130, IMpower150 and KEYNOTE-189 give some support to the efficacy benefit of targeted treatment in the 1L. Of note, despite the many limitations of this type of analyses and high censoring of OS (mOS not reached), the OS 12-month landmark in ARROW –82% of 75 1L patients still alive– seems promising in comparison to data from the above-mentioned studies and other trials in 1L.

About three quarters of patients present high-grade AEs and SAEs were reported for more than half of them. Most of the specific events from pralsetinib have also been seen with other TKIs used in lung cancer, but their frequency and severity seem to be higher with pralsetinib. However, interruptions and/or dose reductions are possible and may help managing the safety profile of pralsetinib in clinical practice. Importantly, the toxicity profile of pralsetinib does not seem to differ substantially between treatment-naïve and pretreated patients.

3.7.1. Balance of benefits and risks

In patients with advanced RET fusion-positive NSCLC, the ARROW study reported high rates of durable responses for pralsetinib together with a manageable safety profile. The B/R balance is therefore positive.

3.7.2. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed. It is agreed that benefit-risk is positive across all lines. The line agnostic indication has been sufficiently justified.
- It is likely that the applicant will be able to provide comprehensive data. The applicant will provide confirmatory data from the ongoing AcceleRET study (BLU-667-2303), an open-label, randomized, controlled multicentre phase III study in RET fusion-positive NSCLC patients. This study is designed to assess the efficacy of pralsetinib as compared to Investigator's choice platinum-based chemotherapy regimen for patients with metastatic NSCLC harbouring an oncogenic RET fusion and who have not received prior systemic therapy. This study is currently recruiting and the submission of the final clinical study report (CSR) is expected by Q4 2026. In addition, results from a longer follow up of efficacy evaluable patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy) from the relevant cohorts from study ARROW (BLU-667-1101), will be submitted by 31 December 2022 to confirm the B/R of Gavreto. Additional safety data including comparative data will be provided as part of the specific obligations. Longer follow-up from the ARROW study will allow a better characterisation of the long-term safety and the randomised phase 3 study AcceleRET will allow a contextualisation of the safety data compared to the control arm. Results from both studies are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA.
- Patient with RET-fusion positive advanced NSCLC are usually treated per NCCN and ESMO guidelines for NSCLC testing negative for ALK/BRAF/EGFR/ROS1 with platinum doublet-based cytotoxic chemotherapy and/or immunotherapy with a checkpoint inhibitor. As of February 2021, selpercatinib is the first RET inhibitor authorised in the EU as a CMA for the treatment of RET-fusion positive NSCLC following prior treatment with immunotherapy and/or platinum-based chemotherapy. Unmet medical needs will be addressed, in view of the high overall response rate and the long duration of response, regardless of line of therapy in the RET fusion-positive NSCLC population. Gavreto is considered to have a major therapeutic advantage over existing therapies based on the convenience of oral administration, a differential safety profile, and the provision of a treatment alternative with a novel mechanism of action in the context of a reported activity of such a magnitude that allows to expect that pralsetinib would be at least similarly active to first line available chemotherapy, immunotherapy or immunochemotherapy options. In previously treated RET fusion-positive NSCLC patients, Gavreto is expected to address the unmet medical need to a similar extent to selpercatinib in view of the observed response rate and duration of response.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Given the positive benefit/risk and the unmet medical need in the applied indications as described above, this is considered fulfilled.

3.8. Conclusions

The overall B/R of Gavreto is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Gavreto is favourable in the following indication:

Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

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

Description	Due date
In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should conduct and submit the results of a longer follow-up of efficacy evaluable patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy) of study BLU-667-1101, a Phase 1/2 Study of pralsetinib in patients with thyroid cancer, NSCLC and other advanced solid tumours.	31 December 2022
In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC, the MAH should submit the results of study BLU-667-2303, a randomized, open-label, Phase 3 Study of pralsetinib versus standard of care for first line treatment of RET fusion-positive, metastatic NSCLC.	31 December 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that pralsetinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Appendix

Not applicable.