EU RISK MANAGEMENT PLAN FOR GAVRETO® /PRALSETINIB

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Rationale for Submitting an Updated RMP

This updated E.U. RMP v1.8 was prepared to include the findings from Study GP43163, a clinical trial evaluating the pharmacokinetics and safety of pralsetinib in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function.

Summary of Significant Changes in This RMP

- Part II: Module SIV.1 - Exclusion criteria and pivotal clinical studies: In Table 7 rationale for concomitant medication exclusion criterion has been updated
- Part II: Module SVII.1.2 - Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP: Missing Information Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part II: Module SVII.2 - New Safety Concerns and Reclassification with a Submission of an Updated RMP: Use in patients with severe hepatic impairment previously classified as missing information is no longer presented in this EU RMP
- Part II: Module SVII.3.2 - Presentation of the Missing Information: Text on Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part II: Module SVIII - Summary of the Safety Concerns: In table 16, missing information of Use in patients with severe hepatic impairment has been deleted as the milestone of Category 3 study (GP43163) has been fulfilled
- Part III.3 – Summary Table of Additional Pharmacovigilance Activities: (Table 17 On-going and Planned Additional Pharmacovigilance Activities) - Study GP43163 has been deleted from table 17 as the milestone (GP43163) has been fulfilled
- Part V.1 Routine Risk-Minimization Measures: In table 18 missing information of Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part V.3 Summary of Risk Minimization Measures: In table 19 missing information of Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part VI: Summary of the Risk Management Plan – II.A List of Important Risks and Missing Information: missing information of Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part VI: Summary of the Risk Management Plan - II.B Summary of Important Risks: missing information of Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled
- Part VI: Summary of the Risk Management Plan – Module II.C.2: Other studies in post-authorization development plan missing information of Use in patients with severe hepatic impairment has been deleted as the milestone (GP43163) has been fulfilled

- Annex 2: Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme – Moved study GP43163 from ongoing to completed studies table.
- Annex 3: Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan – Updated to align with the PV plan.
- Annex 8: Summary of changes updated to include above changes

Other RMP Versions under Evaluation

RMP Version Number: 1.7, submitted with the responses to the 2nd RSI for procedure EMEA/H/C/005413/II/0012.

Details of Currently Approved RMP

RMP Version Number: 1.5

Approved with Procedure Number: EMEA/H/C/005413/II/0010

Date of approval (Opinion date): 22 June 2023

See page 1 for signature and date

Dr. PPD (QPPV)	Date

See page 1 for signature and date

PPD	Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Pralsetinib
Pharmacotherapeutic group(s) (ATC Code)	Other antineoplastic agents, protein kinase inhibitors (L01EX23)
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	GAVRETO
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Pralsetinib is a small molecule tyrosine kinase inhibitor (TKI)
	Summary of mode of action: Pralsetinib is a potent and selective inhibitor of both wild type and the oncogenic mutant forms of the receptor tyrosine kinase known as rearranged during transfections (RET)
	Important information about its composition: None
Hyperlink to the Product Information	Refer to Product Information
Indication(s) in the EEA	Current: GAVRETO is indicated as monotherapy for the treatment of adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 400 mg pralsetinib once daily (QD). Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg QD.
	Proposed : Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Hard capsule Each capsule contains 100 mg of pralsetinib
	Proposed : Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

EEA = European Economic Area; INN= International non-proprietary name; NSCLC = non-small cell lung cancer; QD = once daily; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical classification system
BRAF	B-rapidly accelerated fibrosarcoma
CDS	Core Data Sheet
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
DSR	Drug Safety Report
ECG	Electrocardiogram
EGFR	epidermal growth factor receptor
EMA	European Medicine Society
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
FGFR	fibroblast growth factor receptor
GLDH	gamma-glutamyl transferase
GLP	good laboratory practice
GPS	global product strategy
GVP	Good Pharmacovigilance Practice
hERG	human ether-à-go-go-related gene
HNSTD	highest non-severely toxic dose
IARC	International Agency for Research on Cancer
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ILD	interstitial lung disease
IMD	international medical director
IND	investigational new drug application
ISD	international scientific director
MAA	Marketing Authorization Application
JAK	janus kinase
JAK2	janus kinase 2
KRAS	Kirsten rat sarcoma
MEN2	multiple endocrine neoplasia syndrome type 2

Abbreviation	Definition
MKI	multikinase inhibitor
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
PD-L	programmed death-ligand
PD-L1	programmed death-ligand 1
PI	Product Information
PV	Pharmacovigilance
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval formula
RAF	rapidly accelerated fibrosarcoma
RAI	radioactive iodine
RET	rearranged during transfection
ROS-1	c-ros oncogene 1
RMP	Risk Management Plan
RTK	receptor tyrosine kinase
SAE	serious adverse event
SD	standard deviation
SEOM	Spanish Society of Medical Oncology
SMQ	Standardized MedDRA Query
SPC	summary of product characteristics
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

S I.1 INDICATION(S)

SI.1.1 RET FUSION-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

- **Incidence and Prevalence**

Lung cancer is the most common cause of cancer death worldwide with an estimated 1.8 million deaths per year and is by far responsible for the largest proportion of total cancer deaths (18.4%) compared to any other type (WHO 2019). Europe has the second highest rate of lung cancer worldwide with an overall incidence of 22.4% and a mortality rate of 22% (WHO 2019). In 2016, more than a quarter of a million (275 thousand) people died from lung cancer in Europe, which represents one-fifth (19.9 %) of all deaths from cancer and 5.4 % of the total number of deaths (Eurostat 2019).

Lung cancer arises from the cells of the respiratory epithelium and can be divided into two broad categories: NSCLC (which accounts for 85% of the lung cancer) and small cell lung cancer (Zappa and Mousa 2016). NSCLC subtypes are 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) (Zappa and Mousa 2016; Szumera-Ciećkiewicz et al. 2013). Approximately 75% of the lung adenocarcinomas harbor genetic alterations that promote the RTK/RAS/RAF signalling pathway including drivers such as KRAS, endothelial growth factor receptor (BRAF, MET, NTRK, and RET, among others EGFR), ALK, and ROS1, (O'Leary et al. 2019).Oncogenic RET fusions have been identified in 1-2% of NSCLC and the RET fusions are typically found in adenocarcinoma histology (though occasionally squamous) (Lin et al. 2015; Takeuchi 2019).

- **Demographics**

The general demographic characteristics of patients with lung cancer/NSCLC seem to differ significantly from the demographic characteristics of RET-driven tumors. While lung cancer is the second most common form of cancer in men (after prostate cancer) and its incidence is two-fold higher than in women (North and Christiani 2013), a meta-analyses of 9 studies in NSCLC patients (including 6,899 patients) showed that the RET fusion gene was identified at significantly higher frequencies in women than men (Lin et al. 2015).The diagnosis of NSCLC is made in majority of cases in patients older than 65 years of age (ACS 2019), while the available data shows that RET rearrangement is commonly found in a younger patient population (<60 years) (Lin et al. 2015; Gautschi et al. 2017).

- **The main existing treatment options**

The treatment strategy should consider factors such as histology, molecular pathology, patient's age, performance status, comorbidities and the patient's preferences.

Locally advanced (stage IIIb) and metastatic NSCLC (stage IV) is usually considered inoperable. Forty percent of patients with newly diagnosed NSCLC have stage IV disease. Treatment goals are to prolong survival and control disease-related symptoms. Treatment options include cytotoxic chemotherapy, targeted agents, and immunotherapy. Factors influencing treatment selection include comorbidity, performance status, histology, and molecular and immunologic features of the cancer. Therefore, assessment of tumor-genomic changes and programmed death-ligand 1 expression is critical before initiating therapy. Radiation therapy and surgery are generally used in selective cases for symptom palliation (Morabito 2018; Planchard et al. 2018).

Currently two therapies are available for RET-targeted treatment in NSCLC: selpercatinib and pralsetinib.

Diagnostic testing for RET is not yet standard of care and, patients with RET rearrangements, and with advanced NSCLC are treated per European Society for Medical Oncology (ESMO) guidelines for EGFR and anaplastic lymphoma kinase-negative NSCLC. This usually includes first line chemotherapy with a platinum doublet chemotherapy with or without immune checkpoint inhibition or bevacizumab. The second line therapy includes single-agent treatment either with docetaxel or a checkpoint inhibitor, or a combination of docetaxel with ramucirumab, gemcitabine, vinorelbine (Garon et al. 2014; Takeda et al. 2009; William et al. 2010). However, clinical response and overall survival with all these agents remains poor (Planchard et al. 2018, 2019; Rosell and Karachaliou 2016; NCCN 2020). Further therapy for refractory patients is best supportive care or enrolment in a clinical trial (Rosell and Karachaliou 2016; Iams and Lovly 2018; Mazieres et al. 2018).

Immune checkpoint inhibitors such as pembrolizumab and nivolumab have been approved for certain populations of patients with NSCLC, with the most significant clinical benefit observed in patients with disease that expresses PD-L1. However, recent data indicate that patients with RET fusion-positive lung cancers are typically not responsive to checkpoint inhibitors (Rosell and Karachaliou 2016; Sabari et al. 2018a; Tufman et al. 2018), regardless of the expression of PD-L. This poor response to immunotherapy is hypothesized to be due to low tumor mutational burden in the majority of RET fusion-positive patients (Offin et al. 2019; Sabari et al. 2018b), which makes them less likely to be responsive to immunotherapy relative to patients with other cancers.

Small-molecule multikinase inhibitors (MKI) cabozantinib, vandetanib, and sorafenib approved for non-NSCLC solid tumor indications, as well as alectinib approved for

treatment of ALK-driven NSCLC have demonstrated clinical activity in patients with known RET fusion-positive NSCLC, suggesting that RET may be a valid target in NSCLC. However, the results were found to be inferior to the response and outcomes seen with the selective TKIs in other oncogene-driven NSCLC forms (Gautschi et al. 2017; Offin et al. 2019; Drilon et al. 2013, 2016; Lee et al. 2017; Mazieres et al. 2019; Yoh et al. 2017). Moreover, duration of response to therapy is typically less than a year. Treatment with MKIs was associated with significant toxicity, requiring dose interruption and/or dose modification, which likely limit exposures required to effectively inhibit RET.

Thus, the currently recommended treatment options for advanced NSCLC patients with documented RET-fusions do not offer the efficacy that has been achieved with other biomarker targeted NSCLC treatment options (EGFR, ALK, ROS1) in NSCLC patients with these identified oncogenes and existing non-targeted therapy for these patients are associated with significant toxicity and safety risks. Given the modest overall clinical benefit of standard therapy in RET-dependent tumors, RET fusion-positive NSCLC remains an unmet need that requires new therapeutic options, ideally that are able to selectively and potently inhibit RET in vivo while limiting the known safety concerns associated with other TKIs. Such therapies could bring a major therapeutic advantage to patient care.

- **Risk factors for the disease**

While several risk factors have been linked to NSCLC in general, their relevance to RET-driven NSCLC is unknown and the risk factors specific to RET-driven NSCLC have not yet been described.

Smoking (both passive and active) represents a major risk factor for the development of NSCLC (NCI 2019); on the other hand, the RET-driven NSCLC is most commonly diagnosed in light or never smokers (Lin et al. 2015; Gautschi et al. 2017).

Beside smoking, the general risk factors for NSCLC include occupational exposure to agents such as asbestos, nickel, arsenic and some forms of silica and chromium, exposure to radiation, including radon gas in homes and exposure to air. Underlying conditions such as emphysema and associated chronic obstructive pulmonary disease (COPD), also increases the risk of lung cancer, as the chronic inflammation and recurrent microbial infections in bronchiectasis favor lung cancer development (Romesser et al. 2019).

- **Natural History of the Indicated Condition in the (Untreated) Population**

Lung cancer is the leading cause of cancer death among males in both more and less developed countries and has surpassed breast cancer as the leading cause of cancer death among females in more developed countries (IARC 2018). In 2018, over 1.7 million deaths occurred due to lung cancer, this accounting for 18.4% of the total cancer deaths (Keith 2018).

The 5-year survival rate for NSCLC varies by stage, from 60 to 70% for patients with stage I disease to <1% for patients with stage IV disease. An estimated 80% of patients with NSCLC receive an initial diagnosis after their cancer has already spread to regional lymph nodes or has metastasised as most patients with NSCLC present with advanced stage unresectable disease (Planchard et al. 2019). Commonly, 25% to 44% of the advanced NSCLC patients experience dissemination in the central nervous system, particularly the ones diagnosed with adenocarcinoma. 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 5 years or more after diagnosis (Campbell et al. 2018). For NSCLCs, including lung adenocarcinomas, no significant difference has been reported for progression-free survival or overall survival between patients with RET-positive and RET -negative tumors in untreated patients (Wang et al. 2012).

About 25% of lung cancers are asymptomatic and are detected incidentally with chest imaging. Symptoms and signs can result from local tumor progression, regional spread, or distant metastases and include hemoptysis, airway obstruction, pneumonia, pleuritic involvement with pain, pleural effusion, superior vena cava syndrome, Pancoast tumor, hoarseness due to laryngeal nerve involvement, neurologic symptoms due to brain metastasis, pathologic fractures due to bone metastasis or jaundice due to liver metastasis (Pelosof and Gerber 2010). Pneumonia and pneumonitis are also commonly seen in lung cancer patients and the underlying disease is a confounding factor for these events (Akinosoglou et al. 2013; Abdel-Rahman and Fouad 2016).

Derangements at the level of the immune system and lung architecture make patients with lung cancer more susceptible to infections, and pneumonia has been reported to occur in 50% to 70% of patients with lung cancer (Akinosoglou et al. 2013; Valvani et al. 2019).

Paraneoplastic syndromes and constitutional symptoms may occur at any stage of the disease and generally result from tumor production of hormones or peptides that lead to metabolic derangements (Keith 2018). Paraneoplastic syndromes occur in approximately 10% of patients with lung cancer and can impair various organ functions and include neurologic, endocrine, dermatologic, rheumatologic, hematologic, and ophthalmological syndromes, as well as glomerulopathy and coagulopathy (Trousseau's syndrome). Although symptoms are not specific to the classification or histology of the cancer, certain complications may be more likely with different types (Sarfati et al. 2016).

- **Important co-morbidities**

Comorbidities are common among cancer patients, potentially affecting the disease development, stage at diagnosis, treatment choice and treatment outcomes (Islam et al. 2015). Among patients with lung cancers of all types, 74% have one or more comorbidities, most of them tobacco -related (Leduc et al. 2017). These include:

COPD

COPD and lung cancer are closely related, mainly due to the shared risk factor of smoking exposure, which is present in 85–90% of those diagnosed with either COPD or lung cancer. Coexisting COPD is associated with worse survival outcomes after surgery in patients with early-stage NSCLC (Islam et al. 2015; Leduc et al. 2017).

Cardiovascular diseases

Cardiovascular diseases are encountered in 23% of lung cancer patients and share smoking as one of the most important risk factor. Heart failure, myocardial infarction and cardiac arrhythmias are associated with the worst prognosis, whereas hyperlipidaemia at baseline is associated with a better prognosis (Islam et al. 2015).

Diabetes mellitus

Lung cancer and diabetes mellitus share common risk factors, explaining the association between these two diseases, such as age, diet and smoking. Diabetes mellitus is associated with higher mortality in patients with lung cancer, increasing the risk of cardiovascular events, postoperative complications and susceptibility to infection (Leduc et al. 2017).

Renal insufficiency

Chronic renal disease is common in patients with lung cancer, even more so as 30% of patients with lung cancer are elderly, and it has an impact on survival in both early-stage and advanced lung cancer (Leduc et al. 2017).

Tuberculosis

Studies confirmed a higher incidence of adenocarcinoma in patients previously diagnosed with tuberculosis, and a poorer prognostic factor for lung cancer survival (Leduc et al. 2017).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical toxicology program was designed to evaluate the safety profile of pralsetinib when administered orally on a daily schedule and to support clinical development and registration of pralsetinib as an anticancer therapeutic. The toxicology program to date consists of oral single- and repeat-dose toxicity studies with durations up to 13 weeks in rats and cynomolgus monkeys, in vitro and in vivo genotoxicity, embryo-fetal developmental toxicity, fertility and early embryonic development toxicity, in vitro and in vivo phototoxicity studies, in vitro safety pharmacology studies and a single-dose cardiovascular safety study in rats.

Daily oral dosing of pralsetinib for up to 13 weeks was well tolerated at dose levels up to 10 mg/kg/day in rats (sex combined $AUC_{0\text{-}24hr}$ 37,800 h*ng/mL) (Study 00124770) and 10 mg/kg/day in monkeys (sex combined $AUC_{0\text{-}24hr}$ 37,500 h*ng/mL) (Study 00124768), which represents approximately 1-fold exposure margin over the clinical AUC at the intended therapeutic dose of 400 mg QD.

The main toxicities of pralsetinib observed in rat and/or monkeys included hematological abnormalities, effects on bony tissues, reproductive/developmental toxicities, metabolic perturbation, and effects on cardiovascular and gastrointestinal systems. With the exception of developmental toxicities, which were attributed to on-target RET inhibition, the majority of the pralsetinib-related toxicologic effects were attributed to off-target kinase inhibition.

Pralsetinib was not mutagenic or clastogenic when evaluated in a standard ICH genotoxicity battery and did not demonstrate phototoxicity *in vitro*.

Overall, the nonclinical safety program provides adequate evidence of safety to support the use of pralsetinib in the proposed clinical population for marketing authorization.

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

Hematologic and Lymphoid Systems

The key common toxicities noted in rat and/or monkey at systemic exposures similar to clinical steady state exposures ($AUC_{0\text{–}24}$) at the 400 mg QD dose included hematological abnormalities (reduced bone marrow cellularity, reduced hemoglobin, reduced reticulocytes), and lymphoid effects (reduced lymphoid cellularity and decreased lymphocyte counts). These effects were dose-dependent and reversible. The primary cellular effects on the bone marrow and erythron parameters were attributed to off-target Janus kinase (JAK) 2 inhibition (Broxmeyer, 2013; Springuel et al, 2015, Parganas et al. 1998; Quelle et al. 1994; Everds et al. 2013). The decreased cellularity of lymphoid organs corresponding with changes in the hemogram, notably

decreased lymphocytes with increased neutrophils and monocytes was attributed to stress response rather than to pralsetinib-related off-target effects (Davis et al. 2014).

Relevance to Human Use:

Reduced bone marrow cellularity was one of the key toxicities observed in rats and monkeys. This is consistent with observations of the clinical development program, where decrease in the blood cell counts was observed in an increased number of subjects. Hence, 53.5% of patients in the overall safety population at 400 mg QD pralsetinib and 54.9% in RET fusion-positive advanced NSCLC patients treated with 400 mg QD pralsetinib, experienced adverse events in the system organ class of 'Blood and lymphatic system disorders'. The primary cellular effects on the bone marrow and erythron parameters is attributed to the pharmacologic effect of JAK2 inhibition.

Anemia and neutropenia were observed with increased frequency in the clinical development program, but these risks were not considered important for inclusion in the RMP.

Bone

Effects on bone including physeal dysplasia in both rodents and non-human primates and incisor tooth degeneration in rats were observed at exposures (AUC_{0-24}) similar to clinical exposures at the 400 mg QD dose. Incisor teeth grow continuously in rodents throughout their life span. These findings are attributed to impaired angiogenesis secondary to off-target VEGFR inhibition (Chen and Cleck 2009; Fletcher et al. 2010; Patyna et al. 2008) and may impact actively growing bones and teeth.

Relevance to Human Use:

As physeal injuries affect the growth plates of children and adolescents and teeth eruption occurs at similar ages, this finding may be relevant for this patient group only. To date no data are available in this patient group.

Metabolic Effects

Elevation of circulating phosphorus concentration with corresponding mineralization in soft tissues was present in the rat. The mineralization was minimal and non-adverse at systemic exposures (AUC_{0-24}) similar to clinical exposures at 400 mg QD, but was adverse at exposures approximately 2-fold of clinical exposures. Mineralization was primarily present in the glandular stomach, and was also observed to a lesser extent within the heart, kidneys, ovaries and spinal cord. These findings are attributed to off-target inhibition of fibroblast growth factor receptor (FGFR). Similar findings were not observed in cynomolgus monkeys.

Relevance to Human Use:

Elevated phosphorus level and mineralization in soft tissue was the main non-clinical adverse metabolic effect at exposures 2-fold of the target exposures and was primarily seen in one animal species. Elevated phosphorus (phosphate) as laboratory abnormality or reported as adverse event was uncommonly seen in patients in the clinical development program. No risk is currently associated with this finding.

Reproductive/Developmental Toxicity

In a GLP enhanced dose-range finding embryo-fetal development study (Study 00124766), pralsetinib administration during the period of organogenesis was tolerated in gravid rats up to the highest tested dose of 30 mg/kg/day. Post-implantation loss (early resorptions) occurred at 10 mg/kg/day (0.6-fold of the human exposure) and increased to 100% incidence at ≥ 20 mg/kg/day (1.8-fold of human exposure). Multiple visceral malformations and developmental variations (primarily of the kidney and ureter) and skeletal malformations (vertebral, rib and costal cartilage) and developmental variations (reduced ossification of ribs) were noted at 5 mg/kg/day, which approximates 0.2-fold of the human exposure. Based on the lack of adverse maternal clinical observations or necropsy findings at any dosage level, a dose of 30 mg/kg/day (3.5-fold of human exposure) was considered the NOAEL for maternal toxicity. Based on the adverse effects on intrauterine survival and/or fetal morphology at all dosage levels, a NOAEL for embryo-fetal development could not be determined.

In a dedicated fertility and early embryonic development study (Study 00124841) conducted in treated male rats mated to treated female rats pralsetinib did not have an effect on male or female mating performance or ability to become pregnant. However, consistent with the findings of the embryo-fetal development toxicology study there was post-implantation loss at doses as low as 5 mg/kg (approximately 0.35-fold 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 2.9-fold the human exposure) 82% of female rats had totally resorbed litters, with 92% post-implantation loss (early resorptions). To further evaluate the potential for pralsetinib exposure in males to contribute to the early embryonic loss observed in the male and female combined fertility study, a second fertility and early embryonic development toxicology study was conducted in male rats administered 20 mg/kg pralsetinib and untreated female rats (Study 21-0310). When only the male rats were administered pralsetinib at 20 mg/kg, no statistically differences in fertility and intrauterine survival were observed.

In a 13-week repeat-dose toxicology study, male rats exhibited microscopic evidence of tubular degeneration/atrophy in the testis with secondary cellular debris and reduced sperm in the lumen of the epididymis, which correlated with lower mean testis and epididymis weights and gross observations of soft and small testis. Female rats

exhibited degeneration of the corpus luteum in the ovary. For both sexes, these effects were observed at pralsetinib doses ≥10 mg/kg/day, approximately 1-fold the human exposure based on AUC at the clinical dose of 400 mg.

No findings were noted in the reproductive organs in a 13-week repeated-dose toxicology study in sexually immature monkeys at dose levels up to 10 mg/kg/day (approximately 1-fold of the human exposure).

No information is available on the safety or efficacy of pralsetinib in lactating females.

Relevance to human use:

No pregnancies occurred during the clinical development program for pralsetinib.

The embryo-fetal development studies in rats showed severe pralsetinib-related embryo-fetal toxicity at all dosage levels. The observed renal malformations are attributed to on-target inhibition of RET signaling (Jain 2009; Drillon et al. 2018) and are the only RET-inhibition associated toxicities observed. Furthermore, embryo-toxicity and teratogenicity have been reported with other selective RET inhibitors (e.g. selpercatinib) (Lenvima SPC). Embryo-fetal toxicity is an important potential risk associated with pralsetinib (Section SVII.1.2).

Degeneration/atrophy in the testis in males and degeneration of the corpus luteum in the ovary of the females was noted at the highest dosage in the 13-weeks studies in rats, effects that are possibly attributed to vascular endothelial growth factor receptor (VEGFR) inhibition. Reproductive toxicity is a potential risk associated with pralsetinib.

Transaminase Elevations

Pralsetinib administration was associated with dose-dependent and reversible increases of the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GLDH) in rats at approximately 2-fold of clinical exposures at 400 mg QD dose. However, there were no correlating gross or histologic findings.

Relevance to human use:

Mainly Grade 1 or Grade 2, asymptomatic, and transient elevations in hepatic enzymes have been reported in patients exposed to pralsetinib within the clinical development program. Overall, these events were manageable and did not result in clinically significant consequences. Considering the high occurrence of events and with some observed with high severity, the impact on the benefit risk profile of pralsetinib is significant.

Transaminase Elevations is an important identified risk associated with pralsetinib (Section SVII.3.1.1.4).

Gastrointestinal System

Local tolerance of pralsetinib in the gastrointestinal tract of rats and Cynomolgus monkeys has been characterised in the GLP-compliant 28-day toxicology studies (Study WIL-124570 and WIL-124571). In rats at the severely toxic dose in 10% of animals (STD10; 30 mg/kg/day) there was evidence of soft tissue mineralization within the glandular stomach mucosa attributed to FGFR inhibition-mediated hyperphosphatemia. There was no evidence of test article related oropharyngeal/esophageal injury up to the non-tolerated dose (75 mg/kg/day). In monkeys at the HNSTD there was no evidence of gastrointestinal disturbances. At doses of 15 and 40 mg/kg/day deaths were seen secondary to bacteremia and septicemia resulting from gastrointestinal epithelial erosion and ulceration attributed to VEGFR inhibition. There was no evidence of test article related oropharyngeal/esophageal injury up to and including the non-tolerated doses.

Relevance to human use:

Gastrointestinal effects including constipation, diarrhea and nausea were observed with increased frequency in the clinical development program but did not impact the benefit risk profile of pralsetinib.

Genotoxicity

Three GLP-compliant assays were conducted for pralsetinib: 5-strain Ames bacterial reverse mutation assay with and without metabolic activation (Study WIL-124573); in vitro micronucleus assay in human lymphoblast cells with and without metabolic activation (Study 00124797); and in vivo micronucleus assay in Sprague Dawley rats administered oral doses of pralsetinib of up to 300 mg/kg/day for 2 consecutive days (Study 00124769). In addition, GLP compliant in vitro bacterial reverse mutation assays were conducted for one impurity of pralsetinib drug substance (Study WIL-124598).

Pralsetinib was not mutagenic in the bacterial reverse mutation assay. Furthermore, pralsetinib did not induce micronuclei in vitro in human lymphoblast cells, nor in vivo in the repeated-dose micronucleus study in rats.

Overall, pralsetinib is non-genotoxic. One specific impurity identified in pralsetinib drug substance was also tested and shown to be non-mutagenic in the bacterial reverse mutation assay.

Relevance to human use:

There was no evidence of genotoxicity in in vitro and in vivo non-clinical toxicology studies conducted within the non-clinical development program for pralsetinib. No genotoxic potential is foreseen in humans.

Carcinogenicity

Consistent with the current ICH S9 guidance on the nonclinical evaluation of anti-cancer pharmaceuticals (U.S. Department of Health and Human Services 2010), no carcinogenicity studies have been conducted with pralsetinib. Pralsetinib is not genotoxic, and there was no evidence of pralsetinib-related pre-neoplastic or neoplastic lesions in the completed toxicity studies. Carcinogenicity studies will be conducted as a post-market commitment to support indications outside of ICH S9.

Relevance to human use:

Carcinogenicity studies will be conducted to support indications outside of ICH S9.

General safety pharmacology

Cardiovascular System

Pralsetinib inhibited human ether-à-go-go-related gene (hERG) current by 17.4% ± 2.0% (mean ± standard deviation [SD]) at 1 µM (n=2), 33.7% ± 1.2% at 3 µM (n=2), 64.6% ± 1.8% at 10 µM (n=2), and 87.2% ± 1.5% at 30 µM (n=2). The half maximal inhibitory concentration (IC_{50}) for the inhibitory effect of pralsetinib on hERG potassium current was 5.18 µM (Hill coefficient = 0.92) (Study cpb-25-15-010a-0169), which is >40-fold greater than the steady-state unbound Cmax of pralsetinib in patients at 400 mg daily oral dose. This data suggesting a low potential for prolonging the QT interval (Redfern et al. 2003). These findings are consistent with the 28-day and 13-week studies in monkeys (Study WIL-124571 and 00124768) which showed no pralsetinib-related changes to ECG waveform morphology, heart rate, or PR, QRS, RR, QT, or QT corrected for heart rate by Bazett's formula interval duration at C_{max} (total or unbound) levels greater than that of the 400 mg QD in patients. These results support a low risk for cardiac arrhythmias with administration of pralsetinib at clinically relevant dose levels.

In radio-telemetry-implanted male Sprague Dawley rats (Study WIL-124581 and WIL-124606), a single oral dose of pralsetinib at dose levels ≥25 mg/kg (approximately 2-fold the human clinical Cmax at 400 mg based on the toxicokinetic data at 20 mg/kg from the 28-day rat toxicology study) resulted in higher systolic, diastolic, and mean blood pressure, with a concomitant decrease in heart rate. These effects were attributed to VEGFR inhibition. Lower body temperature was additionally observed in the 200 mg/kg group. There were no clinical observations associated with any of the dose levels. No changes in cardiovascular function or body temperature were observed following

administration of 10 mg/kg pralsetinib; therefore, the no observed effect level was 10 mg/kg.

Relevance to human use:

Based on the available data, the QT prolongation events seen in clinical studies with pralsetinib were mostly mild with no apparent clinical consequences.

In Study BLU-667-1101/ARROW (hereafter referred as Study BO42863), an analysis of continuous ECG (Holter) data from the expansion part (Part 2) along with an analysis of events in patients with potential QT-related events were performed to satisfy the requirement for a definitive QT assessment of pralsetinib.

Additionally, an exposure-effect regression analysis was performed. Following repeated 400 mg QD doses of pralsetinib in a subset of 34 patients, the observed geometric C_{max} was 2090 ng/mL. At this concentration, the estimated ΔQTcF was - 0.9 ms, with a 2 sided 90% CI upper bound of 4.0 ms. Further, at the maximum observed concentration of pralsetinib, 6270 ng/mL, the estimated ΔQTcF was 2.2 ms, with a 2 sided 90% CI upper bound of 13.5 ms, which is below the threshold of 20 msec.

Pralsetinib administration at 400 mg QD was observed to have no clinically relevant and statistically significant effects on the ECG or specifically was not associated with evidence for prolongation of the QTc interval.

Hypertension occurred with increased frequency in the clinical development program and represents an important identified risk (Section SVII.3.1.1.2).

Other toxicity-related information or data

Phototoxicity

Pralsetinib was not phototoxic in a GLP-compliant phototoxicity study in 3T3 fibroblasts when exposed to UVR exposure.

Relevance to human use:

Based on the nonclinical data, pralsetinib does not pose a phototoxic risk for humans.

Conclusion from the non-clinical safety evaluation: The non-clinical safety development of pralsetinib has contributed in identifying the following risks: Hematological risks, such as anemia, neutropenia and thrombocytopenia; non-hematological risks, such as hypertension; and potential risk related to embryo-fetal and reproductive toxicity, as well as physeal dysplasia and tooth development.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

The primary evidence supporting the efficacy and safety of pralsetinib was collected in the ongoing Study BLU-667-1101/ARROW (hereafter referred as Study BO42863) in patients with one of the following conditions:

- RET fusion-positive advanced NSCLC previously treated with platinum therapy
- Platinum naïve RET fusion-positive advanced NSCLC
- Medullary thyroid cancer (MTC) treated with cabozantinib and/or vandetanib
- Cabozantinib/vandetanib naïve MTC
- RET fusion-positive solid tumors previously treated with standard of care and not eligible for other groups
- RET altered tumors previously treated with selective RET TKI
- RET mutated solid tumors previously treated with standard of care and not eligible for other groups

The safety population treated with 400mg QD pralsetinib consists of patients exposed to 400 mg QD pralsetinib with RET fusion-positive advanced NCSLC [N=281] and overall safety patient population([N=540) (CCOD: 4 March 2022). Refer to Table 2 for the duration of exposure and, Table 3, Table 5, and Table 6 for demographic characteristics of exposed patients within the safety population treated with 400mg QD pralsetinib. Table 4 summarizes the overall exposure by dose in the safety population treated with 400 mg QD pralsetinib as well as the overall safety-evaluable population (N=590).

Exposure information for all dose groups can be found in Annex 7A.

Table 2 Duration of Exposure (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Duration of Pralsetinib Exposure for Risk Management Plan for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

	RET Fusion-positive NSCLC Patients (N=281)		All Patients (N=540)	
Duration of exposure	Patients	Person time*	Patients	Person time*
<6 Months	80 (28.5%)	232.3	155 (28.7%)	418.7
>= 6 months to < 12 months	45 (16.0%)	396.3	75 (13.9%)	655.1
>= 1 year to 2 years	79 (28.1%)	1411.9	127 (23.5%)	2280.5
>= 2 years to 3 years	55 (19.6%)	1613.1	124 (23.0%)	3594.9
>= 3 years	22 (7.8%)	880.0	59 (10.9%)	2402.3
Total	281 (100%)	4533.6	540 (100%)	9351.6

* Person-time is the sum of exposure across all patients in months.
NE - Not Evaluable.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp01_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp01_lung_400_SE_04Mar2022_42863.out
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Table 3 Exposure by Age Group and Gender (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Extent of Pralsetinib Exposure by Age Group and Gender for Risk Management Plan for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

	RET Fusion-positive NSCLC Patients (N=281)			All Patients (N=540)		
Age Group	Male	Female	Total	Male	Female	Total
<65 years						
Patients	74 (57.4%)	102 (67.1%)	176 (62.6%)	185 (66.1%)	188 (72.3%)	373 (69.1%)
Person time*	1294.0	1804.0	3098.0	3762.3	3322.2	7084.5
>=65 years						
Patients	55 (42.6%)	50 (32.9%)	105 (37.4%)	95 (33.9%)	72 (27.7%)	167 (30.9%)
Person time*	657.6	778.0	1435.6	1235.7	1031.5	2267.1
Total						
Patients	129 (100%)	152 (100%)	281 (100%)	280 (100%)	260 (100%)	540 (100%)
Person time*	1951.6	2582.0	4533.6	4998.0	4353.6	9351.6

* Person-time is the sum of exposure across all patients in months.
NE - Not Evaluable.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp03_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp03_lung_400_SE_04Mar2022_42863.out
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Table 4 Exposure by Dose – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Extent of Pralsetinib Exposure for Risk Management Plan for Lung Indication, Safety Evaluable Patients
Protocol: BO42863

	RET Fusion-positive NSCLC Patients (N=299)		All Patients (N=590)	
Dose of exposure	Patients	Person time*	Patients	Person time*
30 mg QD	0	NE	2 (0.3%)	2.2
60 mg QD	1 (0.3%)	55.0	6 (1.0%)	172.9
100 mg QD	3 (1.0%)	30.1	5 (0.8%)	87.9
100/100 mg BID	2 (0.7%)	20.2	5 (0.8%)	94.1
200 mg QD	6 (2.0%)	96.0	13 (2.2%)	262.1
200/100 mg BID	0	NE	4 (0.7%)	114.9
300 mg QD	4 (1.3%)	63.2	11 (1.9%)	286.8
400 mg QD	281 (94.0%)	4533.6	540 (91.5%)	9351.6
600 mg QD	2 (0.7%)	23.1	4 (0.7%)	75.7
Total	299 (100%)	4821.3	590 (100%)	10448.1

* Person-time is the sum of exposure across all patients in months.
NE - Not Evaluable.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp02_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp02_lung_SE_04Mar2022_42863.out
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Table 5 Exposure by Ethnic Origin (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Extent of Pralsetinib Exposure by Ethnic Origin for Risk Management Plan for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

	RET Fusion-positive NSCLC Patients (N=281)		All Patients (N=540)	
Ethnicity	Patients	Person time*	Patients	Person time*
Hispanic or Latino	10 (3.6%)	191.1	22 (4.1%)	518.5
Not Hispanic or Latino	246 (87.5%)	3960.4	474 (87.8%)	8231.7
Not Stated	8 (2.8%)	56.6	24 (4.4%)	227.8
Unknown	17 (6.0%)	325.4	20 (3.7%)	373.7
Total	281 (100%)	4533.6	540 (100%)	9351.6

* Person-time is the sum of exposure across all patients in months.
NE - Not Evaluable.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp04_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp04_lung_400_SE_04Mar2022_42863.out
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Table 6 Exposure by Racial Origin (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Extent of Pralsetinib Exposure by Race for Risk Management Plan for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

	RET Fusion-positive NSCLC Patients (N=281)		All Patients (N=540)	
Race	Patients	Person time*	Patients	Person time*
Asian	128 (45.6%)	2020.3	205 (38.0%)	3359.0
Black or African American	1 (0.4%)	13.9	5 (0.9%)	114.0
Native Hawaiian or other Pacific Islander	2 (0.7%)	26.5	2 (0.4%)	26.5
White	130 (46.3%)	2138.4	293 (54.3%)	5313.6
Other	2 (0.7%)	15.4	3 (0.6%)	16.9
Unknown	18 (6.4%)	319.0	32 (5.9%)	521.6
Total	281 (100%)	4533.6	540 (100%)	9351.6

* Person-time is the sum of exposure across all patients in months.
NE - Not Evaluable.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp05_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp05_lung_400_SE_04Mar2022_42863.out
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PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 7 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Included as missing information? (Yes/No)	Rationale (if not included as missing information)
Hepatically impaired patients (moderate or severe impairment) Defined by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) if no hepatic metastases are present or > 5 × ULN if hepatic metastases are present; and total bilirubin > 1.5 × ULN or > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease	This exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy and safety of pralsetinib.	Yes (prior to version 1.8) No (from version 1.8 on)	A dedicated study (GP43163) was conducted to assess the PK and safety of pralsetinib in subjects with moderate and severe hepatic impairment. The assessment showed that no specific warnings or exclusions are required in patients with hepatic impairment. No further analysis is deemed necessary.
Severe infections prior to study start, or ongoing infections		No	Given the life-threatening nature of the proposed indications, treatment with pralsetinib should be an option for such patients. No specific warning or exclusion is included in the SmPC, since it is considered part of routine oncology practice to assess a patient's fitness for treatment.
CNS metastases or a primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids		No	Given the life-threatening nature of the proposed indications, treatment with pralsetinib should be an option for such patients. No specific warning or exclusion is included in the SmPC, since it is considered part of routine oncology practice to assess a patient's fitness for treatment.

Malignancies other than lung cancer i.e., hx of other primary malignancy		No	Given the life-threatening nature of the proposed indications, treatment with pralsetinib should be an option for such patients. No specific warning or exclusion is included in the SmPC, since it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Renally impaired patients (severe impairment) Defined by the estimated Cockroft-Gault formula or measured creatinine clearance < 30 mL/min	This exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy and safety of pralsetinib.	No	Pralsetinib fecal excretion was the predominant route of elimination of drug-related material (approximately 72.5%) and excretion in urine was a minor route of elimination (approximately 6.1%). In the population pharmacokinetics analysis, pralsetinib apparent oral clearance was similar among 179 subjects with mild renal impairment, 19 subjects with moderate renal impairment, and 156 subjects with normal renal function. Additionally, no trends were identified for apparent oral clearance by measures of renal function (serum creatinine, creatinine clearance, and estimated glomerular filtration rate). The adverse events reported in subjects with mild or moderate renal impairment were manageable, with a minimal impact over the quality of life. No dose adjustment is recommended in patients with mild or moderate renal impairment. Considering no effects of potential concerns were observed in patients with mild to moderate renal impairment, and renal excretion is only a minor route of elimination, no significant impact is foreseen in severe renally impaired patients and no further analysis is deemed necessary.

Patients who have a QTcF > 470 msec; patients with a history of prolonged QT syndrome or Torsades de pointes; patients with a familial history of prolonged QT syndrome	Pralsetinib inhibits hERG channel activity in vitro with an average IC50 of 5.18 µM, suggesting only low potential for prolonging the QT interval. As such, these exclusion criteria were established as a precautionary measure to minimise any confounding effects on study findings of patients that had pre-existing prolongation of QT interval on the evaluation of safety of pralsetinib.	No	A QT effect has been associated with MKIs such as vandetanib, cabozantinib and lenvatinib; however, the in vivo non-clinical data and clinical data collected with pralsetinib indicate no clinically meaningful risk of QT prolongation. An analysis of continuous ECG (Holter) performed in Study BO42863 to provide a definitive QT assessment of pralsetinib indicated that pralsetinib had no clinically relevant and/or statistically significant effect on QT prolongation.
Patients with clinically symptomatic ILD or interstitial pneumonitis (including radiation pneumonitis)	Pneumonitis has been commonly observed with the use of many TKIs. As such, this exclusion criterion was established as a precautionary safety measure.	No	Pneumonitis is considered an important identified risk associated with the use of pralsetinib. The risk factors and special populations at risk for such events are presented in detail in Section SVII.3.1.1.1)
Female patients who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 30 days after the last dose of study drug; Female patients who are pregnant, as documented by a serum beta human chorionic gonadotropin pregnancy test consistent with pregnancy, obtained within 7 days prior to the first dose of study drug.	Pralsetinib was teratogenic and embryotoxic in rats (refer to Section 2. Therefore, the above exclusion criteria represented a standard measure to avoid any adverse effects on pregnancy.	No	Pregnant or lactating women were excluded from the clinical development program, and women of child-bearing potential were required to use appropriate methods of contraception during the treatment course with pralsetinib and for 30 days after the last administered dose. As such, there are no data on the use of pralsetinib in this special patient population. However, non-clinical studies showed that pralsetinib is teratogenic and embryotoxic. As such, embryo-fetal toxicity is considered as an important potential risk (Section SVII.3.1.2.1)

Breastfeeding women	Exclusion of breastfeeding women represents a standard ethical measure. No non-clinical studies were conducted to evaluate whether pralsetinib or its metabolites are excreted in the milk of a lactating female. As such, the effects of pralsetinib on this population could not be anticipated, and a risk to the breastfed child could not be excluded (refer to Part II Module SI)	No	There are no data regarding the secretion of pralsetinib or its metabolites in human milk nor on their effects on the breastfed infant or on milk production. Because of the potential for adverse reactions in breastfed infants from pralsetinib, breast-feeding should be discontinued during treatment with pralsetinib and for two weeks after the last administered dose. As such, it is expected that pralsetinib will not be used by breastfeeding women, and no data on use in this population are expected to be collected from the post-marketing setting.
Concomitant use of strong CYP3A4 inhibitors, strong CYP3A4 inducers, and/or combined P-gp and strong CYP3A4 inhibitors		Yes (prior to version 1.6) No (from version 1.6 on)	In vitro metabolism studies indicate that pralsetinib oxidation is primarily mediated by CYP3A4. Further, in vitro drug transporter studies suggest that pralsetinib is a P-gp substrate and, therefore there is a potential that co-administration of a P-gp inhibitor could increase plasma concentrations of pralsetinib. A previously conducted DDI study (BLU-667-0104) assessed the impact of a dual P-gp and strong CYP3A inhibitor on the PK of pralsetinib and showed that there was a 250% increase in pralsetinib exposure. To assess the individual contributions of P-gp and CYP3A inhibition to this increased exposure observed when pralsetinib is administered with a combined strong CYP3A4 and P-gp inhibitior, a clinical DDI study (GP43162) with a selective P-gp inhibitor (cyclosporine) was conducted. The results of this DDI study showed that systemic exposure of pralsetinib increased

			by 81% when pralsetinib was co-administered with cyclosporine compared to when pralsetinib was administered alone. Potential drug-drug interactions of pralsetinib co-administered with moderate CYP3A inhibitors, dual P-gp and moderate CYP3A inhibitors, and moderate CYP3A inducers were assessed using a Physiologically-based Pharmacokinetic Model (PBPK). Dose adjustment is recommended in patients who cannot avoid concomitant use of P-gp inhibitors, strong/moderate CYP3A4 inhibitors, strong/moderate CYP3A4 inducers, or combined P-gp and strong/moderate CYP3A4 inhibitors. This was added to the SmPC following completion of the PASS and the PBPK model. No further analysis is deemed necessary.
Patient has clinically significant, uncontrolled, cardiovascular disease including congestive heart failure Grade III or IV according to the New York Heart Association NYHA) classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmias that may cause QT prolongation (eg, Type II second degree heart block or third degree heart block).	Impaired end-organ function and associated clinical complications may impair the patient's ability to receive an adequate course of treatment.	No	Hypertension is considered an important identified risk associated with the use of pralsetinib. The risk factors and special populations at risk for such events are presented in detail in Section SVII.3.1.1.2. Pralsetinib administration at 400 mg QD was observed to have no clinically relevant and statistically significant effects on the ECG or specifically was not associated with evidence for prolongation of the QTc interval.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CYP3A4 = cytochrome P450 3A4; ECG = electrocardiogram; ILD = interstitial lung disease; PASS = post authorization safety studies; PBPK = Physiologically-based Pharmacokinetic Model; QTc = corrected QT interval QTcF = QTc by Fridericia's formula; SmPC = summary of product characteristics; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Adverse reactions with a minimal frequency of 1 in 157 patients may have been detected within the clinical development program (i.e. 'very common' or 'common'). However, the clinical development program of pralsetinib is unlikely to detect certain types of adverse reactions such as rare or uncommon adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 8 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in clinical development program
Breastfeeding women	Not included in clinical development program
Pediatric patients	Not included in clinical development program
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	9 subjects with moderate hepatic impairment, 6 subjects with severe hepatic impairment were included in study GP43163 Not included in clinical development program
Population with relevant different ethnic origin	Refer to tables Table 5 and Table 6. for exposures based on race/ethnic origin
Elderly patients	Refer to Table 3 for exposures in patients ≥65 years of age

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

Since the IBD (4 September 2020) until 3 March 2023, an estimated cumulative total of 2067 patients have received pralsetinib from marketing experience. Post-authorization

exposure based on region as of 3 March 2023 was as follows:

United States: The estimated number of patients exposed in the United States was 490 patients (indications: 113 thyroid and 377 NSCLC).

European Economic Area (EEA) and Rest of the World (RoW) Regions: The estimated numbers of patients exposed in EEA were 108 (NSCLC only) and in RoW were 1470 (NSCLC only) patients.

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Considering the mechanism of action of pralsetinib, the potential for misuse for illegal purposes is negligible and does not constitute a safety concern.

POTENTIAL FOR MEDICATION ERRORS

Pralsetinib will be available as capsules in one strength (100 mg) only. No dose adjustment is required for special patient populations; thus, the potential for medication error is minor and does not constitute a safety concern.

POTENTIAL FOR OFF-LABEL USE

Pralsetinib is approved in the EU for the use in adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor. Currently pralsetinib is also in development for use in other tumour types and the paediatric population. This may lead to off-label use in the EU territory.

The SmPC clearly states the indication. Further, routine post-market surveillance will provide data on potential patterns for off-label use.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

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

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

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

- Myalgia
- Rash
- Fatigue

- Gastrointestinal toxicity

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

Important Identified Risk of Pneumonitis

Risk-benefit impact:

Events of pneumonitis (including interstitial lung disease, referred hereafter as ILD) occurred in the clinical development program for pralsetinib, in the overall safety population (400 mg QD) (12.2%). Nineteen patients (3.5%) experienced severe (Grade ≥3) pneumonitis events. Pneumonitis events were reported as serious in 31 patients (5.7%).

Pneumonitis may significantly impact the patient's quality of life, as it may lead to hospitalization and may even lead to death. It also may lead to permanent discontinuation of the therapy. Considering the severity and seriousness of these events, pneumonitis represents an important risk of pralsetinib. The impact on the benefit-risk balance of the product, however, can be considered low to moderate, given the severity of the underlying disease. Although pneumonitis was commonly observed in pralsetinib treated patients, few patients had severe and/or serious events. Appropriate labelling as a risk minimization activity increases the likelihood of an early diagnosis and early interruption of pralsetinib followed by appropriate treatment, further reducing the impact of pneumonitis on the benefit-risk balance of the product.

Important Identified Risk of Hypertension

Risk-benefit impact:

The non-clinical studies showed that pralsetinib doses ≥25 mg/kg led to an increased blood pressure in rats, attributed to VEGFR inhibition (i.e. potentially resulting from pralsetinib off-target pharmacologic effects on VEGFR). These non-clinical findings were confirmed in the clinical setting where 35.0% of patients in the overall safety population treated with 400 mg QD pralsetinib had an event of hypertension (including blood pressure increased). A total of 95 patients experienced severe (≥Grade 3) hypertension events (17.6%) and seven patients experienced serious hypertension events (1.3%).

Hypertension can potentially lead to life-threatening complications like stroke or end organ damage. Considering the off-target profile and high incidence of Grade 3 hypertension events in pralsetinib treated patients, this risk is considered important for pralsetinib. The impact on the benefit-risk balance of the product is considered low due to the following reasons: of those patients who experienced hypertension who received treatment with pralsetinib at 400 mg QD, 38.1% had a history of hypertension at baseline, and hypertension was routinely managed by standard of care anti-hypertensive treatments in the clinical development program for pralsetinib.

Important Identified Risk of Haemorrhage

Risk-benefit impact:

In non-clinical setting, haematological abnormalities (reduced bone marrow cellularity, reduced haemoglobin, reduced reticulocytes), and lymphoid effects (reduced lymphoid cellularity and decreased lymphocyte counts) were observed, particularly in the first 2 weeks of treatment. These findings are consistent with JAK2 inhibition (Part II Module SII). Decrease in blood cell counts was observed in patients treated with pralsetinib, especially anaemia, neutropenia, and thrombocytopenia. These effects tend to occur within the first 2 weeks of treatment and stabilise over time, rarely becoming worse than Grade 2 in severity. Thrombocytopenia can pose patients at risk for severe bleeding.

Haemorrhagic events occurred in 111 patients (20.6%). Severe (i.e. ≥Grade 3) and serious haemorrhage occurred infrequently (4.1% and 3.9% of patients treated with 400 mg QD pralsetinib respectively). Severe haemorrhage may lead to haemorrhagic shock and even death, warranting a statement in the warnings and precautions section of the labeling document. Haemorrhage is considered an important identified risk for pralsetinib.

The impact on the benefit-risk balance of pralsetinib is considered low, given the low incidence of severe bleeding events under pralsetinib treatment and the severity of the underlying disease. The label includes dose modification advice, which will further reduce the impact of severe bleeding on the benefit-risk balance of the product.Important Identified Risk of Transaminase Elevations

Risk-benefit impact:

Events falling under transaminase elevations basket occurred very commonly (53.1% of patients in the overall safety population treated with 400 mg QD pralsetinib). Given this high occurrence of events in general, and the potential for life threatening events, transaminase elevations is considered an important risk for pralsetinib.

The impact on the benefit-risk balance of pralsetinib is considered low as the events were mainly Grade 1 or Grade 2, asymptomatic, and transient. Overall, these events were manageable and did not result in clinically significant consequences. Monitoring and management of transaminase elevations should reduce the potential for the patient of developing hepatotoxicity, and also increase the likelihood of an early diagnosis, and prompt treatment, further reducing the impact of this risk on the benefit-risk balance of the product.

Important Potential Risk of Embryo-fetal toxicity

Risk-benefit impact:

Non-clinical data showed that pralsetinib has embryotoxic effects and similar findings were observed with other selective RET inhibitors (e.g. selpercatinib) (Drilon et al. 2018). Based on the available evidence, a risk to the pregnant woman and the fetus cannot be excluded and represents an important potential risk of pralsetinib.

The impact on the benefit-risk balance of pralsetinib is considered low, as per labeling, pralsetinib treatment is not recommended during pregnancy. Further, women of childbearing potential, as well as male patients with partners of childbearing potential are advised to use contraception.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Safety in patients with hepatic impairment (moderate or severe), previously classified as missing information is no longer presented in this EU RMP. Following the completion of Study GP43163, there are no further associated pharmacovigilance activities pertaining to the safety in patients with hepatic impairment.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

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

SVII.3.1.1 Information on Important Identified Risks

SVII.3.1.1.1 Pneumonitis

MedDRA terms:

Pneumonitis is defined by MedDRA PTs pneumonitis and interstitial lung disease

Potential mechanisms:

The exact mechanism for drug-induced pneumonitis is not known.

Evidence source(s) and strength of evidence:

Pneumonitis is considered a class effect of TKIs (Abdel-Rahman and Fouad 2013; Nishino et al. 2017).

Events of pneumonitis occurred commonly in the clinical development program for pralsetinib, in the overall safety population treated with 400 mg QD pralsetinib (12.2%) and across indications.

The observed rates for pralsetinib are overall consistent with what would be expected with a TKI treatment for this population of patients with advanced cancer (Burotto et al. 2015; Inoue et al. 2003).

Characterization of the risk:

Frequency, severity and nature of risk (including reversibility and long-term outcomes)

Overall safety population (400 mg QD group)

Overall, 66 of 540 (12.2%) patients reported 77 events of pneumonitis (includes PTs Pneumonitis and Interstitial lung disease). In 31/540 (5.7%) patients a pneumonitis event was reported as serious. The majority of patients with a pneumonitis event experienced mild (Grade 1 or 2) pneumonitis. For 19/540 (3.5%) patients, the pneumonitis event was of Grade ≥3 severity, 15/540 patients (2.8%) experienced Grade 3. Three patients (0.6%) and 1 patient (0.2%) experienced at least one Grade 4 and Grade 5 pneumonitis events, respectively. The majority of patients (45/66, 68.2%) had at least one pneumonitis event that is resolved, and 17/66 (25.8%) patients had at least one pneumonitis event that remained unresolved at time of data cut off (Table 9).

Dose interruptions occurred in 44 (8.1%) and 4 (0.7%) patients, respectively due to pneumonitis (PT) and ILD (PT) events. Thirty (5.6%) and one (0.2%) patients had dose reductions due to events of pneumonitis (PT) and ILD (PT), respectively. Eleven patients (2.0%) had pneumonitis (PT) events and one patient (0.2%) had an ILD (PT) event that led to permanent treatment discontinuation (Annex 7b).

The fatal event of pneumonitis occurred in a 57-year-old female patient with RET fusion-positive NSCLC approximately 1 month after initiating treatment with pralsetinib at the 400 mg QD dose. The patient was included in the overall safety population analysis but excluded from subgroup analyses due to prior therapy with RET-inhibitor. Thus, this fatal case is not reflected in RET fusion-positive NSCLC patients section. The patient's relevant medical history included hepatic metastasis and prior therapy with pemetrexed, carboplatin and Loxo-292. The patient was managed with broad spectrum antibiotics and high dose steroids. However, she had complications during hospitalisation with acute myocardial infarction, sepsis and extensive bilateral haemorrhagic cerebral infarcts and passed away.

RET fusion-positive advanced NSCLC patients (400 mg QD group)

Of the RET fusion-positive advanced NSCLC patients treated with pralsetinib 400 mg QD, 40/281 (14.2%) patients experienced 47 events of pneumonitis. In 19/281 (6.8%) patients, the event was reported as serious. Most cases of pneumonitis were Grade 1 or 2 in severity; 7 patients (2.5%) experienced at least one Grade 3 event and 2 patients experienced at least one Grade 4 events (0.7%). No Grade 5 pneumonitis/ILD events were reported. The majority of patients (28/40, 70.0%) had at least one pneumonitis event that resolved, and 10/40 patients (25.0%) had at least one pneumonitis event that remained unresolved at time of data cut off (Table 9).

Dose interruptions occurred in 29 (10.3%) and 3 (1.1%) patients, respectively due to pneumonitis (PT) and ILD (PT) events. Twenty (7.1%) patients and a single patient (0.4%) had dose reductions due to events of pneumonitis (PT) and ILD (PT), respectively. Eight patients (2.8%) had pneumonitis (PT) events and 1 patient (0.4%) had an ILD (PT) event that led to permanent treatment discontinuation (Annex 7b).

Impact on quality of life

Pneumonitis may have a significant impact on patients as it may require additional hospitalization or may lead to treatment interruptions or complete discontinuation of therapy.

Risk factors and risk groups:

Risk factors have not yet been well established.

An analysis of the impact of four baseline demographic variables, namely age, gender, race and region, on the incidence of pneumonitis was performed. The results suggest that there does not appear to be a meaningful difference in the incidence of pneumonitis by any of the criteria assessed.

The majority of patients within the safety population had confounding factors for development of pneumonitis, such as prior history of pneumonitis, prior therapies (before initiation of pralsetinib) that are known to cause pneumonitis (e.g. pemetrexed, pembrolizumab, vandetanib, docetaxel, osimertinib), or external beam radiation to the chest/back/spine area.

Preventability:

No preventive measures were yet established.

Early diagnosis and proper management could decrease mortality and morbidity. The diagnosis of pneumonitis and determination of causal relationship to the drug is often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors such as lung infection and radiation effect due to non-specific signs and symptoms as well as similar radiological appearance.

Patients who present with acute or worsening of respiratory symptoms indicative of pneumonitis (e.g. dyspnoea, cough, and fever) should be investigated to exclude other potential causes. Patients should be advised to contact their healthcare provider immediately to report new or worsening respiratory symptoms.

If Grade 1 or Grade 2 pralsetinib-related pneumonitis is suspected, the dose of pralsetinib should be interrupted and then resumed at a reduced dose upon resolution. Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg QD. Pralsetinib should be permanently discontinued in case of recurring events of pneumonitis.

Pralsetinib should be permanently discontinued in case of Grade 3 or Grade 4 events of pneumonitis.

Impact on the benefit-risk balance of the product:

Although the incidence of pneumonitis seen in clinical trials with pralsetinib in the overall safety population (as well as across indications) was higher in comparison with the literature, pneumonitis is a known adverse effect seen in lung cancer patients and it has been observed in association with EGFR- and ALK-TKIs. Considering the low frequency of serious events and the presence of multiple confounding factors for pneumonitis in patients experiencing this event in the clinical program for pralsetinib, the impact on the benefit-risk of pralsetinib is acceptable.

Public health impact:

Not yet established.

Table 9 Pneumonitis: Frequency, Severity, Seriousness and Outcomes (400 mg Dose) – RET Fusion-Positive Advanced NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Selected Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

Selected Adverse Events: Pneumonitis

	RET Fusion-positive NSCLC Patients (N=281)	All Patients (N=540)
Number of patients with at least one AE	40 (14.2%)	66 (12.2%)
95% CI for % of patients with at least one AE	(10.37%, 18.88%)	(9.58%, 15.29%)
Number of patients with at least one grade 3-5 AE	9 (3.2%)	19 (3.5%)
95% CI for % of patients with at least one grade 3-5 AE	(1.47%, 5.99%)	(2.13%, 5.44%)
Number of patients with at least one serious AE	19 (6.8%)	31 (5.7%)
Total number of AEs	47	77
Number of patients with at least one AE by worst grade		
Grade 1	9 (3.2%)	17 (3.1%)
Grade 2	22 (7.8%)	30 (5.6%)
Grade 3	7 (2.5%)	15 (2.8%)
Grade 4	2 (0.7%)	3 (0.6%)
Grade 5	0	1 (0.2%)
Number of patients with at least one AE by outcome		
Fatal outcome	0	1 (1.5%)
Unresolved	10 (25.0%)	17 (25.8%)
Recovering/Resolving	0	0
Recovered/Resolved	28 (70.0%)	45 (68.2%)
Resolved with sequelae	2 (5.0%)	3 (4.5%)
Unknown outcome	1 (2.5%)	2 (3.0%)
Number of patients with at least one grade 3-5 AE by outcome		
Fatal outcome	0	1 (5.3%)
Unresolved	1 (11.1%)	3 (15.8%)
Recovering/Resolving	0	0
Recovered/Resolved	6 (66.7%)	13 (68.4%)
Resolved with sequelae	2 (22.2%)	2 (10.5%)
Unknown outcome	0	0

AE = adverse event; CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI CTCAE.
Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Percentages are based on the number of patients in the analysis population as given in the column headings,
except for the percentages for "number of patients with at least one AE by outcome" and "number of patients with at least one grade 3-5 AE by outcome"
where the percentages are based on the number of patients with at least one AE and number of patients with at least one grade 3-5 AE respectively.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022

Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp06_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp06_lung_400_SE_04Mar2022_42863.out
01JUL2022 13:26

SVII.3.1.1.2 Hypertension

MedDRA terms:

Hypertension is defined by MedDRA PTs hypertension and blood pressure increased.

Potential mechanisms:

Hypertension is attributed to an off-target pharmacologic effect of pralsetinib on VEGFR.

Evidence source(s) and strength of evidence:

The non-clinical studies showed that pralsetinib doses ⩾ 25 mg/kg resulted in increased blood pressure in rats (refer to Part II Module SI). These findings were confirmed in clinical setting, where 35.0% of patients within the overall 400 mg QD pralsetinib safety population had events of hypertension (grouped events including events of hypertension and blood pressure increased); hypertension was commonly reported across indications.

Inhibition of the kinase insert domain receptor and VEGFR has previously been associated clinically with hypertension, and the effects were seen with many TKIs, including cabozantinib, lenvatinib, and selpercatinib (Drilon et al. 2018; Lenvima SPC; Nishino et al. 2017).

Characterization of the risk:

Frequency, severity and nature of risk (including reversibility and long-term outcomes)

Overall safety population (400 mg QD group)

In clinical setting, 189/540 (35.0%) patients experienced a total of 274 hypertension events. Of all patients, 95/540 (17.6%) had Grade ≥3 AEs. No Grade 4 or Grade 5 hypertension events were reported. The majority of patients (117/189, 61.9%) had at least one hypertension event that is resolved, and 89/189 (47.1%) patients had at least one hypertension event that remained unresolved at time of data cut-off (Table 10).

Forty-three patients (8.0%) had dose interruptions and 26 patients (4.8%) had dose reductions due to hypertension. One patient (0.2%) permanently discontinued treatment due to hypertension (Annex 7b).

RET fusion-positive advanced NSCLC patients (400 mg QD group)

Hypertension (155 AEs) was reported in 104/281 (37.0%) of RET fusion-positive NSCLC patients. Four patients (1.4%) experienced hypertension, which was reported as a serious event. A total of 54/281 (19.2%) patients had at least one hypertension event with a worst intensity of Grade 1 and 2; 50/281 (17.8%) patients experienced Grade 3 hypertension. No Grade 4 or Grade 5 events of hypertension were reported. A total of 64/104 (61.5%) patients had at least one hypertension event that resolved, and 49/104 (47.1%) patients had at least one hypertension event that remained unresolved at time of data cut-off (Table 10).

Twenty-six patients (9.3%) had dose interruptions and 14 patients (5.0%) had dose reductions due to hypertension. One patient (0.4%) permanently discontinued treatment due to the event of hypertension (Annex 7b).

Impact on quality of life

In general, hypertension can lead to serious, potentially life-threatening complications like stroke or end organ damage. However, hypertension seen in the pralsetinib clinical programme was routinely managed by standard of care anti-hypertensive treatments and did not lead to any significant clinical outcomes.

Risk factors and risk groups:

No pralsetinib-specific risk factors were established.

Preventability:

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.

If a Grade 3 event of hypertension persists despite optimal anti-hypertensive therapy, then treatment with pralsetinib should be interrupted and resumed at a reduced dose when hypertension is controlled. Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg QD.

Pralsetinib should be permanently discontinued in case of a Grade 4 event.

Impact on the benefit-risk balance of the product:

Hypertension can potentially lead to life-threatening complications like stroke or end organ damage. However, hypertension seen in pralsetinib clinical program was usually routinely managed by standard anti-hypertensive treatment. Hypertension was not associated to date with any clinically significant outcome. The preventive measures in place in case of hypertension are expected to minimize any potential impact on patients.

Public health impact:

Not yet established.

Table 10 Hypertension: Frequency, Severity, Seriousness and Outcomes (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Selected Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

Selected Adverse Events: Hypertension

	RET Fusion-positive NSCLC Patients (N=281)	All Patients (N=540)
Number of patients with at least one AE	104 (37.0%)	189 (35.0%)
95% CI for % of patients with at least one AE	(31.35%, 42.95%)	(30.98%, 39.19%)
Number of patients with at least one grade 3-5 AE	50 (17.8%)	95 (17.6%)
95% CI for % of patients with at least one grade 3-5 AE	(13.50%, 22.78%)	(14.47%, 21.07%)
Number of patients with at least one serious AE	4 (1.4%)	7 (1.3%)
Total number of AEs	155	274
Number of patients with at least one AE by worst grade		
Grade 1	10 (3.6%)	23 (4.3%)
Grade 2	44 (15.7%)	71 (13.1%)
Grade 3	50 (17.8%)	95 (17.6%)
Grade 4	0	0
Grade 5	0	0
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	49 (47.1%)	89 (47.1%)
Recovering/Resolving	0	0
Recovered/Resolved	64 (61.5%)	117 (61.9%)
Resolved with sequelae	4 (3.8%)	8 (4.2%)
Unknown outcome	2 (1.9%)	2 (1.1%)
Number of patients with at least one grade 3-5 AE by outcome		
Fatal outcome	0	0
Unresolved	22 (44.0%)	40 (42.1%)
Recovering/Resolving	0	0
Recovered/Resolved	28 (56.0%)	57 (60.0%)
Resolved with sequelae	2 (4.0%)	4 (4.2%)
Unknown outcome	1 (2.0%)	1 (1.1%)

AE = adverse event; CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI CTCAE.
Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Percentages are based on the number of patients in the analysis population as given in the column headings,
except for the percentages for "number of patients with at least one AE by outcome" and "number of patients with at least one grade 3-5 AE by outcome"
where the percentages are based on the number of patients with at least one AE and number of patients with at least one grade 3-5 AE respectively.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022
Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp06_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp06_lung_400_SE_04Mar2022_42863.out
01JUL2022 13:26

SVII.3.1.1.3 Haemorrhage

Haemorrhage is defined as Standardized MedDRA Query (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.

Potential mechanisms:

The exact mechanism is unknown, but as pralsetinib also has effects on the vascular endothelial growth factor receptor (VEGFR), this inhibition may lead to increased vulnerability of epithelial and mucosal tissues; hence this risk might be a class effect. Further, thrombocytopenia has frequently been experienced in patients receiving pralsetinib. Thrombocytopenia may dispose for a haemorrhagic diathesis.

Evidence source(s) and strength of evidence:

In clinical trial data from study BO42863 thrombocytopenia has been observed, and also severe bleeding events (although with very low frequency). A clear association has not yet been established. In a meta-analysis of small-molecule VEGFR-TKIs, an increase in the risk of developing severe and fatal haemorrhagic events in solid cancer patients was observed (Je et al. 2009). Further, gastrointestinal epithelial erosion and ulceration has been observed in animal studies and described as secondary to VEGFR inhibition.

Characterization of the risk:

Frequency, severity and nature of risk (including reversibility and long-term outcomes)

Overall safety population (400 mg QD group)

In the clinical setting, 111/540 patients (20.6%) experienced at least one haemorrhagic event. Twenty-two (4.1%) patients experienced severe (Grade ≥3) hemorrhagic events; 20 patients (3.7%) had a Grade 3 event, and one patient each had a Grade 4 (0.2%) and Grade 5 (0.2%) hemorrhagic event. A total of 19 of the 22 patients (86.4%) who experienced severe (Grade ≥3) hemorrhagic events, had at least one severe hemorrhagic event which resolved and 3/22 patients (13.6%) had a severe hemorrhagic event that remained unresolved at time of data cut-off (Table 11).

The severe hemorrhagic events leading to dose interruption included: hematoma (4 patients; 0.7%), gastrointestinal hemorrhage (2 patients; 0.4%), hematochezia (2 patients; 0.4%), epistaxis (2 patients; 0.4%), and a single patient (0.2%) each with cerebellar hemorrhage, cerebral hematoma, hematemesis, hematuria, intracranial hemorrhage, hemorrhagic anemia, muscle hemorrhage, and hemothorax. Events of haematuria and epistaxis in 1 patient (0.2%) each led to dose reduction. Treatment withdrawal occurred due to intracranial hemorrhage in 1 patient (0.2%) (Annex 7b).

RET fusion-positive advanced NSCLC patients (400 mg QD group)

Of the RET fusion-positive advanced NSCLC patients treated with pralsetinib 400 mg QD, 57/281 patients (20.3%) experienced at least one haemorrhagic event. For 12 of these patients (4.3%) at least one serious haemorrhagic event was reported. The majority of events were of Grade 1 severity (40 [14.2%] patients). Six (2.1%) patients had a Grade 2 event and 11 (3.9%) patients had severe hemorrhagic events (ten Grade 3 events, one Grade 5 event) at their worst intensity. Apart from the fatal event, 11 patients had at least one severe hemorrhagic event that resolved and no patients had severe haemorrhagic events that remained unresolved at time of data cut off (Table 11).

Severe hemorrhagic events that led to dose interruptions included the following: hematoma (2 patients; [0.7%]), gastrointestinal hemorrhage (2 patients; [0.7%]), and a single patient (0.4%) each with epistaxis, cerebellar hemorrhage, cerebral hematoma, intracranial hemorrhage, hemorrhagic anemia, and muscle hemorrhage. None of the severe hemorrhagic events led to dose reductions. Treatment withdrawal occurred due to severe intracranial haemorrhage in 1 patient (0.4%) (Annex 7b).

Impact on quality of life

Haemorrhage may lead to haemorrhagic shock and even death. The patient would require hospitalization.

Risk factors and risk groups:

No pralsetinib specific risk factors or risk groups were assessed. In general, patients with severe thrombocytopenia are in general at higher risk for experiencing haemorrhage, including severe haemorrhage. Risk of haemorrhage might be higher and more relevant in the older and frailer population, in whom even a grade 2 haemorrhage is of clinical importance. Furthermore, risk of haemorrhage might be increased by concurrent use of anti-coagulants.

Preventability:

No preventative measures have yet been established. Awareness, and timely and appropriate management could prevent development of severe haemorrhagic events.

Pralsetinib should be withheld until resolution to Grade 1 and resume at a reduced dose in case of severe haemorrhage. Pralsetinib should be discontinued for life-threatening or recurrent severe haemorrhagic events.

Should an association of severe haemorrhage with pralsetinib be established, then patients shall be advised to refrain from over-the-counter medication with anticoagulant effects.

Impact on the benefit-risk balance of the product:

The impact on the benefit-risk balance of pralsetinib is considered low, given the low incidence of severe haemorrhagic events under pralsetinib treatment and the severity of the underlying disease. The label includes dose modification advice, which will further reduce the impact of haemorrhage on the benefit-risk balance of the product.

Public health impact:

Not yet established for pralsetinib.

Table 11 Haemorrhage: Frequency, Severity, Seriousness and Outcomes (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Selected Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

Selected Adverse Events: Haemorrhage

	RET Fusion-positive NSCLC Patients (N=281)	All Patients (N=540)
Number of patients with at least one AE	57 (20.3%)	111 (20.6%)
95% CI for % of patients with at least one AE	(15.74%, 25.47%)	(17.22%, 24.21%)
Number of patients with at least one grade 3-5 AE	11 (3.9%)	22 (4.1%)
95% CI for % of patients with at least one grade 3-5 AE	(1.97%, 6.90%)	(2.57%, 6.10%)
Number of patients with at least one serious AE	12 (4.3%)	21 (3.9%)
Total number of AEs	90	162
Number of patients with at least one AE by worst grade		
Grade 1	40 (14.2%)	77 (14.3%)
Grade 2	6 (2.1%)	12 (2.2%)
Grade 3	10 (3.6%)	20 (3.7%)
Grade 4	0	1 (0.2%)
Grade 5	1 (0.4%)	1 (0.2%)
Number of patients with at least one AE by outcome		
Fatal outcome	1 (1.8%)	1 (0.9%)
Unresolved	16 (28.1%)	33 (29.7%)
Recovering/Resolving	0	0
Recovered/Resolved	46 (80.7%)	89 (80.2%)
Resolved with sequelae	1 (1.8%)	1 (0.9%)
Unknown outcome	0	1 (0.9%)
Number of patients with at least one grade 3-5 AE by outcome		
Fatal outcome	1 (9.1%)	1 (4.5%)
Unresolved	0	3 (13.6%)
Recovering/Resolving	0	0
Recovered/Resolved	11 (100%)	19 (86.4%)
Resolved with sequelae	1 (9.1%)	1 (4.5%)
Unknown outcome	0	0

AE = adverse event; CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI CTCAE.
Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Percentages are based on the number of patients in the analysis population as given in the column headings, except for the percentages for "number of patients with at least one AE by outcome" and "number of patients with at least one grade 3-5 AE by outcome" where the percentages are based on the number of patients with at least one AE and number of patients with at least one grade 3-5 AE respectively.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022
Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp06_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp06_lung_400_SE_04Mar2022_42863.out
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SVII.3.1.1.4 Transaminase Elevations

MedDRA PTs included are aspartate aminotransferase increased, alanine aminotransferase increased, transaminases increased, hypertransaminasaemia.

Potential mechanisms:

The exact mechanism for transaminase elevations associated with pralsetinib is not known.

Evidence source(s) and strength of evidence:

The clinical studies with pralsetinib showed mainly mild or moderate, asymptomatic and transient hepatic laboratory abnormalities without any clinical evidence of drug-induced liver injury. The risk is based on high incidence of increased AST/increased ALT events observed in the clinical development program for pralsetinib.

Characterization of the risk:

Frequency, severity and nature of risk (including reversibility and long-term outcomes)

Overall safety population (400 mg QD group)

In the overall safety population, 287/540 (53.1%) patients experienced a total of 869 elevated transaminases events. The majority of reported events were non-serious. Serious events of elevated transaminases events were reported for 6 patients (1.1%) (Table 12).

The majority of reported events were mild to moderate in severity; 45/540 (8.3%) patients had Grade ≥3 events.

The majority of patients (247/287, 86.1%) had at least one elevated transaminases event that resolved, and 106/287 (36.9%) had at least one elevated transaminases event that remained unresolved at time of data cut off.

Dose interruptions occurred for PTs of aspartate aminotransferase increased (27 patients [5.0%]), alanine aminotransferase increased (21 patients [3.9%]) and transaminases increased (2 patients [0.4%]). Pralsetinib dose was reduced due to elevated aspartate aminotransferase (11 patients [2.0%]), alanine aminotransferase (8 patients [1.5%]) and transaminases (2 patients [0.4%]). Discontinuation of pralsetinib occurred due to the event of transaminases increased in 1 patient (0.2%) (Annex 7b).

RET fusion-positive advanced NSCLC patients (400 mg QD group)

In RET fusion-positive advanced NSCLC patients treated with pralsetinib 400 mg QD, 149/281 (53.0%) patients experienced at least one elevated transaminases event. In 3/281 (1.1%) patients, the event was reported as serious. Most events were Grade 1 or 2 in severity. For 45/281 (8.3%) patients, the elevated transaminases event was of Grade ≥3 severity. The majority of patients (136/149, 91.3%) had at least one elevated

transaminases event that resolved, and 49/149 (32.9%) had at least one elevated transaminases event that remained unresolved at time of data cut off (Table 12).

Dose interruptions occurred due to aspartate aminotransferase increased (13 patients [4.6%]), alanine aminotransferase increased (12 patients [4.3%]) and transaminases increased (1 patient [0.4%]). Dose reductions occurred due to elevated aspartate aminotransferase (5 patients [1.8%]), alanine aminotransferase (3 patients [1.1%]) and transaminases (1 patients [0.4%]). None of the patients experienced an elevated transaminases event that led to permanent treatment discontinuation (Annex 7b).

Impact on quality of life

The impact is not yet established for pralsetinib.

Risk factors and risk groups:

The concomitant use of a hepatotoxic drug represents a known risk factor for development of hepatic laboratory abnormalities.

No other specific risk factors of risk groups have been established for pralsetinib.

Preventability:

ALT and AST should be monitored prior to initiating pralsetinib, every 2 weeks during the first 3 months of therapy, then monthly thereafter and as clinically indicated.

If Grade 3 or Grade 4 event occurs, the treatment with pralsetinib should be interrupted with a weekly monitoring of AST/ALT until resolution to Grade 1 or baseline. Pralsetinib should be resumed at a reduced dose. Patients may have their dose reduced by 100 mg decrements to a minimum dose of 100 mg QD.

If an event recurs at Grade 3 or higher, pralsetinib should be permanently discontinued.

Impact on the benefit-risk balance of the product:

Cases of transaminase elevations have been reported with an increased incidence within the clinical development program of pralsetinib. These events were mainly of mild or moderate intensity, asymptomatic and transient; Grade 3-4 events were observed in 6.9% and 4.8% for AST elevation and ALT elevation, respectively. Since severe events may be indicative of liver injury, the impact on the benefit-risk profile of pralsetinib is significant. Considering the manageable nature of events seen to date, presence of confounding factors for the development of such events (including relevant medical history, concomitant use of hepatotoxic medication [e.g. paracetamol, levofloxacine], concurrent bacteraemia or disease progression with multifocal liver metastases) and lack of clinically significant consequences of these elevations, the risk is considered acceptable.

Public health impact:

Not yet established for pralsetinib.

In general, transaminase elevations can be signs of hepatic dysfunction and severe cases indicative of liver injury. Drug induced liver injury represents a major health concern with the estimated global incidence of 13.9 to 24.0 cases per 100,000 population (Suk and Kim 2012). The relevance of these figures to pralsetinib remains unknown.

Table 12 Transaminase Elevation: Frequency, Severity, Seriousness and Outcomes (400 mg Dose) – RET Fusion-Positive Advanced or Metastatic NSCLC and the Overall Safety Population (Safety Evaluable Patients)

Selected Adverse Events: Seriousness, Outcomes, Severity, Frequency with 95% CI for Lung Indication, 400 mg QD Dose, Safety Evaluable Patients
Protocol: BO42863

Selected Adverse Events: Transaminase Elevation

	RET Fusion-positive NSCLC Patients (N=281)	All Patients (N=540)
Number of patients with at least one AE	149 (53.0%)	287 (53.1%)
95% CI for % of patients with at least one AE	(47.01%, 58.98%)	(48.84%, 57.42%)
Number of patients with at least one grade 3-5 AE	23 (8.2%)	45 (8.3%)
95% CI for % of patients with at least one grade 3-5 AE	(5.26%, 12.03%)	(6.14%, 10.99%)
Number of patients with at least one serious AE	3 (1.1%)	6 (1.1%)
Total number of AEs	477	869
Number of patients with at least one AE by worst grade		
Grade 1	107 (38.1%)	199 (36.9%)
Grade 2	19 (6.8%)	43 (8.0%)
Grade 3	19 (6.8%)	37 (6.9%)
Grade 4	4 (1.4%)	8 (1.5%)
Grade 5	0	0
Number of patients with at least one AE by outcome		
Fatal outcome	0	0
Unresolved	49 (32.9%)	106 (36.9%)
Recovering/Resolving	0	0
Recovered/Resolved	136 (91.3%)	247 (86.1%)
Resolved with sequelae	1 (0.7%)	3 (1.0%)
Unknown outcome	1 (0.7%)	6 (2.1%)
Number of patients with at least one grade 3-5 AE by outcome		
Fatal outcome	0	0
Unresolved	9 (39.1%)	20 (44.4%)
Recovering/Resolving	0	0
Recovered/Resolved	14 (60.9%)	26 (57.8%)
Resolved with sequelae	1 (4.3%)	2 (4.4%)
Unknown outcome	0	2 (4.4%)

AE = adverse event; CI = Confidence Interval; 95% CI were computed using Clopper-Pearson method. Grades are based on NCI CTCAE.
Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Percentages are based on the number of patients in the analysis population as given in the column headings, except for the percentages for "number of patients with at least one AE by outcome" and "number of patients with at least one grade 3-5 AE by outcome" where the percentages are based on the number of patients with at least one AE and number of patients with at least one grade 3-5 AE respectively.
N = number of patients exposed to Pralsetinib.
Data cutoff date: 04Mar2022
Program: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/program/t_rmp06_lung.sas
Output: root/clinical_studies/RO7499790/CDT30370/BO42863/data_analysis/rmp_2022/prod/output/t_rmp06_lung_400_SE_04Mar2022_42863.out
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SVII.3.1.2 Information on Important Potential Risks

SVII.3.1.2.1 Embryo-foetal Toxicity

Potential mechanisms:

The embryo-foetal toxicity associated with pralsetinib, and more specifically, the observed renal malformations in rodents, originate from its mechanism of action and are attributed to on-target inhibition of RET signalling (Jain 2009; Drilon et al. 2018).

Evidence source(s) and strength of evidence:

Data from the rodent embryo-foetal development studies showed that pralsetinib has embryo-toxic effects. These results are further supported by similar findings observed with other selective RET inhibitors like selpercatinib (Drilon et al. 2018). No data on the use of pralsetinib during pregnancy are available.

Characterization of the risk:

Frequency

Pregnant women were excluded from the clinical development program and no events of pregnancy occurred during the pralsetinib clinical trials.

Severity, reversibility and long-term outcome

Not yet established.

The embryo-foetal development studies in rats showed severe pralsetinib-related embryo-foetal toxicity at all dosage levels.

Impact on quality of life

Embryo-foetal toxicity is a significant complication of pregnancy with potential significant impact on both the mother and the foetus/child.

Risk factors and risk groups:

Female patients of child-bearing potential is the risk group.

Preventability:

Women of childbearing potential should be informed that pralsetinib may cause foetal harm.

Pralsetinib is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with pralsetinib.

Female patients of reproductive potential must use effective non-hormonal contraception during treatment with Gavreto and for 2 weeks after the final dose. Gavreto may render hormonal contraceptives ineffective.

Males with female partners of childbearing potential should use effective contraception during treatment with pralsetinib and for at least 1 week after the final dose.

Patients should be advised to contact their healthcare provider immediately if they become pregnant, or if pregnancy is suspected, while taking pralsetinib.

Impact on the benefit-risk balance of the product:

Even though the nature and severity of embryo-fetal toxicity events cannot be fully predicted based on the currently available data, occurrence of such events would have a significant impact on individual patients and has, therefore, impact on the overall benefit-risk profile of pralsetinib.

Public health impact:

Not yet established.

SVII.3.2. Presentation of the Missing Information

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 13 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Pneumonitis Hypertension Haemorrhage Transaminase Elevations
Important potential risks	Embryo-foetal toxicity
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The pharmacovigilance plan does not include any routine pharmacovigilance activities beyond signal management and reporting of adverse reactions.

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection:

- Specific adverse reaction follow-up questionnaires: Not applicable.
- Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding (safety concern: embryo-fetal toxicity): The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy

complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/ PBRERs.

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Tabulated summary of planned pharmacovigilance study is provided in Annex 2.
Protocol for the study in the pharmacovigilance plan is referenced in Annex 3.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 14 On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety uncertainties addressed	Milestones	Due Date
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2 —Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness or risk minimization activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorization				
Not Applicable				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
"A Randomized, Open-Label, Phase 3 Study of Pralsetinib versus Standard of Care for First Line Treatment of RET fusion-positive, Metastatic Non-Small Cell Lung Cancer (AcceleRET Lung/BO42864/BLU-667-2303)" Ongoing	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 randomised, open-label, Phase 3 Study of pralsetinib versus standard of care for first line treatment of RET fusion-positive, metastatic NSCLC.	Confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC	final CSR	12/2026

CSR: clinical study report; NSCLC non-small cell lung cancer; RET: rearranged during transfection

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN

V.1 Routine Risk-Minimization Measures

Table 15 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk-minimization activities
Important Identified Risks	
Pneumonitis	**Routine risk communication:** • SmPC sections 4.2, 4.4, and 4.8 • PL sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation to interrupt the treatment in case of a Grade 1 or 2 event until resolution is included in the SmPC section 4.2. Pralsetinib can be resumed at reduced dose. Pralsetinib must be permanently discontinued if the event recurs. • If a Grade 3 or 4 event occurs, the treatment must be permanently discontinued. • It is recommended in SmPC section 4.4, that patients should be advised to contact their healthcare provider immediately to report new or worsening respiratory symptoms. Further, it is recommended that patients who present with symptoms indicative of pneumonitis should be investigated to exclude other causes. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine
Hypertension	**Routine risk communication:** • SmPC sections 4.2, 4.4, and 4.8 • PL sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation to interrupt the treatment in case of a Grade 3 event that persists despite optimal antihypertensive therapy is included in the SmPC section 4.2. The treatment is recommended to be resumed at a reduced dose when hypertension is controlled.

	• Pralsetinib should be permanently discontinued in case of a Grade 4 event. • In the SmPC section 4.4, it is recommended to not initiate pralsetinib in patients with uncontrolled hypertension. • Monitoring of blood pressure is recommended in the SmPC section 4.4 after 1 week and at least monthly thereafter and as clinically indicated. • Recommendation to initiate and/or adjust anti-hypertensive therapy is included in SmPC section 4.4. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine
Haemorrhage	**Routine risk communication:** • SmPC sections 4.2, 4.4, and 4.8 • PL sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation to withhold treatment in case of a Grade 3 or 4 event until resolution to Grade 1, then resume at a reduced dose. • Pralsetinib should be discontinued in case of life-threatening or recurrent severe haemorrhagic events. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine
Transaminase Elevations	**Routine risk communication:** • SmPC sections 4.2, 4.4, and 4.8 • PL sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation to interrupt treatment in case of a Grade 3 or 4 event is included in the SmPC section 4.2. AST/ALT levels should be monitored once weekly until resolution of the event to Grade 1 or baseline, then treatment can be resumed at reduced dose. • Pralsetinib should be permanently discontinued if the transaminase elevation recurs at Grade 3 or higher.

	• Recommendation to monitor AST/ALT prior to initiating pralsetinib, and every 2 weeks during the first 3 months of pralsetinib treatment and monthly thereafter and as clinically indicated is included in the SmPC section 4.4. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine
Important Potential Risks	
Embryo-foetal Toxicity	**Routine risk communication:** • SmPC sections 4.4, 4.6 and 5.3 • PL section 2 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • The pregnancy status of women of childbearing potential should be verified prior to initiating pralsetinib treatment based on the SmPC section 4.6; and women of childbearing potential should be informed that pralsetinib may cause foetal harm. • Recommendation for women of childbearing potential to use highly effective non-hormonal contraception during treatment and for at least 2 weeks after the final dose of pralsetinib. If hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Recommendation for males with female partners of childbearing potential to use effective contraception during the treatment and at least 1 week after the final dose of pralsetinib is provided in the SmPC sections 4.4 and 4.6 and section 2 of the PL. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine.
Missing Information	
None	

V.2.Additional Risk-Minimization Measures

Routine risk-minimization activities as described in Part V SV.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table 16 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of cumulative data in PSURs/PBRERs. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Recommendation on dose interruptions, dose reduction and discontinuation in SmPC section 4.2. **Additional risk minimization measures:** 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:** None
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

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR GAVRETO ® (PRALSETINIB)

This is a summary of the risk-management plan (RMP) for Gavreto. The RMP details important risks of Gavreto, how these risks can be minimized, and how more information will be obtained about Gavreto risks and uncertainties (missing information).

Gavreto SmPC and its package leaflet give essential information to healthcare professionals and patients on how Gavreto should be used.

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

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

I. THE MEDICINE AND WHAT IT IS USED FOR

Pralsetinib is indicated as monotherapy for the treatment of adult patients with RET fusion-positive advanced non-small cell lung cancer (NSCLC).

Further information about the evaluation of Gavreto benefits can be found in Gavreto EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

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

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

Together, these measures constitute *routine risk minimization* measures.

If important information that may affect the safe use of Gavreto is not yet available, it is listed under “missing Information” below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

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

List of Important Risks and Missing Information	
Important identified risks	Pneumonitis Hypertension Haemorrhage Transaminase Elevations
Important potential risks	Embryo-foetal toxicity
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Pneumonitis	
Evidence for linking the risk to the medicine	Pneumonitis is considered a class effect of TKIs. Events of pneumonitis occurred commonly in the clinical development program for pralsetinib, in the overall safety population treated with 400 mg QD pralsetinib (10.8%) and across indications. The observed rates for pralsetinib are in overall consistent with what would be expected with a TKI treatment for this population of patients with advanced cancer.
Risk factors and risk groups	An analysis of the impact of four baseline demographic variables, namely age, gender, race and region, on the incidence of pneumonitis was performed. The results suggest that there does not appear to be a meaningful difference in the incidence of pneumonitis by any of the criteria assessed. The majority of patients within the safety population had confounding factors for development of pneumonitis, such as prior history of pneumonitis, prior therapies (before initiation of pralsetinib) that are known to cause pneumonitis (e.g. pemetrexed, pembrolizumab, vandetanib, docetaxel, osimertinib), or external beam radiation to the chest/back/spine area.
Risk-minimization measures	**Routine risk-minimization measures:** Sections 4.2, 4.4, and 4.8 of the SmPC "Pneumonitis / Interstitial Lung Disease" provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorization development plan.

QD = once daily; SmPC = summary of product characteristics; TKI = tyrosine kinase inhibitor

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	The non-clinical studies showed that pralsetinib doses ⩾ 25 mg/kg resulted in increased blood pressure in rats. These findings were confirmed in clinical setting, where 30.8% of patients within the overall 400 mg QD pralsetinib safety population had events of hypertension (grouped events including events of hypertension and blood pressure increased); hypertension was commonly reported across indications. Inhibition of the kinase insert domain receptor and VEGFR has previously been associated clinically with hypertension, and the effects were seen with many TKIs, including cabozantinib, lenvatinib, and selpercatinib.
Risk factors and risk groups	No pralsetinib-specific risk factors were established.

Risk-minimization measures	**Routine risk-minimization measures:** Sections 4.2, 4.4, and 4.8 of the SmPC "Hypertension" provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorization development plan.

QD = once daily; SmPC = summary of product characteristics; VEGFR = vascular endothelial growth factor receptor.

Important Identified Risk: Haemorrhage	
Evidence for linking the risk to the medicine	In clinical trial data from study BO42863 thrombocytopenia has been observed, and also severe bleeding events (although with very low frequency). A clear association has not yet been established. In a meta-analysis of small-molecule VEGFR-TKIs, an increase in the risk of developing severe and fatal haemorrhagic events in solid cancer patients was observe. Further, gastrointestinal epithelial erosion and ulceration has been observed in animal studies and described as secondary to VEGFR inhibition.
Risk factors and risk groups	No pralsetinib specific risk factors or risk groups were assessed. In general, patients with severe thrombocytopenia are in general at higher risk for experiencing haemorrhage, including severe haemorrhage. Risk of haemorrhage might be higher and more relevant in the older and frailer population, in whom even a grade 2 haemorrhage is of clinical importance. Furthermore, risk of haemorrhage might be increased by concurrent use of anti-coagulants.
Risk-minimization measures	**Routine risk-minimization measures:** Sections 4.2, 4.4, and 4.8 of the SmPC "Haemorrhage" provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk:-Transaminase Elevation	
Evidence for linking the risk to the medicine	The clinical studies with pralsetinib showed mainly mild or moderate, asymptomatic and transient hepatic laboratory abnormalities without any clinical evidence of liver injury. The risk is based on high incidence of increased AST/increased ALT events observed in the clinical development program for pralsetinib.
Risk factors and risk groups	The concomitant use of a hepatotoxic drug represents a known risk factor for development of hepatic laboratory abnormalities. No other specific risk factors of risk groups have been established for pralsetinib.
Risk-minimization measures	**Routine risk-minimization measures:** Section 4.2, 4.4, and 4.8 of the SmPC “Transaminase Elevations” provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** See Section II.C of this summary for an overview of the post-authorization development plan.

ALT = alanine aminotransferase; AST = aspartate transaminase, SmPC = summary of product characteristics.

Important Potential Risk: Embryo-foetal Toxicity	
Evidence for linking the risk to the medicine	The embryo-foetal toxicity associated with pralsetinib, and more specifically, the observed renal malformations in rodents, originate from its mechanism of action and are attributed to on-target inhibition of RET signalling.
Risk factors and risk groups	Female patients of child-bearing potential is the risk group.
Risk-minimization measures	**Routine risk-minimization measures:** Sections 4.4, 4.6, and 5.3 of the SmPC “Fertility and pregnancy” and “Women of childbearing potiential/Contraception in females and males” provide recommendations on risk management approach. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorization development plan.

RET = rearranged during transfection; SmPC = summary of product characteristics

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies That Are Conditions of the Marketing Authorization

The following study is a condition of the Marketing Authorization:

Study Status	Rationale and Objectives	Deadline
(ANX) Study BO42864/AcceleRET Lung/BLU-667-2303	The primary objective is to assess whether pralsetinib improves progression-free survival as compared to Investigator's choice platinum-containing anticancer treatment regimens for patients with RET fusion-positive advanced NSCLC. As part of the secondary objectives, the safety and tolerability profile of pralsetinib will be further characterised.	12/2026

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

There are no other studies in the post-authorization development plan.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Reactions Follow-Up Forms/Questionnaires

Not applicable.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (If Applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not Applicable.