16 September 2021
EMA/45270/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

GAVRETO

International non-proprietary name: pralsetinib

Procedure No. EMEA/H/C/005413/II/0002/G

Note

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

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	25 Dec 2021	25 Dec 2021	☐
☐	CHMP Rapporteur Assessment Report	18 Feb 2022	18 Feb 2022	☐
☐	PRAC Rapporteur Assessment Report	25 Feb 2022	25 Feb 2022	☐
☐	PRAC members comments	02 Mar 2022	02 Mar 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	03 Mar 2022	03 Mar 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 Mar 2022	10 Mar 2022	☐
☐	CHMP members comments	14 Mar 2022	14 Mar 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 Mar 2022	17 Mar 2022	☐
☐	Request for supplementary Information	24 Mar 2022	24 Mar 2022	☐
	Responses	22 Apr 2022	22 Apr 2022	
☐	Start of procedure	25 Apr 2022	25 Apr 2022	☐
☐	CHMP Rapporteur Assessment Report	24 May 2022	25 May 2022	☐
☐	PRAC Rapporteur Assessment Report	30 May 2022	30 May 2022	☐
☐	PRAC members comments	01 June 2022	01 June 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	02 June 2022	02 June 2022	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 June 2022	10 June 2022	☐
☐	CHMP members comments	13 June 2022	13 June 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 June 2022	16 June 2022	☐
☐	2nd Request for supplementary Information	23 June 2022	23 June 2022	☐
☐	Responses	15 July 2022	14 July 2022	☐
☐	Restart of procedure	18 July 2022	18 July 2022	☐
☐	CHMP Rapporteur Assessment Report	16 Aug 2022	9 Aug 2022	☐
☐	PRAC Rapporteur Assessment Report	19 Aug 2022	11 Aug 2022	☐
☐	PRAC members comments	24 Aug 2022	24 Aug 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	25 Aug 2022	n/a	☐

Status of this report and steps taken for the assessment				
☐	PRAC endorsed relevant sections of the assessment report[3]	01 Sep 2022	01 Sep 2022	☐
☐	CHMP members comments	05 Sep 2022	05 Sep 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 Sep 2022	08 Sep 2022	☐
☒	3rd[d] Request for supplementary Information	15 Sep 2022	15 Sep 2022	☐

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List of abbreviations

ADR	adverse drug reactions
AE	adverse events
AESI	adverse events of special interest
ATC	anaplastic thyroid cancer
AUC	area under the concentration-time curve
BICR	blinded independent central review
BID	twice daily
CBR	clinical benefit rate
CCOD	clinical cut-off date
CMA	Conditional Marketing Authorisation
DCR	disease control rate
DOR	duration of response
DTC	differentiated thyroid cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FIH	first-in-human
FTC	follicular thyroid cancer
HTA	Health Technical Assessment
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
MedDRA	Medical Dictionary for Regulatory Activities
MDP	measurable disease population
MEN2A	multiple endocrine neoplasia type 2A
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
MKI	multikinase inhibitors
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	overall response rate

OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTC	papillary thyroid cancer
QD	once daily
RAI	radioactive iodine
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RP2D	recommended Phase II dose
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SoC	standard of care
TLS	tumor lysis syndrome
TSH	thyroid stimulating hormone

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 30 November 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET-mutant medullary thyroid cancer for Gavreto; based on the efficacy and safety data obtained from the pivotal study BO42863 (ARROW). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. Furthermore, some minor changes to the PI have been implemented in line with the latest Anticancer Guidelines Recommendations.

Extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer for Gavreto; based on the efficacy and safety data obtained from the pivotal study BO42863 (ARROW). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0271/2021 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a waiver for pralsetinib.

At the time of submission of the application, the PIP P/0271/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. However, the MAH withdrew the request during the procedure.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
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Extension of indication to include monotherapy treatment of adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer for Gavreto; based on the efficacy and safety data obtained from the pivotal study BO42863 (ARROW). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

☐is recommended for approval.

☐is not recommended for approval.

☒is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

☒ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)

☐ 60 days (36 days to assess)

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report..

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

Thyroid cancer primarily consists of differentiated thyroid cancer (DTC) (~90% of cases, of which ~85% are papillary thyroid carcinoma (PTC) and ~5% are follicular thyroid cancer [FTC]), followed by medullary thyroid cancer (MTC) (~5% of cases) and anaplastic thyroid cancer (ATC) (~5% of cases).

MTC arises from parafollicular C cells and occurs in both hereditary and sporadic forms, while most cases of DTC and ATC arise sporadically from thyroid follicular cells. In adults, sporadic MTC accounts for 65–75% of MTC. The incidence of thyroid cancer has increased in different populations worldwide in the past 30 years.

Most (approximately 90%) cases of thyroid cancer in childhood are PTC; FTC is uncommon and MTC, ATC, and other types are rare. In paediatric patients, MTC is primarily an inherited disease occurring as a part of a multiple endocrine neoplasia type 2A or 2B (MEN2A or 2B).

RET is a receptor tyrosine kinase expressed in several neural, neuroendocrine and genitourinary tissue types that normally requires ligand and co-receptor binding for activation. Aberrant activation of RET is a critical driver of tumour growth and proliferation across a broad number of solid tumours. Oncogenic activation of RET can occur by two primary mechanisms, chromosomal rearrangements or point mutations. Both mechanisms of oncogenic activation result in constitutively active, ligand-independent RET kinase activity and activation of downstream signalling pathways. The predominance of RET mutations or fusions varies according to tumour histology (mutations more common in MTC, fusions more common in NSCLC and PTC), implying that the clinical behaviour of those tumours will also differ. Nevertheless, it is expected that inhibiting RET should exert an antiproliferative effect in either case, ultimately conducting to an efficacy benefit. Activating mutations of RET are present in 98% of the familial MTC and approximately 40% of the sporadic MTC.

Clinically, RET mutations are associated with poor outcomes, including larger tumour size, metastasis, and poorer survival, when compared with RET wildtype cases among patients with MTC.

State the claimed therapeutic indication

The wording of the proposed indication for Gavreto is:

- *Adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with tyrosine kinase inhibitors and not previously treated with RET inhibitor.*
- *Adults and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with tyrosine kinase inhibitors and not previously treated with a RET inhibitor.*

The proposed dose of pralsetinib is 400 mg once daily (QD).

In Europe, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 16 September 2021, recommending the granting of a conditional marketing authorisation for the treatment of Gavreto in adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor. The Commission Decision was granted on 18 November 2021.

Epidemiology and risk factors, screening tools/prevention

Thyroid cancer is the ninth most common cancer worldwide with an estimated 586,202 incident cases (all ages), accounting for an age-standardized incidence of 6.6 per 100,000 worldwide. Approximately 2 million people are living with thyroid cancer (all ages) globally with a 5-year prevalence of 19.8 per 100,000 in 2020.

In the paediatric population, the estimated incidence of thyroid cancers (per million person-years) is in the range of 5.0 to 45.1 for adolescents, 1.6 to 15.0 in children aged 10-14 years, 0 to 1.9 in children aged 5-9 years, and 0 to 0.7 in children aged 0-4 years.

Thyroid cancer affects more women than men and those of Asian descent. Factors that substantially increase the risk for thyroid cancer include a history of radiation exposure to the head and neck as a child, exposure to radioactive fallout, family history of thyroid cancer in a first-degree relative, and certain genetic conditions, such as familial medullary thyroid cancer or multiple endocrine neoplasia syndrome (type 2A or 2B).

Follicular thyroid cancers are more common in areas of the world where people's diets are low in iodine. On the other hand, a diet high in iodine may increase the risk of papillary thyroid cancer. In EU, most people get enough iodine in their diet because it is added to table salt and other foods. It is not recommended to screen healthy subjects for thyroid cancer.

Aetiology and pathogenesis

In MTC, kinase-activating RET alterations occur in ›95% of hereditary and ~50% of sporadic MTC. In hereditary MTC, these include extracellular domain mutations located in the cysteine rich domain which promote ligand-independent activation of RET, and kinase domains mutations which promote RET auto-activation and consequent oncogenic signalling.

RET fusions are uncommon in thyroid cancer, but are a distinctive feature of PTC, occurring in between 3% and 21% of sporadic PTC in adults, with a higher incidence in children and young adults (40 to 70%). At the time of diagnosis, children are more likely than adults to present with advanced disease. The incidence of distant metastases is estimated to be 25% in children, with lymph node involvement ranging from 40 to 80%.

Clinical presentation, diagnosis and stage/prognosis

Initial symptom is enlarged nodule, pain, changes in voice due to involvement of laryngeal nerve. Hyperthyroidism or hypothyroidism may be associated with a large or metastatic well differentiated tumour. Physical examination, ultrasound, and fine needle aspiration cytology confirms a definitive diagnosis. Thyroidectomy is initial step in treatment. Radioactive iodine-131 is used in papillary or follicular thyroid cancer for ablation of residual thyroid tissue and external radiation is used when is unresectable. Prognosis of thyroid cancer is related to the type of cancer and the stage at time of diagnosis. Early diagnosis has better outcome.

If thyroid cancer has spread to nearby tissues or organs and/or the regional lymph nodes, the disease is locally advanced. The 5-year survival rate for locally advanced papillary thyroid cancer is 99%. For locally advanced follicular cancer, the rate is 97%, and for medullary cancer, the rate is 91%. For anaplastic thyroid cancer, the rate is 10%.

Medullary and anaplastic thyroid cancers, which together make up 3% of all thyroid cancers, are more likely to spread. The 5-year survival rate for metastatic papillary thyroid cancer is 76%. For metastatic

follicular thyroid cancer, the rate is 64%. The rate for metastatic medullary thyroid cancer is 38%. For metastatic anaplastic thyroid cancer, the rate is 3%.

Management

MTC is initially treated with surgery when localized, as per The European Society for Medical Oncology (ESMO) guidelines. In the EU, the current approved treatments for locally advanced and metastatic RET mutation-positive MTC in adults are the same as for all forms of MTC and comprise the TKIs cabozantinib and vandetanib. However, their lack of specificity for RET diminishes their therapeutic impact in patients with RET alterations and clinical outcomes have not been as good as hoped for. Although both cabozantinib and vandetanib target RET to an extent, the antitumor effects of these TKIs is mainly due to their strong inhibition of key angiogenic pathway components such as VEGFR2.

In the EU, treatment options for patients who are refractory or intolerant to vandetanib or cabozantinib are rather limited. Recently a selective RET receptor tyrosine kinase inhibitor, selpercatinib was granted a conditional marketing authorisation (CMA) by the European Medicines Agency (EMA; February 2021) for the treatment of adults and adolescents 12 years and older with advanced RET mutation-positive MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib. Selpercatinib was investigated in a Phase I/II trial (LIBRETTO-001) with patients previously treated with cabozantinib, vandetanib, or both, and patients who had not received these drugs. The ORR for the 55 previously treated patients was 69%; 76% of responding patients had responses lasting 6 months or longer. Efficacy was also evaluated in 88 patients not previously treated with an approved therapy for MTC. Conversion of the CMA to full approval will be contingent upon the submission of comprehensive data from a Phase III global, randomized study comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET mutation-positive MTC.

Generally, DTC is effectively treated by surgery and radioactive iodine (RAI). However, 7% to 23% of patients develop distant metastases, and two-thirds of patients with distant metastases become RAI-refractory. In these cases, the 10-year survival rate can be as low as 10% compared with 56% in cases of metastatic RAI-avid disease. With regard to ATC, no treatment improving OS has been established. In the absence of RET-targeting therapies, the recommended standard of care (SoC) for adults with RET fusion-positive RAI-refractory thyroid cancers has been systemic treatment with the TKIs lenvatinib and sorafenib. However, neither lenvatinib nor sorafenib are approved in the EU or US for paediatric patients with thyroid cancers. In the EU, treatment options for RET fusion-positive thyroid cancer patients who have received prior systemic therapy with MKIs, are rather limited or even lacking. Likewise, as by MTC, selpercatinib was granted a CMA in Europe (February 2021) for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Currently there are no treatment guidelines for RET mutation-positive MTC patients or RET fusion-positive thyroid cancer patients who have failed treatment with non-selective MKIs. To date, of existing selective RET inhibitors, only selpercatinib has recently received a CMA in Europe for RET-altered thyroid cancer.

3.1.2. About the product

Pralsetinib (formerly known as BLU-667) is a highly potent and selective rearranged during transfection (RET) inhibitor that is being studied in patients with unresectable advanced or metastatic solid tumours with RET alterations (RET fusions, activating mutations, and some resistance mutations). It belongs to the pharmacotherapeutic group of antineoplastic agents and tyrosine kinase inhibitors.

Pralsetinib potently and selectively targets oncogenic RET-fusion and -mutant proteins (including gatekeeper mutations), shows potent antitumor activity in RET driven tumour models, and demonstrates tolerability at pharmacologically active doses in toxicology studies in rats and monkeys. This nonclinical in vitro and in vivo evidence of activity was the basis for exploring the clinical activity of pralsetinib in the treatment of patients with RET mutation-positive medullary thyroid cancer (MTC; also referred to as RET-mutant MTC) and RET fusion-positive thyroid cancer.

Pralsetinib is currently approved as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor. This medicine received a conditional marketing authorisation in EU 18 Nov 2021.

3.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek scientific advice from the CHMP concerning the two indications sought from this procedure.

On October 6 2021, the MAH held a pre-submission meeting with the Rapporteur (DKMA) and Co-Rapporteur (AEMPS). The Co-Rapporteur emphasized the absence of clinical data for patients below 18 years of age, and requested inclusion of a robust justification in the dossier to support inclusion of adolescents in the indication. The Danish Clinical Assessor stated that the proposed data package for RET-fusion positive thyroid cancers could support a stand-alone indication.

European Medicines Agency decision of 9 July 2021 on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for pralsetinib (EMEA-002575-PIP02-20) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. Based on the assessment of this application and the additional information provided by the applicant, the PDCO adopted a positive PIP opinion of May 2021 for pralsetinib for children from 12 years to less than 18 years of age, in the condition of treatment of thyroid neoplasms. The PDCO agreed on a waiver in a subset of children on the grounds that this product does not represent a significant therapeutic benefit over existing treatments. The PDCO granted a deferral for the completion of this PIP.

On 27 May 2020, the FDA granted the orphan drug designation for the indication "treatment of RET fusion, RET-mutation, and TRKC-positive poorly DTC, undifferentiated or ATC, MTC, and locally advanced or metastatic follicular or papillary thyroid cancer".

General comments on compliance with GLP, GCP: The MAH claims that the studies are conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

3.2. Non-clinical aspects

3.2.1. Introduction

The Applicant updated section 5.3 of the SmPC to reflect data from toxicity studies WIL-124570, 00124770 and WIL-124571 conducted in rats and Cynomolgus monkeys and submitted as part of the initial MAA (see Gavreto initial MA EPAR).

The Applicant has submitted an updated Environmental Risk Assessment for pralsetinib according to "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use"

(EMEA/CHMP/SWP/4447/00 corr. 2[1*]). The Applicant has submitted prevalence data for the proposed indications and thus a recalculated F_{pen} and $PEC_{SURFACEWATER}$ for pralsetinib as part of the Phase I assessment, as well as results of completed Phase II Tier A/B studies.

3.2.2. Ecotoxicity/environmental risk assessment

OECD GLP-compliant studies included in the report were conducted at Arcadis Schweiz LTD (Switzerland), Charles River (the Netherlands) or at Battelle UK Ltd (UK). Numbers in brackets in the below assessment refer to references provided in the ERA report submitted by the Applicant, unless stated otherwise.

Pralsetinib was not mutagenic in various *in vitro* test systems and in the *in vivo* Micronucleus Test. However, adverse effects on embryo-foetal development were detected at 5 and 10 mg/kg and embryotoxicity/embryolethality at 20 and 30 mg/kg/day. This results in a CLP classification as Reproductive toxicity Category 2, H360d, suspected of damaging the unborn child. Hence, pralsetinib is a substance that is carcinogenic, mutagenic or toxic for reproduction (CMR). However, pralsetinib is not known to be an endocrine disrupter.

PBT screening

Lipophilicity of pralsetinib

The pH-dependent *n*-octanol/water distribution coefficient $logD_{ow}$ was assessed for pralsetinib according to OECD guideline 107 (shake-flask method), conducted in compliance with GLP. The $logD_{ow}$ was assessed at the environmentally relevant pH-values of 5, 7 and 9 and was 3.0, 4.0 and 3.9, respectively (see summary table 5.2.5). At pH 7 and 9 the uncharged molecule prevails. Pralsetinib has a pH-dependent *n*-octanol/water distribution coefficient $logD_{ow}$<4.5. Hence, a specific PBT assessment is not triggered. However, in accordance with "*Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use*' (EMA/CHMP/SWP/44609/2010 Rev. 1) a $logD_{ow}$>3 triggers the conduct of a bioaccumulation study (OECD 305), which was subsequently performed by the Applicant (see summary table 5.2.5 and below)

Bioconcentration of pralsetinib was studied in freshwater fish (*Danio rerio*, Zebrafish) according to OECD 305. One nominal concentration (C1=3.21 ug/l) was prepared and test animals were exposed to this concentration for a period of 13 days (uptake phase). The fish were subsequently transferred to untreated control medium and a depuration phase was performed for 14 days. During the whole test period, the test medium (treated water as well as water-only control and solvent control) was renewed in a flow-through system [11]. All bioconcentration (BCF) factors were <2000 l/kg. Hence, pralsetinib was not considered bioaccumulative (see summary table 5.2.5). Since all BCF values were <100 l/kg, there was also no further need to evaluate secondary poisoning.

Phase I assessment

$PEC_{SURFACEWATER}$ (PEC_{SW}) and action limit

The maximum daily dose of the active substance pralsetinib ($DOSE_{AI}$) is 400 mg. The Phase I predicted environmental concentration for surface water (PEC_{SW}) while using the default fraction of a population receiving the active substance (F_{PEN}) of 0.01 is calculated as follows:

PEC_{SW} = $DOSE_{AI}$ × F_{PEN} ÷ (default amount of wastewater per inhabitant per day (200 L) × default dilution factor (10))

= 400000 µg/d × 0.01 ÷ (200 L/inh/d × 10)

=2 µg/L

Using the default value F_{PEN} of 0.01, the initial Phase I PEC_{SW} is greater than the action limit of 0.01 µg/L, which trigger Phase II assessment. The Applicant performed a new calculation of PEC_{SW} using a calculated refined F_{PEN} based on European disease prevalence data for the sought indications in accordance with the Q&A ERA guideline (EMA/CHMP/SWP/44609/2010 Rev. 1) as summarized below:

Prevalence

Pralsetinib is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), adult and paediatric patients 12 years of age and older with advanced or metastatic RET mutant medullary thyroid cancer (MTC) who require systemic therapy, and adult and paediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) [6].

The estimated prevalence of RET fusion-positive NSCLC is as follows:

- The 5-year prevalence of lung cancer in Europe within Globocan 2020 [15] of the International Agency for Research on Cancer (IARC) amounts to 582,924 cases. According to Molina et al. (2008 [20]) NSCLC accounts for ~85% of lung cancer and 1–2% are RET-rearranged ([18] [25] [26]).
- Considering the upper end of this estimated range for RET-rearrangements (i.e. 2%) and a European population of 747,636,026 in 2020 according to Worldometer (https://www.worldometers.info/worldpopulation/europe-population/) for Eastern, Western, Southern and Northern Europe, this results in **9,910 cases** for RET-rearranged NSCLC in Europe.

The estimated prevalence of RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer (MTC) is as follows (see Ref. [6] for an overview of the estimated prevalence):

- The 5-year prevalence of thyroid cancer in Europe within Globocan 2020 [16] of the International Agency for Research on Cancer (IARC) amounts to 325,708 cases.
- About 90% of overall thyroid cancer are differentiated thyroid cancer (DTC) of which about 85% are papillary thyroid cancer (PTC [13]) and about 10% are follicular thyroid cancer (FTC [22]). The locally advanced/metastatic subsets account for 15% of both, PTC and FTC [27]. With 20% each of RET altered [13] and compared with the population of Eastern, Western, Southern and Northern Europe, this results in **7,475 cases** for locally advanced/metastatic RET altered PTC and **879 cases** for locally advanced/metastatic RET altered FTC in Europe.
- About 5% of overall thyroid cancer are anaplastic thyroid cancer (ATC [22]), of which 16.7% are RET altered ATC [17]. Compared with the population of Eastern, Western, Southern and Northern Europe, this results in **2,720 cases** for RET altered ATC in Europe.
- According to Romei and Elisei (2012 [22]) medullary thyroid cancer (MTC) account for about 10% of overall thyroid cancer, whereas 75% are sporadic MTC and 25% are hereditary MTC, respectively ([14],[21]). 65% of sporadic MTC are RET sporadic MTC [21] and 97% of hereditary MTC are RET hereditary MTC [19]. Compared with the population of Eastern, Western, Southern and Northern Europe, this results in 15,878 cases for RET sporadic MTC and 7,898 cases for RET hereditary MTC, i.e. **23,777 cases** for overall RET altered MTC in Europe.
- According to the International Thyroid Oncology Group (cited in [6]) poorly differentiated thyroid cancer account for about 5% of overall thyroid cancer of which 12.9% are RET positive poorly differentiated thyroid cancer [24]. Compared with the population of Eastern, Western,

Southern and Northern Europe, this results in **2,101 cases** for RET positive poorly differentiated thyroid cancer in Europe.

The total estimated 5-y prevalence of RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer (MTC) is **36,952 cases** in Europe.

Combined prevalence

The combined 5-year prevalence for RET-rearranged NSCLC (**9,910 cases**) and RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer (MTC) (**36,952 cases**) amount to **a total of 46,861 cases** in Europe. Compared to the European population of 747,636,026 in 2020 according to Worldometer, the 46,861 cases result in a prevalence for whole Europe of **0.00006**.

Refined PECsw

The ($F_{PEN\text{-}REFINED}$) is calculated as follows:

$F_{PEN\text{-}REFINED}$ = (prevalence × duration of one treatment × treatments per year) ÷ number of days per year

= (0.00006 × 365 days × 1) ÷ 365

= 0.00006

The refined Phase I PEC_{SW} is calculated as follows:

PEC_{SW} = ($Dose_{AI}$ × $F_{PEN\text{-}REFINED}$) ÷ (default wastewater per inhabitant × default dilution)

= (400,000 µg/d × 0.00006) ÷ (200 L/inh/d × 10)

= 0.013 µg/L

The PEC_{SW} for all indications amounts to 0.013 µg/L. This value is greater than the action limit of 0.01 µg/L which triggers entry into Phase II. Hence, pralsetinib advanced to initial ERA Phase II Tier A and part of Tier B as described below.

Phase II assessment

Phase II Tier A – Physical-chemical properties and fate

Adsorption-desorption (OECD 106), ready biodegradability (OECD 301 F) and aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) studies (all GLP-compliant) were performed with pralsetinib. The outcome of the ready biodegradability test (see summary table 5.2.5) indicates that pralsetinib is not readily biodegradable.

In the GLP-compliant adsorption-desorption study (OECD 106), adsorption and desorption constants to the organic carbon fraction in three soils and two activated sewage sludges were determined using ^{14}C-labelled pralsetinib. Pralsetinib was shown to be stable for the duration of the definitive study for all solid phases, with all supernatants and extracts analysed which were >LOQ (limit of quantification), indicating that [^{14}C]-Pralsetinib accounted for >92%. Parental mass balances were determined by LSC and HPLC analysis of the 1 mg/L adsorption and desorption supernatants and solvent extracts during the definitive phase. Greater than 90% of the applied radioactivity was determined to be [^{14}C]-pralsetinib in all soil and sludges. The calculated Freundlich coefficient ($K_{F,\ ads}$-values) for adsorption ranged from 159-317 mL/g ode (oven-dried equivalent) in the three soils and 1193-1742 mL/g ode in the sludges with a geomean of 463. The corresponding values for $K_{FOC,\ ads}$ ranged from 8361-28825 mL/g ode in the three soils to 5965-8799 mL/g ode for the two sludges. The relationship between the solid phase and solution concentrations gave 1/n values in the range of 0.811-0.923. Based on this data, pralsetinib was classified as being immobile in soils and sludges, according to the McCall classification scheme [27]. The highest single K_{fOC} value for sewage sludges ($K_{fOC,\ des}$) was 8799 L/kg

and, therefore, below the threshold of 10000 L/kg from the EMA 2006 ERA guideline. Accordingly, no consideration of the soil compartment through landspreading of sewage sludge was deemed necessary for pralsetinib. The results are summarised in summary table 5.2.5. The K_{foc} obtained was further used for risk assessment of chronic sediment ecotoxicity in Phase II Tier B (see "Phase II Tier B"-section below)

In the GLP-compliant sediment/water fate study (OECD 308), ^{14}C-labelled pralsetinib rapidly partitioned from the water phase into the sediment in the two systems tested (Calwych Abbey Lake (CA, silt loam) and Lumsdale Middle Pond (LD, sand)). The mean proportion of radioactivity associated with the water phase declined quickly over time from 92.2% applied radioactivity at 0 days after treatment to 3.7% at 30 days after treatment in the CA system. In the LD system applied radioactivity declined from 94.2% to 10.7% from day 0 to day 30 after treatment. The proportion of total radioactivity extracted from sediment samples increased over time from 6.7% to 66.4% from day 0 to day 100 after treatment in the CA system, though extractability tended to plateau from day 30 after treatment onwards. In the LD system, total radioactivity extracted from the sediment increased from 5.5% to 65.5% from day 0 to day 100 after treatment, with a similar plateau seen. Unextracted sediment residues (bound) increased throughout incubation, reaching maximum levels of 26.4% applied radioactivity in the CA system and 30.4% in the LD system at 100 days after treatment

The DT_{50}-values in the water phase were determined by the Applicant to be 1.77 and 10.5 days for CA and LD systems, respectively. The DT_{50}-values for the total systems were 165 and 156 days for CA and LD systems, respectively. However, no 12°C normalisations were provided for these DT_{50}-values and no DT_{50}-value for the sediment was provided. Accordingly, the Applicant is asked to include the following 12°C normalized DT_{50}-values (and 20°C DT_{50}-value for sediment) in the ERA:

Water phase: 15.5 d/ 22.4 d (CA/LD, 12 °C)

Sediment phase: 239 d/318 d (CA/LD, 20 °C), 510 d/679 d (CA/LD, 12 °C)

Total system: 352 d/327 d (CA/LD, 12 °C)

Based on the above, the Applicant is further asked to classify pralsetinib as very persistent (vP) in sediment and the total system in the ERA **(OC)**. Volatile degradation products were insignificant and no major metabolites were detected. Based on more than 90% of the applied radioactivity as extractables plus non-extractables/bound residues being contained in the sediment (exceeding the guideline threshold of 10% any time after day 13), a sediment risk assessment study in *Chironomus riparius* was subsequently performed (OECD 218, see summary table 5.2.5 and the section "Phase II Tier B" further below).

Phase II Tier A – Effect studies

In Phase II Tier A, an acute immobilisation test with *Daphnia* species (OECD 202) and an activated sludge respiration inhibition test (OECD 209) was performed in compliance with GLP (see summary table 5.2.5). The acute immobilisation test was performed over 48 hours, and indicated that pralsetinib had no acute toxic effects on *Daphnia magna* up to its solubility limit in test water. The $NOEC_{48h}$ was 1.50 mg/L. The respiration inhibitory effects of pralsetinib to the microorganisms of activated sludge of a municipal sewage treatment plant were investigated under aerobic static conditions over an exposure time of 3 hours. The $EC_{50, 3h}$ and the $NOEC_{3h}$ was reported as >1000 mg/L and 1000 mg/L, respectively, indicating no effect of pralsetinib on microbial communities. However, taking into account the solubility limit of 2.73 mg/L of pralsetinib, this value was established as the NOEC in the activated sludge respiration inhibition test (OECD 209).

Chronic ecotoxicity tests were performed with pralsetinib according to OECD guidelines 201, 211 and 210 with algae (*Raphidocelis subcapitata*), daphnids (*Daphnia magna* Straus) and fish (*Danio rerio*),

respectively (see summary table 5.2.5). A short summary of the outcome of chronic ecotoxicity tests is provided below:

An *algal growth inhibition test* according to OEDC 201 over 72 hours was performed in compliance with GLP with the green alga *Raphidocelis subcapitata* [4]. A nominal concentration of 100 mg/L was tested. The concentrations of pralsetinib were measured by LC-UV analysis. The test item was not fully dissolved, but the concentrations remained stable over the whole 72h incubation period. The analyses confirmed the low solubility of pralsetinib. The endpoints were assessed based on the geometric mean of the measured concentrations (GMC), which was 1.24 mg/L GMC at the loading rate of 72 h. The 72 h ErC50 based on growth rate was estimated to be >100 mg/L nominal concentration and >1.24 mg/L GMC. The 72 h NOEC based on growth rate was 1.24 mg/L GMC [4].

A *daphnids reproduction test* according to OECD 211 over 21 days was performed in compliance with GLP with the cladoceran *Daphnia magna*. A water-soluble fraction was prepared by stirring 10 mg/l for 24 h ± 3 h. 25.0, 35.4, 50.0, 70.7 und 100% of the filtrate were tested. The concentrations of pralsetinib were measured by LC-MS analysis. The endpoints reproduction rate, mortality, body length and intrinsic rate of population increase were assessed based on time-weighted mean measured concentrations (TWM). The 21 d EC10 was determined at 1.02 mg/L TWM based on the effects on reproduction [12].

A *fish early life stage test* according to OECD 210 over 35 days was performed in compliance with GLP with the zebrafish *Danio rerio*. A water-soluble fraction was prepared by stirring 10 mg/L for 24 h ± 3 h. 9.96, 17.7, 31.6, 56.2 und 100% of the filtrate were tested. The concentrations of pralsetinib were measured by LC-MS analysis. The endpoints hatching success, survival of juvenile fish, body length, wet weight and dry weight were assessed based on geometric mean measured concentrations (GMC). Since an EC10 for the wet and dry weight of surviving fish could not be derived, the corresponding 35 d NOEC of 0.110 mg/L GMC was considered the relevant endpoint, and was carried forward to the surface water risk assessment (see below) [13].

Based on the outcome of the chronic ecotoxicity tests above, and the outcome of an activated sludge respiration test (OECD 209, see summary table 5.2.5), risk assessments for surface water, groundwater and sewage treatment were performed by the Applicant:

Surface water PEC/PNEC risk ratio

The surface water PNEC is calculated as the lowest of the three chronic surface water ecotoxicity EC10/NOEC values divided by an assessment factor of 10 [11]. In the case of pralsetinib, with a NOEC of 1.24 mg/L GMC for the algae, an EC10 of 1.02 mg/L TWM for the daphnids and a NOEC of 0.110 mg/L GMC for the fish as argued above, the fish early life stage NOEC of 0.110 mg/L (i.e. 110 µg/L) drives the PNEC:

$PNEC_{SW}$ = 110 µg/L ÷ 10 = 11.0 µg/L

The surface water PEC÷PNEC risk characterisation ratio is:

PEC÷PNEC risk ratio = 0.013 µg/L ÷ 11.0 µg/L = **0.001**

In view of the PEC÷PNEC risk characterisation ratio of 0.001 based on Phase II Tier A procedures, there is no concern for risk caused by pralsetinib to surface waters.

Groundwater PEC/PNEC risk ratio

The groundwater PEC is approximated as the surface water PEC x 0.25:

PEC_{GW} = 0.013 µg/L x 0.25 = 0.00325 µg/L

The groundwater PNEC is approximated as the chronic EC10 for daphnids of 1.02 mg/L divided by an assessment factor of 10 [11]:

$PNEC_{GW}$ = 1020 µg/L ÷ 10 = 102 µg/L

The groundwater PEC÷PNEC risk characterisation ratio is:

PEC÷PNEC risk ratio = 0.00325 µg/L ÷ 102 µg/L = **0.00003**

In view of the PEC÷PNEC risk characterisation ratio of 0.00003, there is no concern for risk caused by pralsetinib to groundwater.

Sewage treatment plant PEC/PNEC risk ratio

The sewage works PEC is approximated as the pralsetinib surface water PEC multiplied by 10 (the default surface water dilution factor used in the PEC_{SW} calculation):

PEC_{STP} = 0.013 µg/L × 10 = 0.13 µg/L = 0.00013 mg/L

An activated sludge respiration inhibition test according to OECD 209 over 3 hours was performed in compliance with GLP [3], from which the Applicant reported a NOEC of 1000 mg/L NC. However, as mentioned, the solubility limit of 2.73 mg/L of pralsetinib was considered as the NOEC, and this value was used for the calculation of PNEC:

The bacterial PNEC for sewage treatment is calculated as the activated sludge respiration inhibition NOEC divided by an assessment factor of 10 [11]:

$PNEC_{STP}$ = 2.73 mg/L ÷ 10 = 0.273 mg/L

Hence, the sewage works PEC÷PNEC risk characterisation ratio is:

PEC÷PNEC risk ratio = 0.00013 mg/L ÷ 0.273 mg/L = **0.0005**

In view of the PEC÷PNEC risk characterisation ratio of 0.0005, there is no evidence for risk caused by pralsetinib to sewage treatment plants.

Phase II Tier B assessment

Sediment chronic effects and risk assessment

A GLP-compliant chronic toxicity study (OECD 218) was performed to assess the risk of pralsetinib for sediment-dwelling organisms (*Chironomus riparius*). The study was triggered by a previously described OECD 308 study, in which a shift from the water phase to the sediment was observed for [^{14}C]-labelled pralsetinib, where applied radioactivity reached values of more than 10% at any time point after or at 14 days. For the OECD 218 study, applied concentrations of pralsetinib were 6.25, 12.5, 25, 50 and 100 mg/kg, and the organic carbon in the test system was 2.5%. The following results were obtained: 28-day EC50 = >66.4 mg/kg dry sediment (ds); 28-day EC10 = 30.7 mg/kg ds; 28-day LOEC = 28.0 mg/kg ds; and 28-day NOEC = 12.5 mg/kg ds. These values were based on overall effects on emergence rate and development rate of pooled sexes (the 28-day EC10 was based on emergence rate of pooled sexes).

The Applicant subsequently compared a calculated sediment PEC (PEC_{SED}) for pralsetinib, with a sediment PNEC ($PNEC_{SED}$) derived from OECD study 218. The PEC_{SED} was calculated using data from the OECD 106 adsorption-desorption study (highest KFOC in soil: 37105 l/kg) and the calculated PEC_{SW}-value from Phase I, as described below:

$PEC_{SED,\ wet} = (K_{SUSP\text{-}WATER}/RHO_{SUSP}) \times PEC_{SW} \times 1000$

$=((Fwater_{SUSP} + (Fsolid_{SUSP} \times Kp_{SUSP} \times RHO_{SOLID} \times 10^{-3}))/RHO_{SUSP}) \times PEC_{SW} \times 1000$

$=((Fwater_{SUSP} + (Fsolid_{SUSP} \times Foc_{SUSP} \times Kfoc_{SOIL} \times RHO_{SOLID} \times 10^{-3}))/RHO_{SUSP}) \times PEC_{SW} \times 1000$

$=((0.9 + (0.1 \times 0.1 \times 37105\ L/kg \times 2.5\ kg.m^{-3} \times 10^{-3}))/1.15\ kg.m^{-3}) \times 0.000013\ mg/L \times 1000$

= 0.010 mg/kg wet weight

$PEC_{SED,\ dry\ weight} = PEC_{SED,\ wet} \times 4.6 = 0.010\ mg/kg \times 4.6 = 0.047\ mg/kg$ dry weight

The $PNEC_{SED}$ was derived using the EC10-value (30.7 mg/kg) from the GLP-compliant OECD 218 study. The EC10 was recalculated into a standard sediment with an organic carbon content of 10% (fraction of 0.1):

$EC10_{ST,\ SED} = EC10_{TEST,\ SED} \times (Foc_{,\ ST,\ SED}/Foc_{TEST,\ SED})$

= 30.7 mg/kg x (0.1/0.021) = 123 mg/kg standard sediment.

With one single chronic EC10 available, the deterministic sediment PNEC was derived by dividing the EC10 by an assessment factor of 100.

$PNEC_{SED} = EC10_{ST,\ SED}/100$ = 123 mg/kg/100 = 1.23 mg/kg standard sediment.

The sediment PEC/PNEC risk characterization ratio is:

PEC/PNEC = 0.047 mg/kg/1.23 mg/kg = 0.038

Considering the PEC/PNEC ratio is below 1, there is no concern for risk caused by pralsetinib to sediments.

Table 5.2.5. Summary of main study results

Substance (INN/Invented Name): pralsetinib; (cis)-N-((S)-1-(6-(4-Fluoro-1H-pyrazol-1-yl)pyridin-3-yl)ethyl)-1-methoxy-4-(4-methyl-6-(5-methyl-1H-pyrazol-3-yl-amino)pyrimidin-2-yl)cyclohexanecarboxamide			
CAS-number (if available): 2097132-94-8			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH=5.0: $logD_{ow}$=3.0 pH=7.0: $logD_{ow}$=4.0 pH=9.0: $logD_{ow}$=3.9	$LogD_{ow}$<4.5: no need to conduct definitive PBT assessment $LogD_{ow}$>3.0: bioconcentration study in fish (OECD 305) triggered.
PBT-assessment			
Bioaccumulation/*Danio rerio*	OECD 305	BCF_K = 7.5 L/kg BCF_{ss} = 7.3 L/kg BCF_{KL} = 5.6 L/kg BCF_{SSL} = 5.4 L/kg DT_{50} = 1-5 days	Not considered bioaccumulative
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.013	µg/L	> 0.01 threshold (Y), phase II assessment triggered

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Test system	$K_{FOC, ads}$ (L/kg)	$K_{FOC, des}$ (L/kg)	Highest K_{FOC} for sludges (8799 L/kg) below the threshold of 10000 mL/g, hence, terrestrial assessment is not triggered
		RefesSol 02-A (soil)	28825	37105	
		Hareby (soil)	8361	6247	
		Speyer 2.2 (soil)	9340	13491	
		Basildon cake (sludge)	8799	5960	
		Chelmsford cake (sludge)	5965	7127	
Ready Biodegradability Test	OECD 301 F	0% after 28 days.			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Compartment	DT_{50} (days) 20°C	DT_{50} (days) 12 °C	Phase II Tier B assessment for sediment is triggered Very Persistent (vP) in sediment and total system
		CA water	1.77	15.5	
		CA sediment	239	510	
		CA total system	165	352	
		LD water	10.5	22.4	
		LD sediment	318	679	
		LD total system	156	327	
		% shifting to sediment (extractable+nonextractable): CA: 92.8% LD: 95.9%			

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	$NOEC_{72h}$	1.24	mg/L GMC	$NOEC_{72h}$ based on growth rate
Daphnia sp. Acute immobilisation Test	OECD 202	$NOEC_{24h}$	1.49	mg/L NC HTC	*Daphnia magna* Straus
		$NOEC_{48h}$	1.50		
Daphnia sp. Chronic Reproduction Test	OECD 211	$NOEC_{21days}$	0.803	mg/L TWM	*Daphnia magna* Straus
		$EC_{10, 21days}$	1.02	mg/L TWM	EC_{10} based on effects on reproduction
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	$NOEC_{35days}$	0.110	mg/L GMC	LC_{10} based on survival of juvenile fish
		$LC_{10, 35days}$	0.396		
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3 hours)	>2.73	mg/L	No effect on microbial communities at solubility limit
		NOEC	2.73		
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	$EC10_{, 28 days}$	30.7	mg/kg	Risk Quotient<1

3.2.3. Discussion on non-clinical aspects

In view of the new target population (paediatric) in the sought indication, the applicant proposed to reflect in section 5.3 of the SmPC, relevant data from toxicology studies submitted and reviewed as part of the initial MAA.

In a 4-week repeat-dose toxicology study in non-human primates (study WIL-124571), physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as incisor tooth abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies (WIL-124570 and 00124770 respectively) at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicology study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study (see section 5.3 of the SmPC). The additional data are considered relevant for inclusion in the SmPC.

In accordance with an application for a type II variation (extension of indication), an updated ERA was submitted for pralsetinib. Based on the updated ERA, a recalculated PEC_s triggered entry into Phase II, and accordingly several Phase II Tier A studies and two Phase II Tier B studies were performed.

The submitted data indicate that pralsetinib does not pose a significant risk to the environment. Pralsetinib should still be used and disposed of according to the precautions stated in the SmPC in order to minimize any potential risks to the environment. In line with the recommendations put forward in the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2), the Applicant should also include the following statement in the patient information leaflet:

"Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment"

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

The MAH is recommended to submit the results of the ongoing bioaccumulation study as part of the final updated ERA.

The MAH is recommended to submit the results of the ongoing sediment toxicity study in compliance with GLP conducted in the context of an EMA Phase II Tier B assessment.

In addition, the MAH is recommended to submit the results from the adsorption-desorption study (OECD 106).

3.3. Clinical aspects

3.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1: Summary of Available Data

Study	Study Description	Dose (Formulation/Process)	n	PK Sampling	Analysis
BLU-667-0101	An open-label, randomized, single-dose, 2-way crossover study to evaluate the effect of food on the pharmacokinetics of pralsetinib in healthy adult subjects	2 x 100 mg (Process II capsules) following an overnight fast 2 x 100 mg (Process II capsules) overnight fast followed by a high-fat meal 30 min before dosing	20 20*	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6, 7, 8, 10, 12, 24, 48, & 72, 96, 120, 144, 168, 192h	Exposure comparison Dose proportionality
BLU-667-0102	An open-label, randomized, single-dose, 2-period crossover, bioequivalence study comparing four 100 mg tablets with four 100 mg capsules of BLU-667 in healthy adult subjects	4 x 100 mg (Process II capsules) following an overnight fast of at least 10 hours 4 x 100 mg (Tablets) following an overnight fast of at least 10 hours	87 90*	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6, 8, 10, 12, 24, 48, 72, 96, 120, & 168h	Exposure comparison Dose proportionality
BLU-667-0103	A Phase 1, Open-Label Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of [14C]-BLU-667 Following a Single Oral Dose in Healthy Adult Male Subjects	300 mg (Process III capsules) BLU-667 and 1 capsule containing 9 mg (100 μ Ci) [^{14}C]-BLU-667 administered on Day 1 at Hour 0.	6	Predose (0), 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312 hours post-dose	Dose proportionality
BLU-667-0104	A two-part, open-label, fixed-sequence study to evaluate the effect of multiple doses of itraconazole and rifampin on the single-dose pharmacokinetics of pralsetinib in healthy adult subjects	Part 1: Itraconazole 2 x 100 mg (Process III capsules) following an overnight fast 2 x 100 mg (Process III capsules) following an overnight fast + itraconzole 200 mg BID on day 1 followed by 200 mg QD (Total 14 days of itraconazole dosing, co-administered with pralsetinib on day 4.)	 25 25**	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6.25, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, & 192h†	Exposure comparison Dose proportionality
BLU-667-0105	An open-label, fixed-sequence study to evaluate the effect of esomeprazole and gastric pH-altering on the pharmacokinetics of pralsetinib in healthy adult subjects	4 x 100 mg (Process III capsules) following an overnight fast	36	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, & 192 h	Exposure comparison Dose proportionality

Continued on next page. *Pralsetinib administered as a tablet, or in the fed state was not included in the analysis. **PK data obtained from co-administration with either itraconazole, rifampicin, or esomeprazole were not included in the analysis. †Sampling schedule following pralsetinib administration alone. Only phase 1 of study BLU-667-0101 was used in analysis. Only part 1 of study BLU-667-0104 was used in analysis. Only part 1 of study BLU-667-0105 was used in analysis.

Study	Study Description	Dose (Formulation/Process)	n	PK Sampling	Analysis
BLU-667-1101	A phase 1 study of the highly-selective RET inhibitor, pralsetinib, in patients with thyroid cancer, non-small cell lung cancer (NSCLC) and other advanced solid tumors‡	Dose-Escalation (Phase 1) Once daily: 30, 60, 100, 200, 300, 400, 600 mg Twice daily: 200 mg in the morning, 100 mg in the evening, 100 mg in the morning, 100 mg in the evening fasted 2 hours before & until 1 hour after dosing (Process I/II capsules)	 31 6	C1D1: Predose, 0.5, 1, 2, 4, 8, 24 hours§ C1D15: Predose, 0.5, 1, 2, 4, 8, 24 hours§ C2-4: Predose	Graphical comparison and covariate analysis from population PK model
		Dose-Expansion (Phase 2: 9 groups) Once daily: 400 mg fasted 2 hours before & until 1 hour after dosing (Process I/II/III capsules)		C1D1: Predose, 0.5, 1, 2, 4, 8, 24 hours C1D15: Predose, 0.5, 1, 2, 4, 8, 24 hours C2-4: Predose	
		Group 1: NSCLC with a RET fusion (previously treated with a platinum-based chemotherapy)	≈90		
		Group 2: NSCLC with a RET fusion (not previously treated with a platinum-based chemotherapy)	≈40		
		Group 3: MTC (previously treated with cabozantinib and/or vandetanib)	63‡		
		Group 4: MTC (not previously treated with cabozantinib or vandetanib)	27‡		
		Group 5: Other solid tumors with a RET fusion (previously treated with SOC appropriate for the tumor type)	9‡		
		Group 6: Any solid tumors with a RET alteration (fusion or mutation) (previously treated with a selective RET TKI	1‡		
		Group 7: Other solid tumors with a RET mutation (previously treated with SOC appropriate for the tumor type)	≈20‡		
		Group 8: NSCLC with a RET fusion that was previously treated with a platinum-based chemotherapy extension cohort	≈30		
		Group 9: MTC not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced metastatic disease extension cohort	≈30‡		

NSCLC = non-small cell lung cancer. ‡Only pralsetinib administered to patients with RET-altered thyroid cancer (from Groups 3, 4, 5, 6) were included in the analysis for Objective 1. §2 patients receiving pralsetinib BID do not have a 24 h sample collected, instead a 12 h sample was collected following the second dose.

The clinical pharmacology of pralsetinib was studied in five Phase I clinical pharmacology studies in healthy subjects and in the ongoing Phase I/II efficacy and safety study BO42863 in patients with RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered solid tumors to support pralsetinib approval for the treatment of patients with RET-altered thyroid cancers, including a subset of patients with RET mutation-positive MTC (medullary thyroid cancer). See summary of PK studies in Table 1 above.

3.3.2. Pharmacokinetics

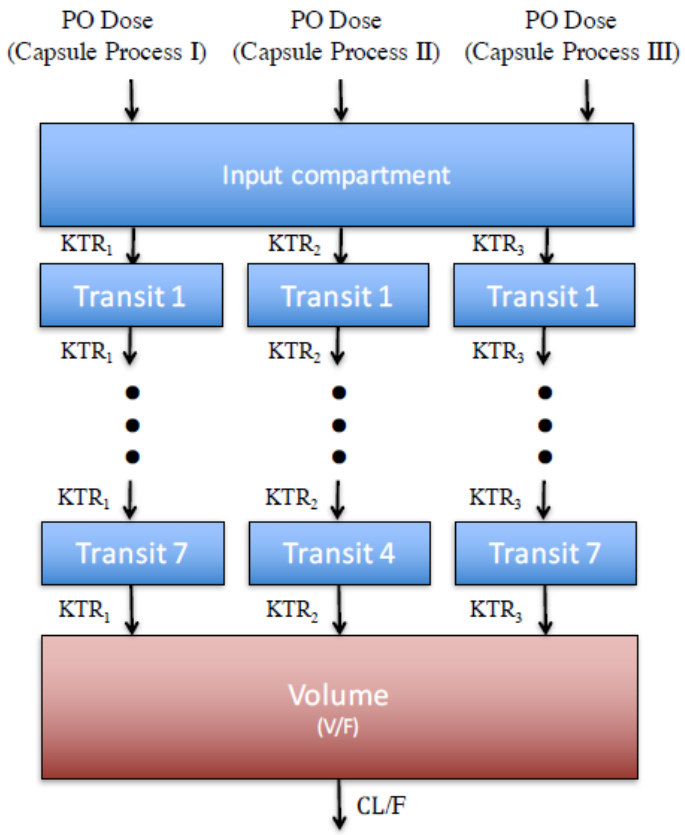
Bioanalysis and Pop PK analysis

A validated liquid chromatography/tandem mass spectrometry assay was used for analysis of plasma concentrations of pralsetinib in Study BO42863. The dynamic range of the assay was 2 to 2000 ng/mL.

Additional data collected in patients with RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered solid tumors in ongoing Study BO42863 was used to characterise the PK of pralsetinib in thyroid cancer (including RET mutation-positive MTC). Exposure metrics were estimated by noncompartmental methods using WinNonlin version 8.2.0.4383.

A previous Pop PK model developed for pralsetinib to describe the concentration-time data obtained in studies conducted in healthy subjects, in patients with NSCLC, and in patients with RET-altered thyroid cancers was used to fit the additional data from patients recruited in Study BO42863. NONMEM version VII level 4.0 and PsN version 5.0.0 was used for the modelling. The complete dataset was comprised of 8510 observations from 694 subjects, of which 4645 observations came from study BO42863. BLQ observations were excluded (709 (7.1%) were pre-dose and 623 (6.2%) were post-dose BLQ observations). The previous Pop PK model was a one-compartment disposition model with transit absorption and linear elimination. Pralsetinib was modeled in terms of apparent oral clearance (CL/F), apparent volume of distribution (V/F), and absorption transit rate constant (KTR). Absorption was described by a series of transit compartments (7, 4, and 7 transit compartments for capsule Process I, II, and III, respectively). BSV was included on CL/F, V/F, and KTR. BOV was included on KTR and oral bioavailability (F).

Figure 14: Schematic of the Previously Developed Population PK Model



KTR_1 = absorption transit rate constant for capsule Process I; KTR_2 = absorption transit rate constant for capsule Process II; KTR_3 = absorption transit rate constant for capsule Process III; V/F = apparent volume of distribution; CL/F = apparent oral clearance.

Initially, the previous PK model was fitted to the additional data without parameter estimation. Subsequently, the structural model parameters and random effects were re-estimated and all covariates included in the previous model were evaluated (Table 16).

Table 16: Covariates Assessed in the Population PK Analysis

Covariate	Code	Value	Parameters
Age at baseline (yr)	AGE	Continuous	CL/F, V/F
Creatinine clearance at baseline[a] (mL/min)	CRCL	Continuous	CL/F
Estimated glomerular filtration rate at baseline[b] (mL/min/1.73m^2)	EGFR	Continuous	CL/F
Alanine aminotransferase at baseline (U/L)	ALT	Continuous	CL/F
Aspartate aminotransferase at baseline (U/L)	AST	Continuous	CL/F
Bilirubin at baseline (μmol/L)	BILI	Continuous	CL/F
Albumin at baseline (g/L)	ALB	Continuous	CL/F
Sex	SEX	Categorical	CL/F, V/F
Patient population (healthy volunteers, NSCLC, RET-altered thyroid cancer)	DSSTAT	Categorical	CL/F, V/F, KTR
Concomitant CYP3A4 inhibitor	CYPINB	Categorical	CL/F, F
Concomitant CYP3A4 inducer	CYPIND	Categorical	CL/F, F
Concomitant PPI	PPI	Categorical	CL/F, KTR, F

CL/F = apparent clearance, V/F = apparent volume of distribution, KTR = absorption transit rate constant, F = relative oral bioavailability.

[a]CRCL(male)[6] = ((140 - AGE) · WT) / (Serum Creatinine (mg/dL) · 72)
[a]CRCL(female)[6] = ((140 - AGE) · WT · 0.85) / (Serum Creatinine (mg/dL) · 72)
[b]eGFR[6] = 175 · (Serum Creatinine (μmol/L))$^{-1.154}$ · (AGE)$^{-0.203}$ · (0.742 if female) · (1.212 if African American)

In addition, capsule process was evaluated as a covariate effect on the bioavailability and the absorption transit rate constant (KTR). Covariate effects included in the final updated model were: body weight on oral clearance (CL/F) and apparent volume of distribution (V/F), patients with RET-altered thyroid cancer on absorption transit rate constant (KTR) at C1D1 (relative to patients with NSCLC or healthy subjects), patients with NSCLC on F (relative to patients with RET-altered thyroid cancers or healthy subjects), patients with NSCLC administered Process I capsules on F (relative to patients with RET-altered thyroid cancers or healthy subjects), concomitant CYP3A4 inducer on CL/F, and capsule process on KTR. Sex was also a significant covariate of CL/F but correlated with body weight and thus not included. Body weight was included on disposition parameters using allometric scaling with estimated exponents.

All parameters of the final updated model were estimated with good precision with acceptable SEs (<30%). See Table 17. The ratio of largest to smallest eigenvalues was 61.84 (i.e. <1000), indicating that the model was not over-parameterized and there was no evidence of collinearity.

Table 17: Parameter Estimates for the Final Updated PK Model for Pralsetinib

Parameter Name	Prior Value (%RSE)	Updated Value (%RSE, [95% CI])[a]
Apparent Clearance (CL/F, L/h)*	16.1 (2.7)	15.6 (3.8, [14.6 – 16.9])
Covariate Effect of Body Weight on CL/F (-)	0.265 (37.3)	0.300 (27.8, [0.151 – 0.467])
Covariate Effect of Age on CL/F (-)	-0.548 (17.2)	-0.592 (13.8, [-0.758 – -0.435])
Age Threshold for Covariate Effect of Age on CL/F (years)	37.2 (4.0)	37.5 (2.7, [31.9 – 43.9])
Covariate Effect on CYP3A4 Inducer Use on CL/F (Fold)	1.23 (7.6)	1.13 (4.2, [1.04 – 1.23])
Apparent Volume of Distribution (V/F, L)**	383 (2.8)	374 (2.7, [357 – 396])
Covariate Effect of Body Weight on V/F	0.496 (25.5)	0.475 (18.7, [0.304 – 0.652])
Rate of Transit Absorption for Capsule Process I (KTR_1, 1/h)	5.56 (4.6)	5.59 (4.1, [5.14 – 6.04])
Rate of Transit Absorption for Capsule Process II (KTR_2, 1/h)	3.22 (3.2)	3.22 (2.2, [3.08 – 3.35])
Rate of Transit Absorption for Capsule Process III (KTR_3, 1/h)	7.69 (3.1)	7.60 (3.4, [7.07 – 8.12])
Covariate Effect of Thyroid Cancer on KTR on C1D1 (Fold)†	1.27 (5.3)	1.27 (4.2, [1.17 – 1.38])
Relative Bioavailability for NSCLC Patients (Fold)‡	1.37 (6.1)	1.38 (4.4, [1.26 – 1.49])
Covariate Effect of Capsule Process I on Bioavailability in NSCLC Patients (Fold)	0.759 (10.2)	0.739 (5.5, [0.661 – 0.821])
Between Subject Variability for CL/F (% CV)	48.7 (5.2)	47.6 (6.2, [44.9 – 50.7])
Between Subject Variability for V/F (% CV)	45.9 (5.0)	47.2 (8.3, [43.8 – 51.4])
Correlation between CL/F-V/F (-)***	0.146 (6.8)	0.141 (9.0, [0.120 – 0.168])
Between Subject Variability for KTR (% CV)	32.7 (4.9)	32.6 (8.6, [30.2 – 35.6])
Between Occasion Variability for Bioavailability (% CV)	37.4 (5.8)	36.4 (10.1, [32.7 – 39.7])
Between Occasion Variability for KTR (% CV)	27.5 (9.2)	27.0 (16.9, [22.2 – 31.4])
Residual Unexplained Variability for Healthy Volunteers (Proportional) (% CV)	26.5 (3.7)	26.5 (2.4, [25.9 – 27.1])
Residual Unexplained Variability for Study BLU-667-1101 (Proportional) (% CV)	37.5 (3.2)	37.1 (2.7, [36.1 – 38.1])

RSE = relative standard error, CI = confidence interval

* $CL/F = 15.6 \cdot (Weight/71)^{0.3} \cdot (Age/37.5)^{-0.592}$ If Age ≥ 37.5 · 1.13 (If CYP3A4 Inducer Use)

** $V/F = 374 \cdot (Weight/71)^{0.475}$

*** Reported as covariance estimate

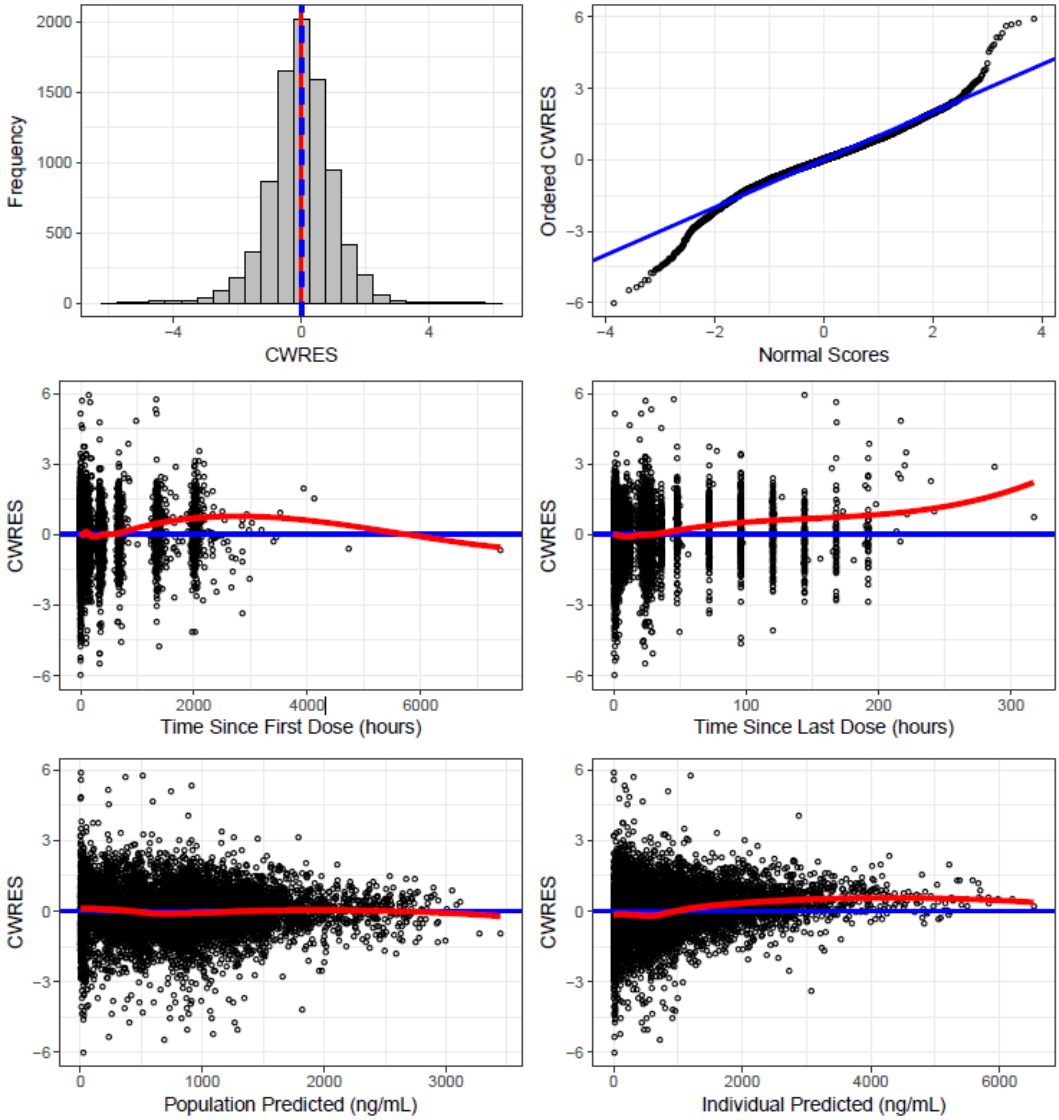
† KTR = 5.59 (if Process I) or 3.22 (if Process II) or 7.60 (if Process III) · 1.27 (if Thyroid Cancer on Cycle 1 Day 1)

‡ F in patients with NSCLC = 1.38 · 0.739 (if Process I)

[a] RSE and 95%CI for the updated model were derived from SIR.

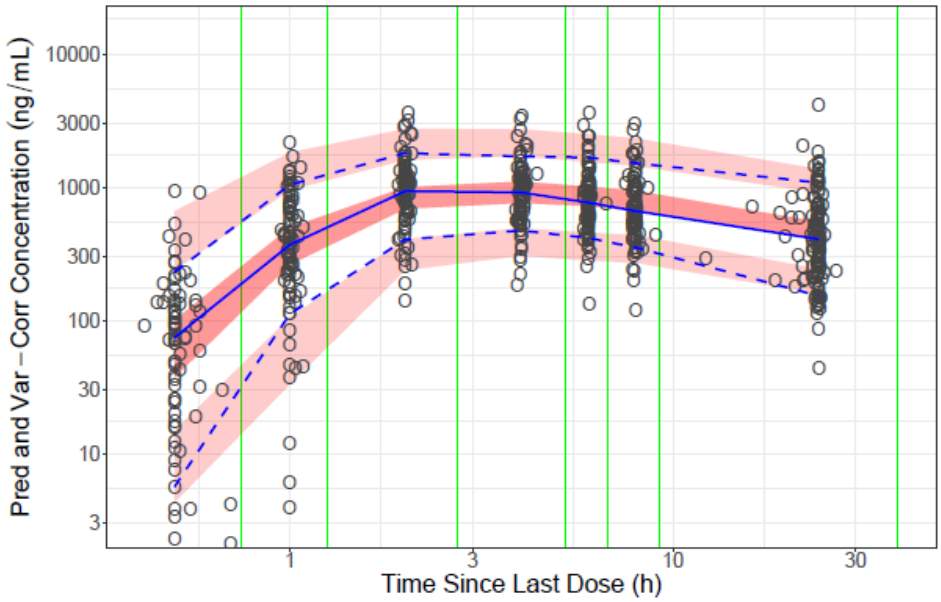
The final updated model was evaluated by SIR, GoF plots and VPCs. A selection is shown in the following figures.

Figure 32: CWRES Plots for the Final Updated PK Model



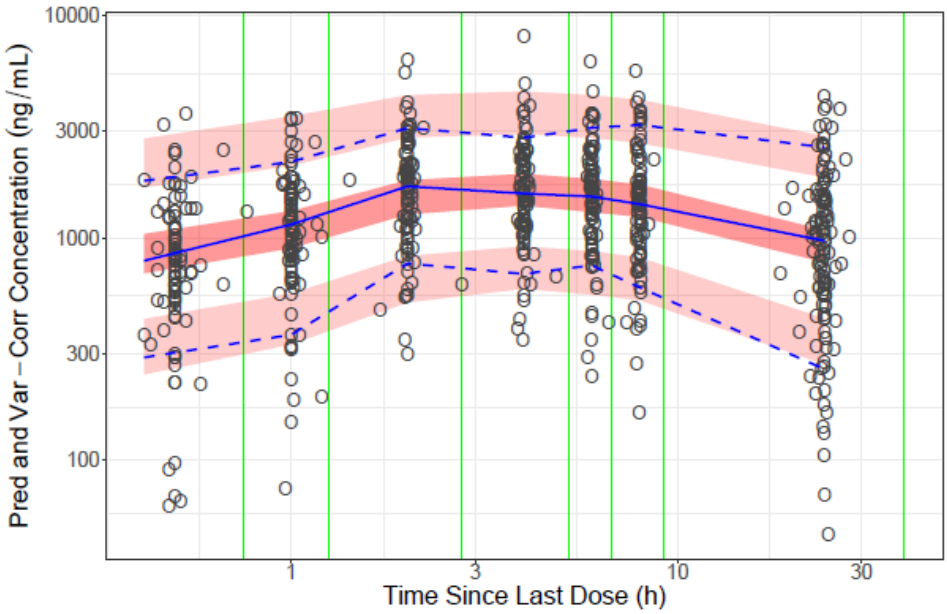
The solid blue lines represents the line of identity or zero, the red lines represents the trend in the data (Loess smooth) or the mean.

Figure 39: pvcVPC for Final Updated PK Model for Pralsetinib – Patients with RET-mutation Positive MTC (C1D1)



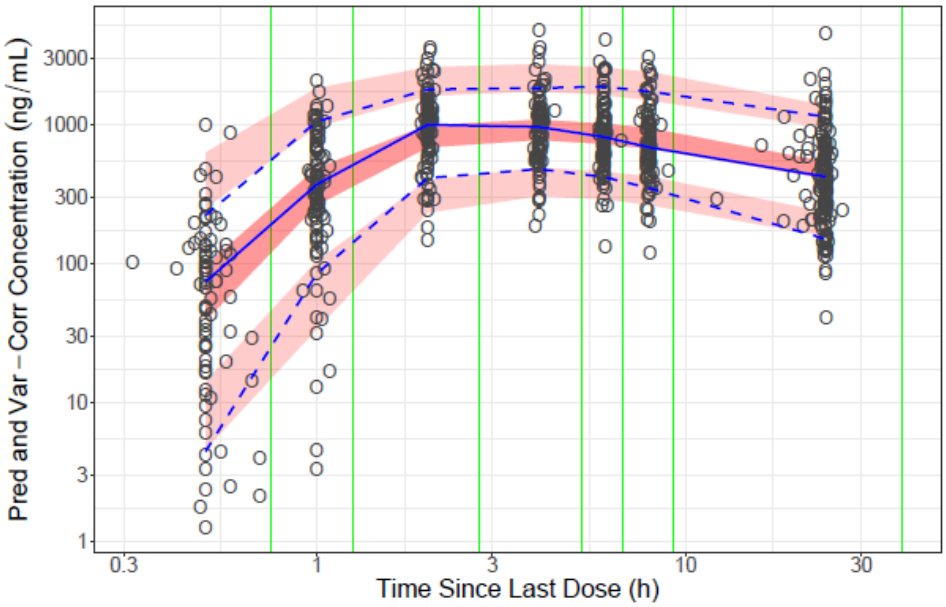
Open circles = individual observed (prediction/variability corrected), dashed blue lines = 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Figure 40: pvcVPC for Final Updated PK Model for Pralsetinib – Patients with RET-mutation Positive MTC (C1D15)



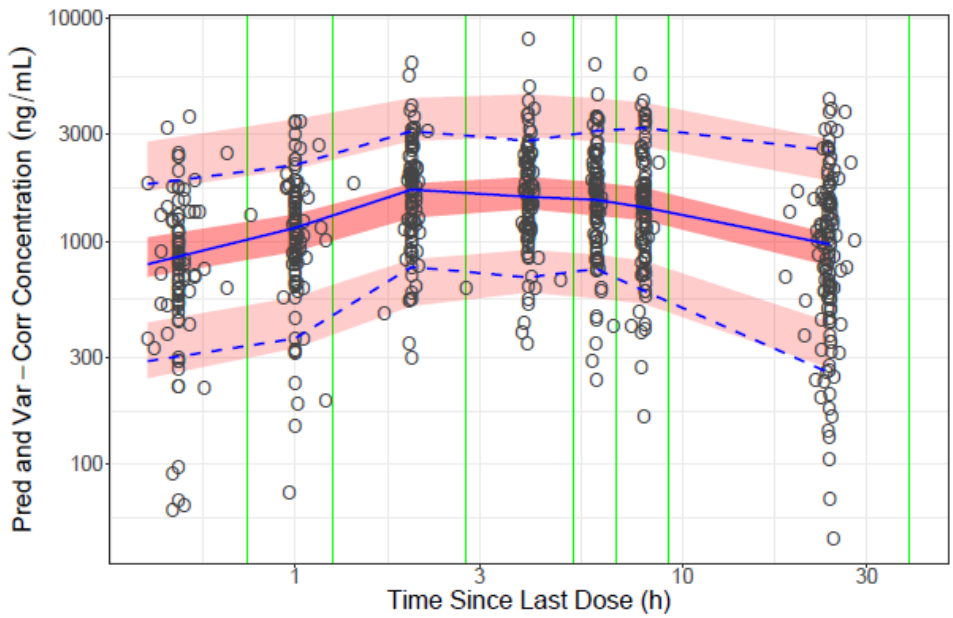
Open circles = individual observed (prediction/variability corrected), dashed blue lines = 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Figure 41: pvcVPC for Final Updated PK Model for Pralsetinib – Patients with RET-altered Thyroid Cancer (C1D1)



Open circles = individual observed (prediction/variability corrected), dashed blue lines = 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Figure 42: pvcVPC for Final Updated PK Model for Pralsetinib – Patients with RET-altered Thyroid Cancer (C1D15)

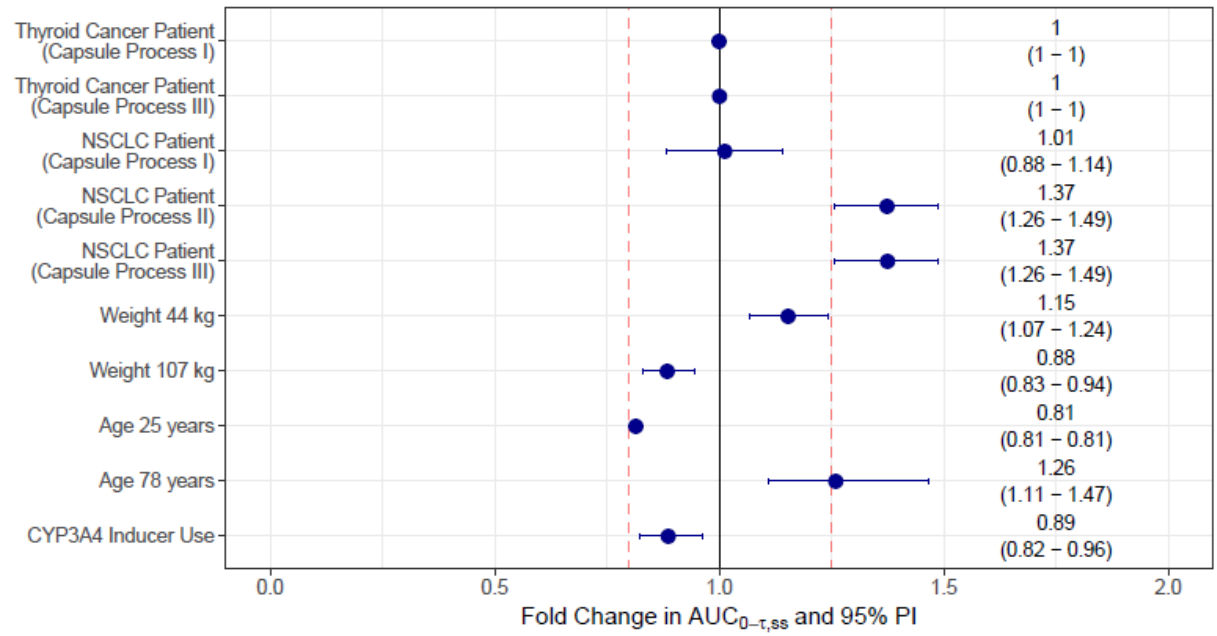


Open circles = individual observed (prediction/variability corrected), dashed blue lines = 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles, green lines = bin limits. Note: Log-log scale is used.

Patients with RET-altered thyroid cancer were found to have an increased KTR on Cycle 1 Day 1 (C1D1), with an estimated 25% increase in KTR compared to healthy volunteers after accounting for other intrinsic and extrinsic factors. The reason for the increased KTR may be related to differences in study design, with healthy volunteers fasted for 10 hours before & 4 hours after drug administration,

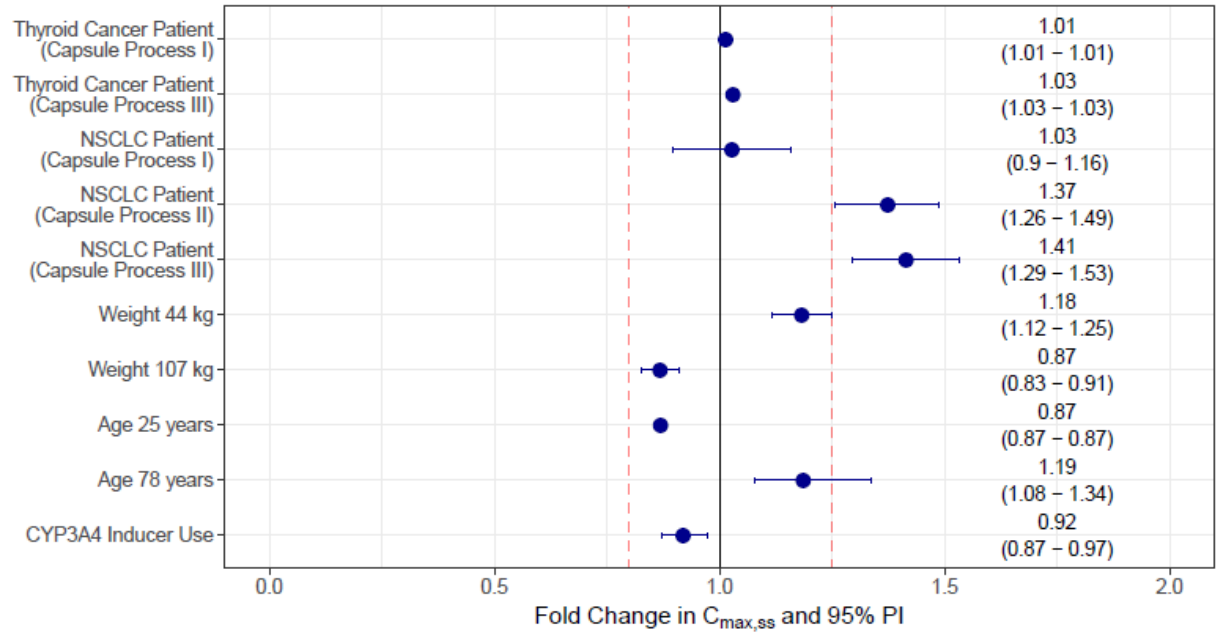
while the patients were fasted for only 2 hours before & 1-hour post-drug administration. As pralsetinib has a large food effect (>2-fold exposure following a high fat meal), the difference in fasting conditions between the studies may contribute to the increased absorption observed in study BO42863. Considering the thyroid cancer patient population, the magnitude of covariate effects on pralsetinib exposure was not expected to be clinically relevant compared to the high between-subject variability. The 95% PI was fully contained within the 80-125% range for the reference subject for most covariates except for old age as shown in the Forest plots Figure 49, 51.

Figure 49: Model Predicted Effect of Covariates on Fold Change in $AUC_{0-\tau,ss}$



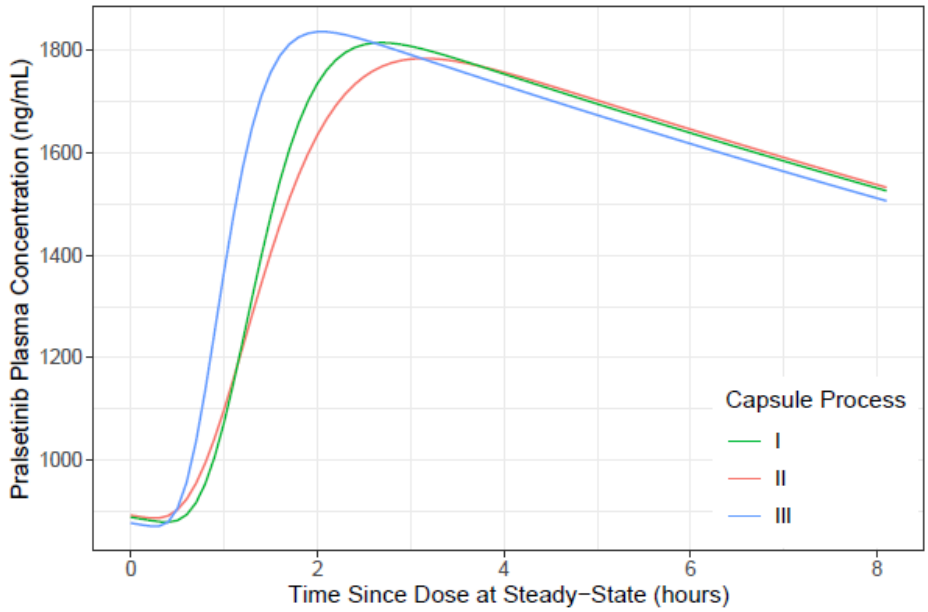
The solid black line represents no impact of the covariate with the reference subject referring to a patient with RET-altered thyroid cancer with median age (53 years) and weight (71 kg) receiving 400 mg dose of pralsetinib (capsule Process II) QD in a fasted condition, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80-125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group including uncertainty on the fixed effect. Note: healthy volunteers are not included in the plot. Age and weight ranges represent the approximate 95% range of the analysis population.

Figure 51: Model Predicted Effect of Covariates on Fold Change in $C_{max,ss}$



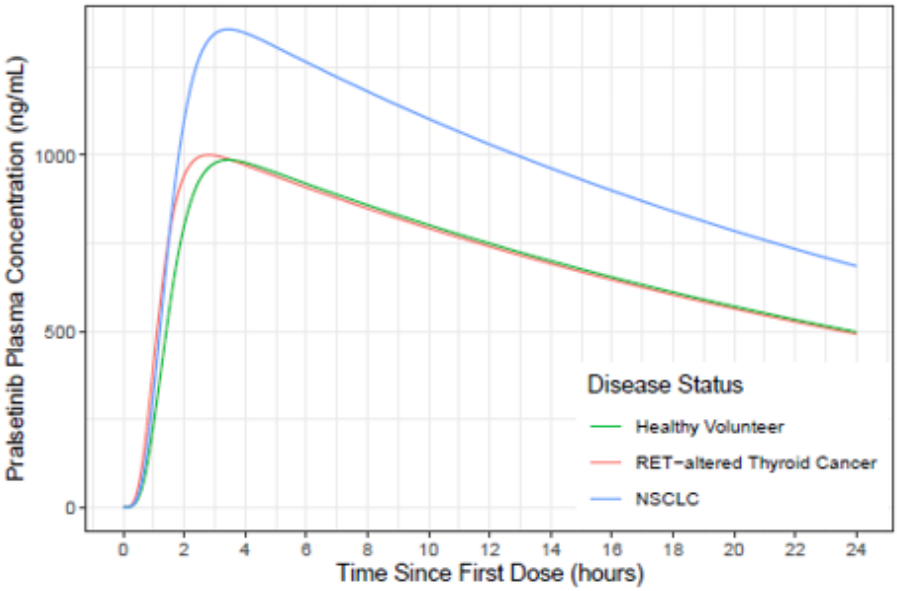
The solid black line represents no impact of the covariate with the reference subject referring to a patient with RET-altered thyroid cancer with median age (53 years) and weight (71 kg) receiving 400 mg dose of pralsetinib (capsule Process II) QD in a fasted condition, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80-125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group including uncertainty on the fixed effect. Note: healthy volunteers are not included in the plot. Age and weight ranges represent the approximate 95% range of the analysis population.

Figure 48: Model Predicted Effect of Capsule Process on Pralsetinib Concentration-time Profiles



Solid lines represent a simulated median concentration-time profile assuming a patient with RET-altered thyroid cancer receiving 400 mg pralsetinib once daily. Note: time has been truncated to 8 h post-dose at steady-state for visualization.

Figure 46: Model Predicted Effect of Patient Population on Pralsetinib Concentration-time Profiles



Solid lines represent a simulated median concentration-time profile assuming a subject with median age (53 years) and weight (71 kg) receiving 400 mg pralsetinib (capsule Process II) once daily. Note: time has been truncated to 24 h post-dose at Day 1 for visualization.

Comparison of parameter estimates using the Final Pop PK model (including NSCLC data and estimated exponents for weight effects) with updated versions of the Final Pop PK model: Model 1 (without NSCLC data and fixed exponents for weight effects) and Model 2 (without NSCLC data and estimated exponents for weight effects) are shown in Table 1.

Table 1 Comparison of Parameter Estimates Derived from the Final Model (Estimated Exponents for Weight Effect) and Updated Model (Fixed Exponents for Weight Effect)

Parameter Name	Final Model[a] (%RSE, [95% CI])[d]	Updated Model 1[b] (%RSE, [95% CI])[d]	Updated Model 2[c] (%RSE, [95% CI])[d]
Apparent Clearance (CL/F, L/h)	15.6 (3.8, [14.6 – 16.9])	14.8 (4.1, [13.7 – 16.1])	15.3 (4.2, [14.1 – 16.5])
Covariate Effect of Body Weight on CL/F (-)	0.300 (27.8, [0.151 – 0.467])	0.75 Fixed	0.247 (9.9, [0.212 – 0.302])
Covariate Effect of Age on CL/F (-)	-0.592 (13.8, [-0.758 – -0.435])	-0.353 (30.4, [-0.561 – -0.147])	-0.371 (9.8, [-0.444 – -0.304])
Age Threshold for Covariate Effect of Age on CL/F (years)	37.5 (2.7, [31.9 – 43.9])	36.7 (17.2, [25.0 – 49.9])	37.0 (9.7, [30.1 – 44.2])
Covariate Effect on CYP3A4 Inducer Use on CL/F (Fold)	1.13 (4.2, [1.04 – 1.23])	0.94 (7.7, [0.81 – 1.09])	0.94 (8.0, [0.81 – 1.08])
Apparent Volume of Distribution (V/F, L)	374 (2.7, [357 – 396])	354 (2.6, [333 – 371])	369 (3.2, [346 – 391])
Covariate Effect of Body Weight on V/F	0.475 (18.7, [0.304 – 0.652])	1 Fixed	0.334 (9.7, [0.256 – 0.388])
Rate of Transit Absorption for Capsule Process I (KTR_1, 1/h)	5.59 (4.1, [5.14 – 6.04])	5.70 (6.1, [5.08 – 6.43])	5.74 (7.8, [4.90 – 6.75])
Rate of Transit Absorption for Capsule Process II (KTR_2, 1/h)	3.22 (2.2, [3.08 – 3.35])	3.20 (2.8, [3.04 – 3.38])	3.21 (3.5, [2.98 – 3.41])
Rate of Transit Absorption for Capsule Process III (KTR_3, 1/h)	7.60 (3.4, [7.07 – 8.17])	7.67 (3.3, [7.17 – 8.18])	7.67 (4.1, [7.06 – 8.75])
Covariate Effect of Thyroid Cancer on KTR on C1D1 (Fold)	1.27 (4.2, [1.17 – 1.38])	1.26 (4.9, [1.15 – 1.38])	1.25 (5.6, [1.13 – 1.41])
Relative Bioavailability for NSCLC Patients (Fold)	1.38 (4.4, [1.26 – 1.49])	–	–
Covariate Effect of Capsule Process I on Bioavailability in NSCLC Patients (Fold)	0.739 (5.5, [0.661 – 0.821])	–	–
Between Subject Variability for CL/F (% CV)	47.6 (6.2, [44.9 – 50.7])	51.0 (7.9, [47.0 – 54.8])	50.2 (6.0, [47.3 – 53.3])
Between Subject Variability for V/F (% CV)	47.2 (8.3, [43.8 – 51.4])	45.5 (8.8, [42.1 – 49.5])	43.9 (7.1, [40.8 – 47.0])
Covariance Estimate for CL/F-V/F	0.141 (9.0, [0.120 – 0.168])	0.173 (9.7, [0.140 – 0.205])	0.163 (6.9, [0.141 – 1.83])
Between Subject Variability for KTR (% CV)	32.6 (8.6, [30.2 – 35.6])	32.4 (8.9, [29.7 – 35.4])	32.4 (8.7, [29.4 – 35.2])
Between Occasion Variability for Bioavailability (% CV)	36.4 (10.1, [32.7 – 39.7])	40.0 (14.0, [34.8 – 45.1])	39.8 (8.6, [36.1 – 42.8])
Between Occasion Variability for KTR (% CV)	27.0 (16.9, [22.2 – 31.4])	26.1 (25.8, [19.1 – 32.5])	25.7 (14.6, [23.2 – 30.6])
Residual Unexplained Variability for Healthy Volunteers (Proportional) (% CV)	26.5 (2.4, [25.9 – 27.1])	26.5 (2.5, [25.9 – 27.2])	26.5 (3.0, [25.7 – 27.3])
Residual Unexplained Variability for Study BLU-667-1101 (Proportional) (% CV)	37.1 (2.7, [36.1 – 38.1])	37.5 (4.0, [35.9 – 39.0])	37.6 (4.5, [35.8 – 39.2])
Objective Function Value	-5398.939	-4679.063	-4700.608

[a] The final PK model with allometric exponents estimated and PK data from all populations included (Report 267337).
[b] Model 1: only HVs and patients with RET-altered TC were included with allometric exponents fixed to 0.75 for CL/F and 1 for V/F.
[c] Model 2: only HVs and patients with RET-altered TC were included with allometric exponents estimated.
[d] RSE and 95%CI were derived from Sampling importance resampling (SIR).

PK simulations in adolescents

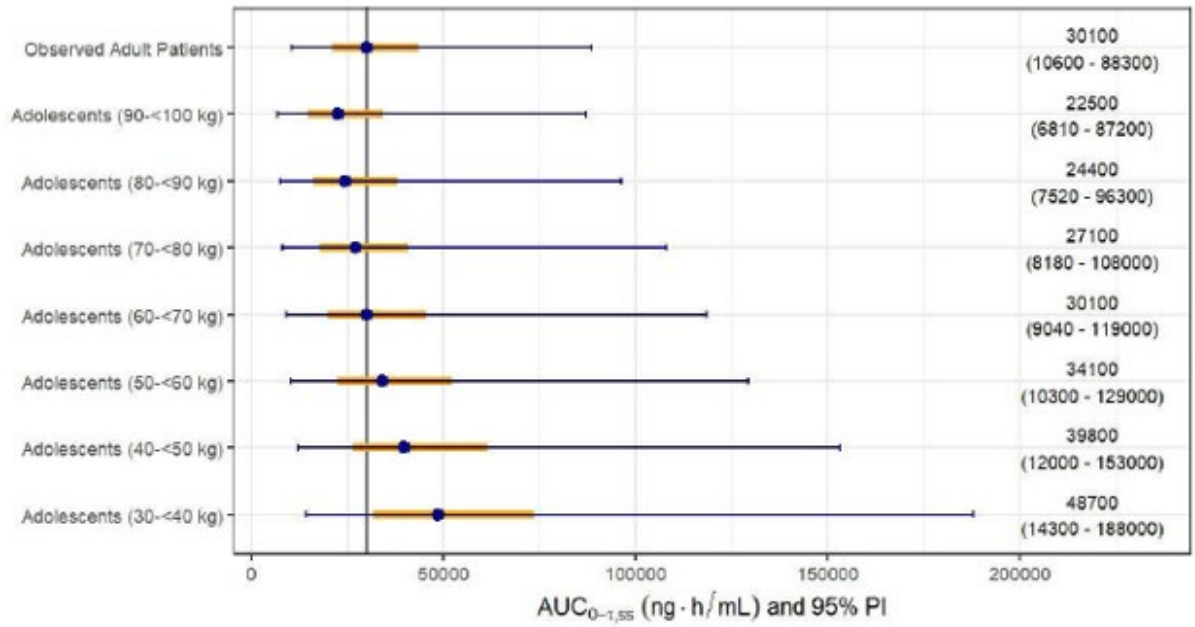
A virtual adolescent subject database was constructed using US growth charts to describe body weights in the age group of 12-<18 years. Simulations were conducted using a pralsetinib QD dose of

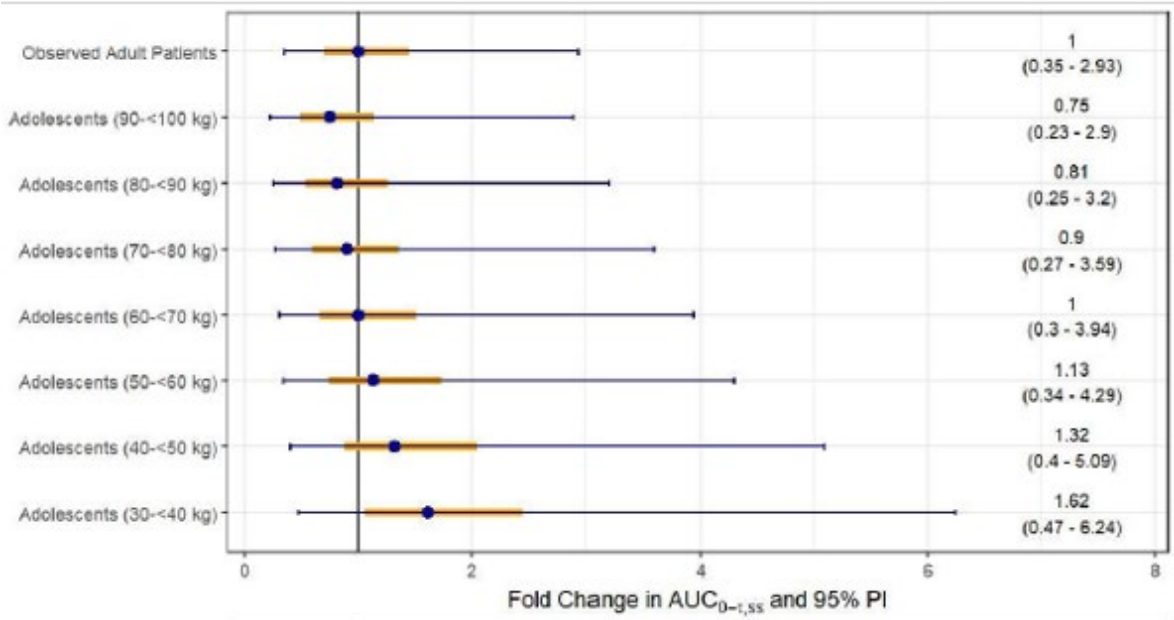
400 mg (capsule Process III). All adolescents were assumed to be patients with RET-altered thyroid cancer with no concomitant medication.

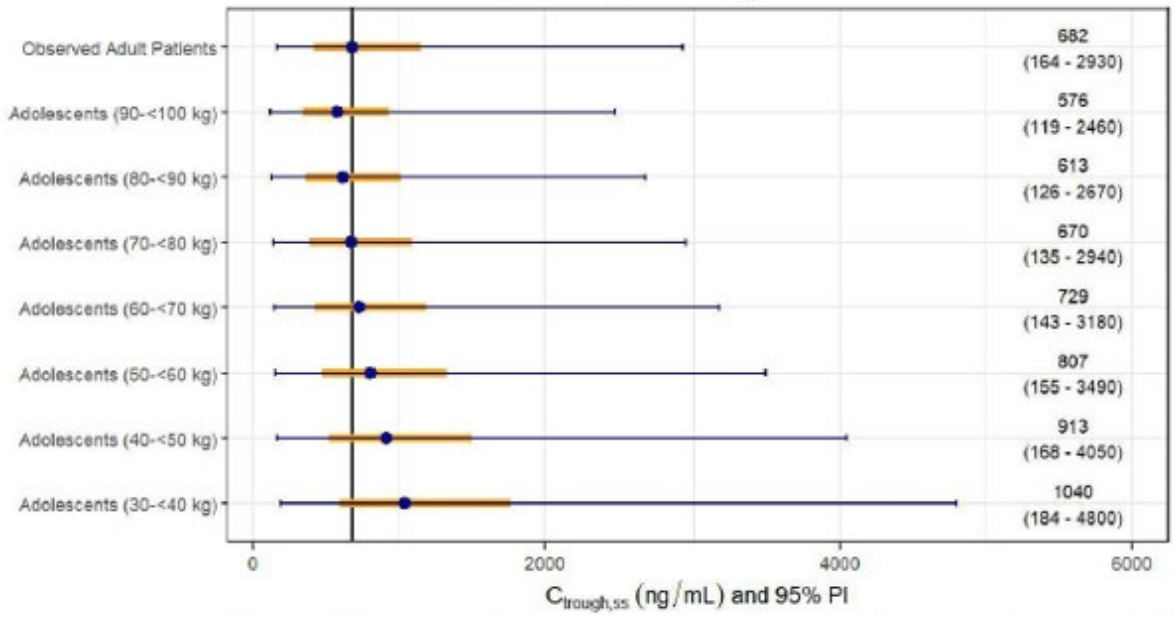
PK exposure metrics (Cmax,ss; Ctrough,ss; AUC0-24h,ss) were derived using the Final Pop PK model, Model 1 or Model 2 using sampling time points of 0, 0.5, 1, 2, 4, 8, 12 and 24 h post-dose on Day 15.

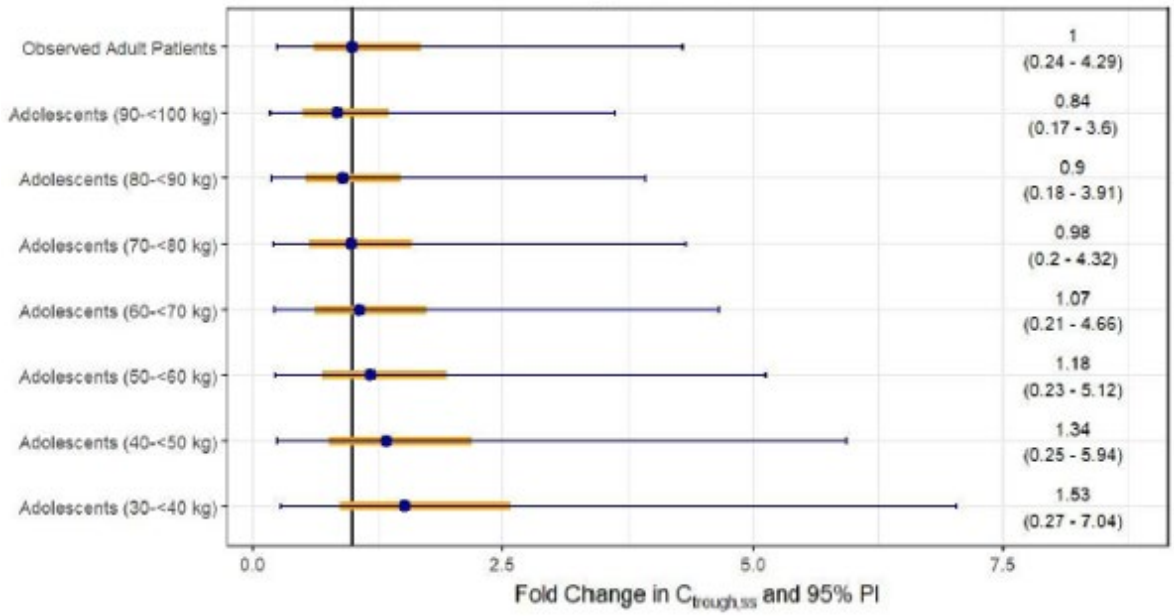
Using Model 1 with fixed weight exponents, the median fold change for AUC0-tau,ss, Ctrough,ss, and Cmax,ss in the lowest body weight range in adolescents (30 to < 40 kg) compared to adult patients with thyroid cancer were 1.62, 1.53, and 1.46, respectively. See Figure 3.

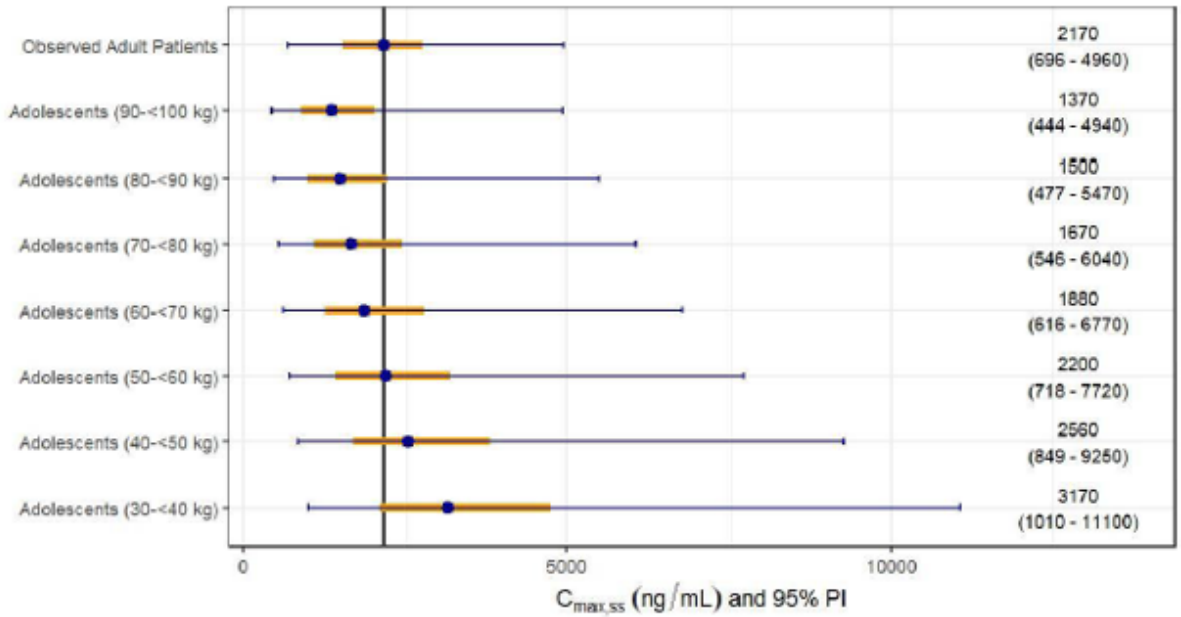
Figure 3 Model Predicted Pralsetinib Exposure for Adolescents by Weight Group – Model 1

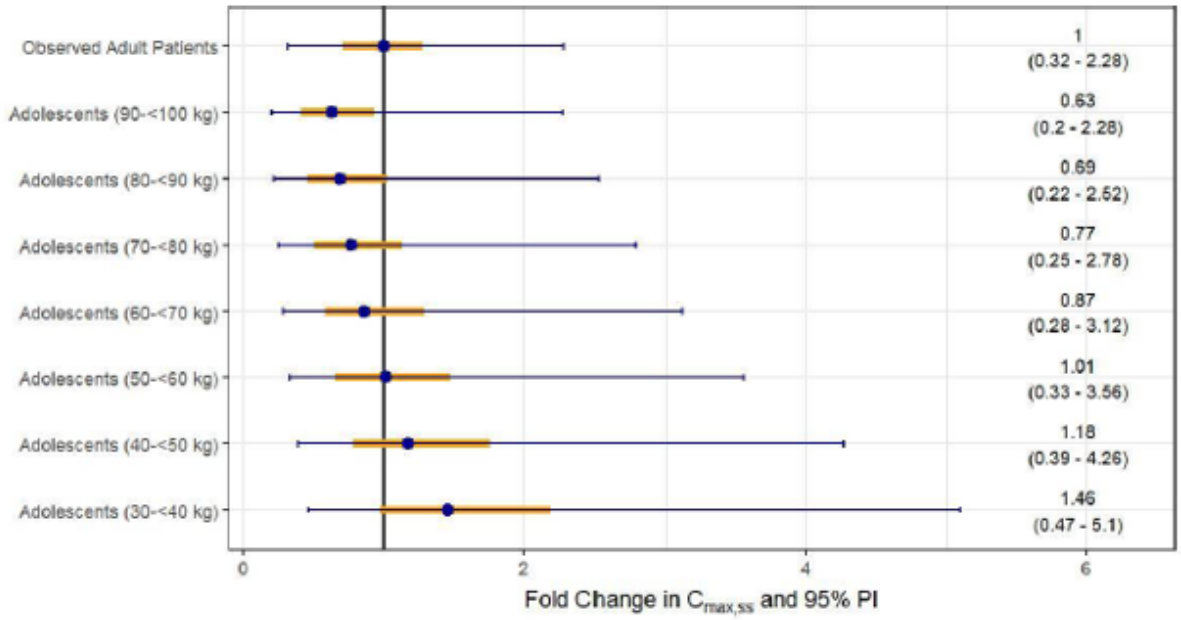



Observed Adult Patients
Adolescents (90-<100 kg)
Adolescents (80-<90 kg)
Adolescents (70-<80 kg)
Adolescents (60-<70 kg)
Adolescents (50-<60 kg)
Adolescents (40-<50 kg)
Adolescents (30-<40 kg)
1 (0.35 - 2.93)
0.75 (0.23 - 2.9)
0.81 (0.25 - 3.2)
0.9 (0.27 - 3.59)
1 (0.3 - 3.94)
1.13 (0.34 - 4.29)
1.32 (0.4 - 5.09)
1.62 (0.47 - 6.24)
0
2
4
6
8
Fold Change in $AUC_{0-t,ss}$ and 95% PI


Observed Adult Patients
Adolescents (90-<100 kg)
Adolescents (80-<90 kg)
Adolescents (70-<80 kg)
Adolescents (60-<70 kg)
Adolescents (50-<60 kg)
Adolescents (40-<50 kg)
Adolescents (30-<40 kg)
682 (164 - 2930)
576 (119 - 2460)
613 (126 - 2670)
670 (135 - 2940)
729 (143 - 3180)
807 (155 - 3490)
913 (168 - 4050)
1040 (184 - 4800)
0
2000
4000
6000
$C_{trough,ss}$ (ng/mL) and 95% PI


Observed Adult Patients
Adolescents (90-<100 kg)
Adolescents (80-<90 kg)
Adolescents (70-<80 kg)
Adolescents (60-<70 kg)
Adolescents (50-<60 kg)
Adolescents (40-<50 kg)
Adolescents (30-<40 kg)
1 (0.24 - 4.29)
0.84 (0.17 - 3.6)
0.9 (0.18 - 3.91)
0.98 (0.2 - 4.32)
1.07 (0.21 - 4.66)
1.18 (0.23 - 5.12)
1.34 (0.25 - 5.94)
1.53 (0.27 - 7.04)
0.0
2.5
5.0
7.5
Fold Change in $C_{trough,ss}$ and 95% PI

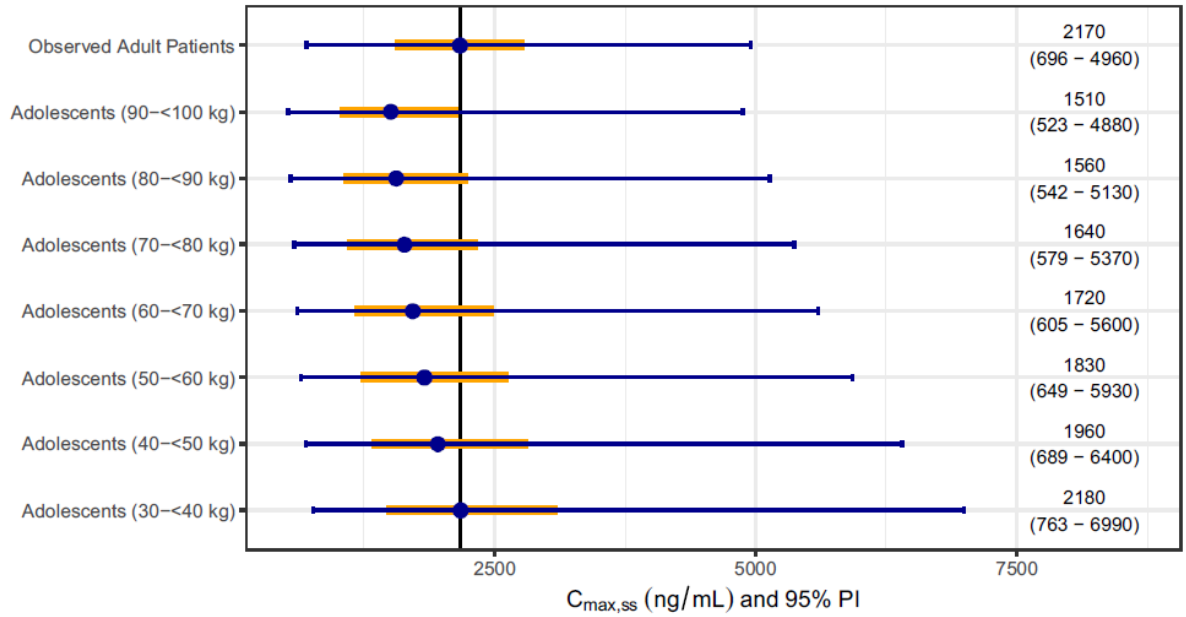




The solid black line represents the median of the reference group ("Observed Adult Patients"), defined as RET-altered thyroid cancer patients receiving 400 mg dose of pralsetinib QD on Day 15 (steady state) (data sourced from NCA Report BLUE202006, Table 4). The orange box represents the interquartile range between 25th – 75th percentiles of the simulations. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) of the subgroup based on 1000 simulated subjects within each group including between subject variability of the simulations.

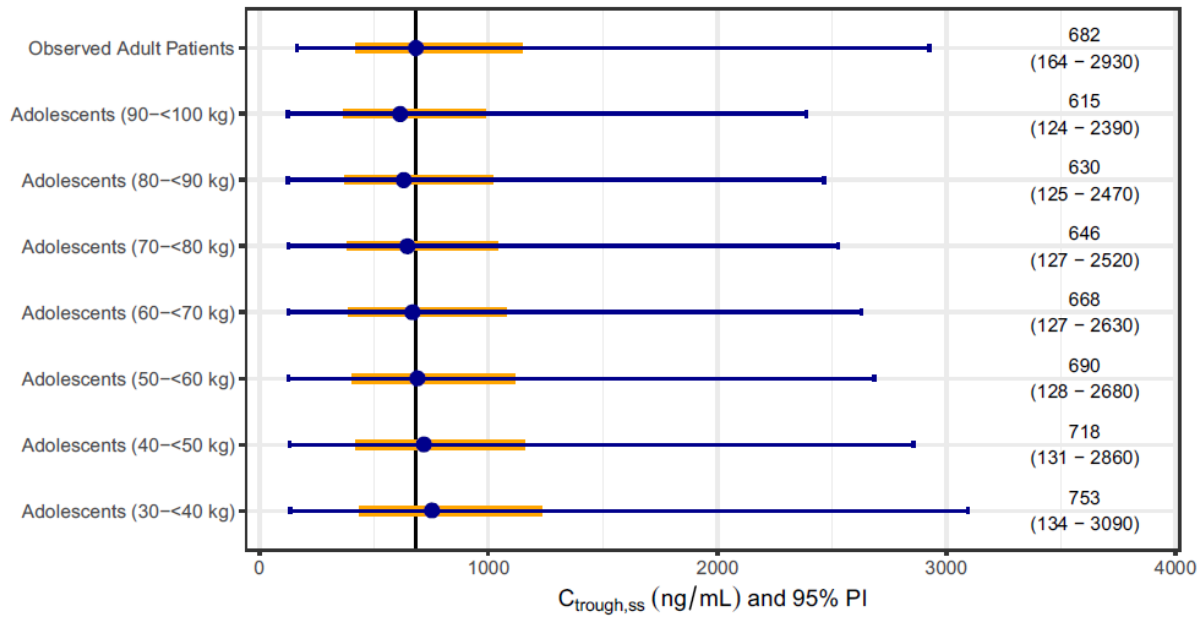
Using Model 2 or the Final Pop PK model with estimated exponents for weight effects, adolescents are expected to achieve similar PK exposure in terms of Cmax, Ctrough and AUC0-24h at steady state compared to the adult reference group administered 400 mg QD. See Figures 1, 3 and 5 (simulations of the Final Pop PK model).

Figure 1: Model Predicted Effect of Weight on $C_{max,ss}$ in Adolescents



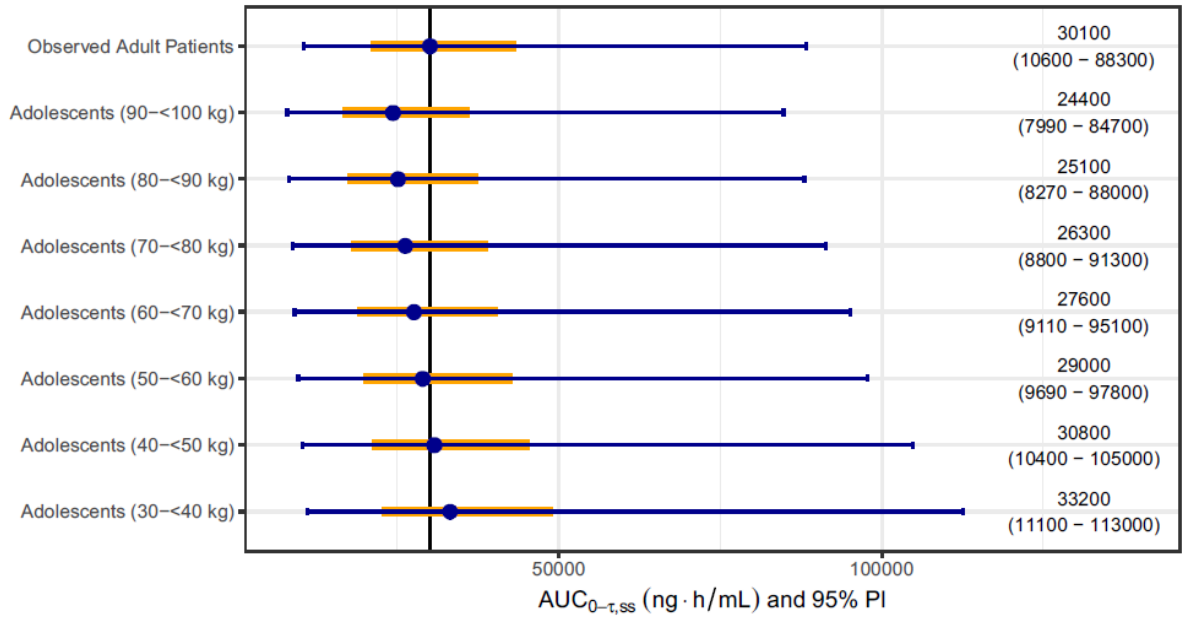
The solid black line represents the median of the reference group ("Observed Adult Patients"), defined as RET-altered thyroid cancer patients receiving 400 mg dose of pralsetinib QD on Day 15 (steady state). The orange box represents the inter-quartile range between 25^{th} – 75^{th} percentiles of the simulations. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) PIs based on 1000 simulated subjects within each group including between subject variability of the simulations.

Figure 3: Model Predicted Effect of Weight on $C_{trough,ss}$ in Adolescents



The solid black line represents the median of the reference group ("Observed Adult Patients"), defined as RET-altered thyroid cancer patients receiving 400 mg dose of pralsetinib QD on Day 15 (steady state). The orange box represents the inter-quartile range between 25^{th} – 75^{th} percentiles of the simulations. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) PIs based on 1000 simulated subjects within each group including between subject variability of the simulations.

Figure 5: Model Predicted Effect of Weight on $AUC_{0-\tau,ss}$ in Adolescents



The solid black line represents the median of the reference group ("Observed Adult Patients"), defined as RET-altered thyroid cancer patients receiving 400 mg dose of pralsetinib QD on Day 15 (steady state). The orange box represents the inter-quartile range between 25^{th} – 75^{th} percentiles of the simulations. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) PIs based on 1000 simulated subjects within each group including between subject variability of the simulations.

Assessor's comments:

Regarding quantification of pralsetinib in plasma samples from Study BO42863 (BLU-667-1101), all samples were analysed within established storage stability.

Data from study BO42863 was fitted to a previous model with re-estimation of model parameters and random effects. This included additional data from patients with NSCLC and RET-altered thyroid cancer (including RET mutation-positive MTC). A report of model update was submitted with this variation (Report 267337) with a more recent data cut (June 2021). The previous Pop PK model was a one-compartment disposition model with transit absorption and linear elimination. The number of transit absorption compartments varied dependent upon the capsule Process. The statistically significant covariates included in the final updated model were age, body weight, disease status, capsule process, and concomitant CYP3A4 inducer use. Parameters of the final model were estimated with adequate precision. BSV and BOV were moderately high. Eta shrinkage was 32.5%, 11.7%, 24.3% for KTR, CL/F and V/F while shrinkage of BOV estimates were very high (range: 39%-90.7%) and thus not informative on the individual level. Parameter estimates were verified by importance resampling and included the 95%CI. GoF plots did not indicate major misspecification but some slight trends were observed in WRES plots. VPCs indicated the updated model could capture the observations from patients with RET-altered thyroid cancer and RET-mutation positive MTC. Forest plots showed that capsule process II and III had impact on PK exposure (Cmax and AUC) in a reference subject compared to capsule process I (the 95% prediction intervals fell outside the 80-125% range) in patients with NSCLC. This effect was not seen in patients with thyroid cancer. Simulations indicated that although Cmax was almost similar in patients with thyroid cancer, Tmax differed between the capsule processes I, II and III (Figure 48). The PK of NSCLC patients was different from HV and TC patients, but the factor of relative bioavailability incorporated in the final model seem to provide adequate adjustment for the difference. The effect of weight was incorporated in the final Pop PK model by allometric scaling using estimated exponents. Adult TC data could be fitted across all weight percentiles at C1D1 and C1D15. Few data were presented in the lowest weight percentiles <60kg and

60 kg to <71kg for adult TC patients. Eta plots for IIV in CL/f and V/F did not indicate any trends between parameter estimates and weight in the adult population. The final PopPK model appears overall acceptable and is deemed useful for descriptive purposes in the adult TC patient population.

The dose selection proposed for adolescent patients is based on an allometric extrapolation exercise using the population PK model developed in adult healthy volunteers and patients. There are no data in adolescents. The estimated allometric exponents on disposition parameters (CL and V) demonstrate a low impact (0.3 and 0.475, respectively) of body weight on the PK properties of pralsetinib. This situation could be influenced by a narrow distribution of body weights or a biased enrolment of individuals. Simulations using an updated version of the Final Pop PK model without NSCLC data "Model 2" did not indicate much impact of weight for virtual TC adolescents across a weight range of 30-100 kg. The use of fixed exponents for effects of weight was tested using an updated version of the Final Pop PK model without NSCLC data "Model 1" and resulted in a slightly worse model fit of the adult data. It is acknowledged that model parameters between the Final Pop PK model, Model 1 and Model 2 are only slightly different, but the simulation or extrapolation properties of the models are quite different due to the different magnitudes of the relationships between bodyweight and pharmacokinetic parameters. Using Model 1 with fixed exponents of weight effect, patients in the lowest bodyweight category (30-40 kg) were estimated to have a median fold change for AUC0-tau,ss, Ctrough,ss, and Cmax,ss of 1.62, 1.53, and 1.46 compared to an adult patient, respectively.

Thyroid cancers are considered biologically similar diseases in adults and in adolescents and no PK difference of pralsetinib is expected in adolescents due to maturation. It is suggested, the body weight range in the adult TC population (32.1 kg to 149 kg) will overlap with the body weight range expected in 12-<18-year-old TC patients (29.2 kg to 97 kg, based on US population. Diseased adolescents with TC are not expected to have lower body weights than healthy adolescents, and the onset of puberty is not expected to be altered in adolescents with TC. Eight patients ≥18 years in Study BLU-667-1101 had body weights below 40 kg. Six of them maintained the 400 mg dose throughout treatment. However, it is not clear whether these patients had TC. The lightest adult TC patient in Study 1101 weighted 32.1 kg which is close to the lowest body weight of 30 kg set for adolescents. Thus, it is considered more appropriate to define the lowest adolescent bodyweight category from 25-40 kg.

The PK bridge is based on adult data and very few adult patients had a body weight <60 kg. There are no data in adolescents. Therefore, a more conservative approach using fixed exponents for the allometric scaling of weight effects is considered necessary for extrapolation to adolescent patients. The final Pop PK model including NSCLC data can be accepted if updated with fixed exponents of weight effects. The fixed allometric scaling exponents are considered to have a physiological basis, as also outlined in the EMAs modelling and simulation Q&A (November 2018) document. A further argument in favour of fixed exponents of weight effects is the toxicity profile of Graveto, with a high incidence of SAEs (54.4%), AEs leading to death (13.1%) and permanent discontinuation due to AEs (18%), is already considered quite serious, and might become even worse in case of higher exposures.

For these reasons, the PK major objection is not considered resolved (**new MO**)

Exposure-response modelling

Data came from study BO42863 with 497 patients available for the integrated safety analysis (312 RET fusion-positive NSCLC patients, 177 RET mutation-positive MTC patients, and 28 other RET-altered TC patients), and 188 and 164 for the efficacy evaluations of RET-altered TC and RET mutation-positive MTC, respectively.

The pralsetinib exposure measures were starting dose and average plasma concentration (Cave); derived from the population PK model until the time of event or censoring. For PFS and the grade 3+ AEs, extended Cox models were developed, where Cave was specified as time-varying. The time-

dependent models were developed to overcome the likely bias observed in graphical analysis due to dose titration from 300 mg to 400 mg. The exposure metrics were calculated as the average exposure within the defined time period. The time periods for efficacy outcomes were defined as the intervals between measures of efficacy (computerized tomography scans). The time periods for safety outcomes were defined as 28 days in duration, working backwards from the safety event or end of study participation if the event did not occur. Exposure metrics were scaled to a relative change in concentration equivalent to approximately increasing the dose of pralsetinib concentration from 300 mg to 400 mg. For Cave, this represented an increase in pralsetinib concentration of 312.5 ng/mL for thyroid cancer patients.

The final time-varying Cox model for PFS in the RET mutation-positive MTC population showed improvement in PFS as exposure increased, with a corresponding HR of 0.78 (95% CI 0.67 – 0.91, p<0.001) for every 312.5 ng/mL increase in Cave (≈100 mg QD). Prior systemic cancer therapy was identified as a significant covariate in the final Cox model for PFS. Results from the efficacy analysis in the RET-altered TC population were largely comparable to those in the RET mutation-positive MTC population.

Table 9: Final PFS Time-Varying Exposure-Response Model: RET Mutation-positive MTC

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	0.78 (0.67 – 0.91)	< 0.001
Prior Systemic Cancer Therapy = No	0.41 (0.23 – 0.74)	< 0.001

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for prior systemic cancer therapy are relative to 'yes' category.

The final time-varying exposure-response model for all grade 3+ AEs in the safety population showed increased risk of events as exposure increased, with a corresponding HR of 1.14 (95% CI 1.10 – 1.17, p < 0.001) for every 312.5 ng/mL increase in Cave. Age group was identified as a significant covariate in the final Cox model for all grade 3+ AEs.

Table 12: Final All Grade 3+ Time-Varying Exposure-Response Model

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	1.14 (1.10 – 1.17)	< 0.001
Age Group ≥65 years	1.69 (1.36 – 2.09)	< 0.001

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for age group are relative to <65 years.

The final time-varying exposure-response model for grade 3+ anaemia in the safety population showed increased risk of events as exposure increased, with a corresponding HR of 1.30 (95% CI 1.21 – 1.39, p < 0.001) for every 312.5 ng/mL increase in Cave. Although BSA, geographic region, and sex were identified as potential covariates in the graphical analysis, none were significant in the Cox model after pralsetinib exposure was accounted for.

Table 13: Final Grade 3+ Anemia Time-Varying Exposure-Response Model

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	1.30 (1.21 – 1.39)	< 0.001

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for baseline ECOG score are relative to a score of 0.

The final time-varying exposure-response model for grade 3+ pneumonia in the safety population showed increased risk of events as exposure increased, with a corresponding HR of 1.23 (95% CI 1.14 – 1.32, p < 0.001) for every 312.5 ng/mL increase in Cave. Baseline ECOG score was identified as a significant covariate in the final Cox model.

Table 14: Final Grade 3+ Pneumonia Time-Varying Exposure-Response Model

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	1.23 (1.14 – 1.32)	< 0.001
Baseline ECOG = 1 or 2	2.02 (1.10 – 3.71)	0.02

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for baseline ECOG score are relative to a score of 0.

The final time-varying Cox model for grade 3+ hypertension in the safety population showed no relationship between grade 3+ hypertension events and average pralsetinib exposure. Age group, was identified as a significant covariate in the final model where patients >65 years of age at 2.2-fold increase in the risk of an event (p < 0.001).

Table 15: Final Grade 3+ Hypertension Time-Varying Exposure-Response Model

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	1.05 (0.98 – 1.12)	0.19
Age Group ≥65 years	2.20 (1.45 – 3.34)	< 0.001

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for age group ≥65 years are relative to age <65 years.

The final time-varying Cox model for grade 3+ lymphopenia in the safety population showed increased risk of events as exposure increased, with a corresponding HR of 1.23 (95% CI 1.10 – 1.36, p < 0.001) for every 312.5 ng/mL increase in Cave. Race was identified as a significant covariate in the final model.

Table 16: Final Grade 3+ Lymphopenia Time-Varying Exposure-Response Model

Parameter	Hazard ratio (95% CI)	p value
C_{ave}	1.23 (1.10 – 1.36)	< 0.001
Non-white Race	0.09 (0.03 – 0.30)	< 0.001

For C_{ave}, the hazard ratio and 95% CI shown are per 312.5 ng/mL. The hazard ratios for non-white race is relative to subjects of white race.

Assessor's comments:

For evaluation of potential relations between exposure and PFS in the RET mutation-positive MTC population and grade 3+ safety events in the safety population (including NSCLC patients), longitudinal Cox models were applied to capture the change in dose during the treatment period. The hazard ratios (HR) were estimated per 312.5 ng/mL Cavg increase which corresponds to a dose increment of 100 mg QD.

For PFS, the HR for Cave was 0.78 which indicated an improvement in PFS as exposure increased in the RET mutation-positive MTC population. No prior systemic cancer therapy was as a significant covariate with a HR of 0.41.

For all grade 3+ AEs in the safety population, the HR for Cave was 1.14 indicating increased risk of events as exposure increased. Age group ≥65y was a significant covariate with a HR of 1.69.

For grade 3+ anaemia in the safety population, the HR for Cave was 1.30 indicating increased risk of events as exposure increased. No covariates were significant.

For grade 3+ pneumonia in the safety population, the HR for Cave was 1.23 indicating increased risk of events as exposure increased. Baseline ECOG score 1 or 2 was a significant covariate with HR 2.02.

For grade 3+ hypertension in the safety population, no relationship to pralsetinib exposure was shown. Age group ≥65y was identified as a significant covariate with HR 2.20.

For grade 3+ lymphopenia in the safety population, the HR for Cave was 1.23 indicating increased risk of events as exposure increased. Non-white race was identified as a significant covariate with a HR of 0.09.

Only 10 subjects experienced at least one grade 3+ pneumonitis AEs in the safety dataset. No model was applied.

The clinical pharmacology of pralsetinib was studied in the ongoing Phase I/II efficacy and safety study in patients with RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered solid tumours (BO42863) only data from patients with RET-altered thyroid cancers were included in the NCA analysis for the current submission.

Five Phase I clinical pharmacology studies investigated the single-dose PK of pralsetinib in healthy subjects (which were already assessed during the initial MAA): Study BLU-667-0101 (hereinafter referred to as BP42858): The effect of food, compared with fasted conditions, on the relative bioavailability of pralsetinib 100 mg capsules.

Study BLU-667-0102 (hereinafter referred to as BP42859): Bioequivalence of pralsetinib 100 mg tablets and 100 mg capsules.

Study BLU-667-0103 (hereinafter referred to as BP42860): Mass-balance of pralsetinib after single-dose administration of ~310 mg (~100 µCi) [14C] pralsetinib (administered as 3 × 100 mg capsules together with 1 capsule containing ~10 mg/100 µCi [14C] pralsetinib). In addition, plasma, urine, and faeces samples from this study were used for analyzing the metabolic profile of pralsetinib.

Study BLU-667-0104 (hereinafter referred to as BP42861): A 2-part drug-drug interaction study conducted in healthy subjects to assess the effect of concomitant (steady state) administration of itraconazole (a strong CYP3A and P-gp inhibitor) or rifampin (a strong CYP3A and P-gp inducer) on the single-dose PK of pralsetinib administered as 100 mg capsules.

Study BLU-667-0105 (hereinafter referred to as BP42862): A drug-drug interaction study conducted in healthy subjects to assess the effect of concomitant administration of esomeprazole (a proton pump inhibitor [PPI] drug that inhibits gastric acid secretion) and gastric pH alteration on the single-dose PK of pralsetinib administered as 100 mg capsules.

Study BO42863 is an ongoing Phase I/II, first-in-human study to evaluate the safety, efficacy, tolerability, PK, and pharmacodynamics of pralsetinib in patients with advanced, unresectable, RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered solid tumours. Pralsetinib was administered as immediate-release hydroxypropyl methylcellulose (HPMC) hard capsules to all patients in this study. The study included two phases.

1. a dose-escalation phase (Phase I) to determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D), based on administration of pralsetinib at doses of 30 to 600 mg QD; the MTD/RP2D was determined to be 400 mg QD.

2. an expansion (registration-enabling) phase (Phase II) to further evaluate the safety, tolerability, and PK of pralsetinib, and to assess clinical efficacy, at the MTD/RP2D.

The PK population consists of all patients in Study BO42863 who received at least one dose of pralsetinib (60-600 mg QD or 100/100, 200/100 mg twice daily [BID]) and from whom at least one post dose PK sample was collected. As of the CCOD of 12 April 2021, a total of 224 thyroid cancer patients (195 MTC patients and 29 other thyroid cancer patients, including 26 PTC, 1 ANPTC, 1 poorly differentiated thyroid cancer, 1 poorly differentiated carcinoma), irrespective of their RET status, met the analysis inclusion criteria and were included in the PK population.

Absorption

Following administration of single oral doses of pralsetinib ranging from 60-600 mg, pralsetinib was rapidly absorbed, with a median time to achieve maximum plasma concentration (Tmax) around 2 hours post-dose. After multiple QD dosing, the Tmax was similar with a median around 2.1 hours.

Co-administration with a high-fat meal increased pralsetinib exposure (~2-fold increase in maximum plasma concentration (Cmax) 2.2-fold increase in area under the plasma concentration-time curve [AUC]).

Gastric pH altering agent esomeprazole had no clinically significant effect on exposure (25% decrease in Cmax, and 15% decrease in AUC).

Distribution

Apparent volume of distribution (V/F, L) was 374 (2.7% standard error).

Elimination

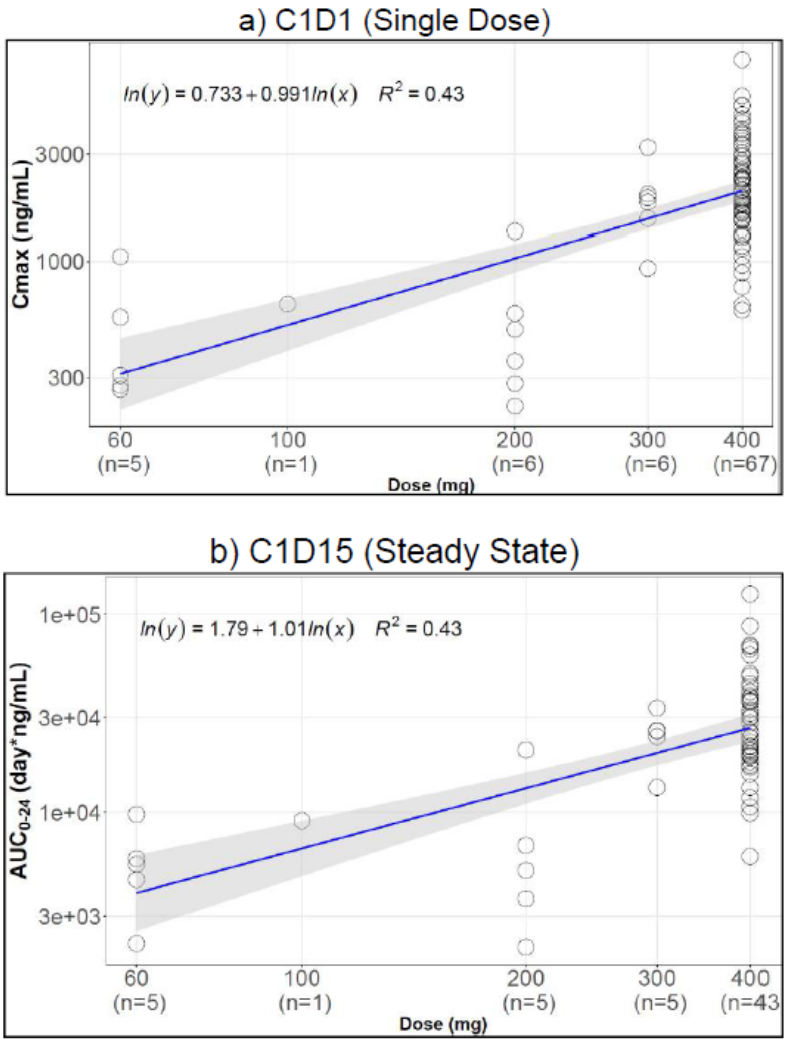
In the human mass balance study, unchanged pralsetinib was the predominant drug-related moiety. Oxidative and glucuronide metabolites were detected in small to trace amounts in plasma, urine, and faeces and were primarily mediated by CYP3A4 and UGT1A4, respectively.

The mean elimination half-life (t1/2) was 16.4 hours following a single 400 mg dose.

Dose proportionality and time dependencies

The exposure of pralsetinib increased proportional to the dose within the dose range tested (30-600 mg) in Study BO42863.

Figure 22 Dose Proportionality for Pralsetinib Systemic Exposure C_{max} and AUC_{0-24} on C1D15 (Steady State) Following Multiple Once Daily Doses (60–400 mg, All Thyroid Patients)



Blue Line: Linear Regression; Grey Shaded Area=90%CI; n=number of patients in each dose level
Source: Study BO42863 Update CSR, Report 1109798, Figure 13.

Approximately 2-fold accumulation was observed at steady state following once daily dosing.

No time dependent changes in pralsetinib PK was observed when comparing the trough concentrations C1D16, C2D1, C3D1 and C4D1 at 400 mg dose with C1D15.

Target and special populations

At the 400 mg dose level, the NCA of pralsetinib PK indicated that exposure to pralsetinib was generally similar in patients with all thyroid cancers (MTC and thyroid) and in healthy subjects. This observation was consistent with the covariate analysis of the pooled population PK model indicating that disease status (patients with RET-altered thyroid cancers versus healthy subjects, and patients with NSCLC versus RET-altered thyroid cancers) had no clinically relevant effect on the bioavailability of pralsetinib.

After single- and repeat-dose administration of pralsetinib at a dose of 400 mg, the interindividual variability (calculated using NCA) for Cmax and AUC parameters ranged between approximately 41%

and 68% in patients with all thyroid cancers. With a single dose of 400 mg administered to healthy subjects under fasted conditions, the inter-individual variability for PK parameters ranged between approximately 40% and 50%.

At the 400 mg dose level, the intra-individual variability was generally higher (67%) in patients with all thyroid cancers than in healthy subjects. Across the 4 studies in healthy subjects in which single doses of 200 or 400 mg pralsetinib alone were administered, the intra-individual variability ranged between 28.5% and 43.2% for Cmax, and between 23.1% and 44.0% for AUC parameters.

Assessor's comments:

The exposure to pralsetinib at 400mg was similar in patients with all thyroid cancers (MTC and thyroid) and in healthy subjects, only the intra-individual variability was generally higher (67%) in patients with all thyroid cancers than in healthy subjects.

No clinical studies in special populations have been conducted. The effects of intrinsic factors on the PK of pralsetinib were evaluated using covariate analysis of the final population PK model for pralsetinib.

Based on the pooled population PK analysis, sex, race, disease status (patients with NSCLC versus patients with RET-altered thyroid cancers) were predicted to have no clinically relevant effects on the bioavailability of pralsetinib.

Age was found to be a statistically significant covariate on CL/F, where CL/F was predicted to decrease for patients > 37.5 years of age.

Increasing body weight was predicted to increase CL/F and V/F.

Overall, the magnitude of the effect of these covariates on pralsetinib exposure was within < 0.5-fold change compared with the reference patient with RET-altered thyroid cancer having the median age (51 years) and body weight (71 kg) of the analysis population, with the 95% PI overlapping with the 80% to 125% range for the reference patient. Age and body weight were therefore predicted to have no clinically relevant effect on the bioavailability of pralsetinib.

Assessor's comments:

The extrapolation from adults to adolescents is solely based on the Pop-PK model, which is not considered robust for this purpose. There are no data on subjects < 18 years of age.

It is acknowledged that the Applicant conducted evaluations of dose modifications and AEs among adult patients treated with pralsetinib at a dose of 400 mg QD in Study BO42863 which showed similar frequencies among body weight groups (29 to < 60 kg, 60 to 75 kg, and > 75 kg), the lowest of which (29 to < 60 kg) coincides with the anticipated weight range in adolescent patients.

Age and weight were found to be statistically significant covariates on CL/F in opposite directions.

Taken together the pharmacokinetics in adolescents is not considered clarified.

As hepatic elimination is a major route of excretion for pralsetinib, hepatic impairment may result in increased plasma concentrations of pralsetinib. However, in the pooled population PK analysis of pralsetinib, no correlation was observed between CL/F and markers of hepatic function (ALT, AST,

bilirubin, and albumin), and no relevant difference in CL/F was observed among patients with mild (n=62) or moderate (n=2) hepatic impairment, as compared with patients with normal hepatic function (n=624).

The mass-balance study in healthy subjects demonstrated that the renal excretion of

pralsetinib is low, with only 6.1% of the administered dose ([14C] pralsetinib) recovered in urine. In the pooled population PK analysis of pralsetinib, no correlation was observed between CL/F and markers of renal function

(CLcr, eGFR), and no relevant difference in CL/F was observed among patients with mild

(n=317) or moderate (n=41) renal impairment, as compared with patients with normal renal

function (n=336).

Assessor's comments:

The SmPC recommendations on renal and hepatic impairment were established at first MA assessment and are accepted, as there are no new data.

Pharmacokinetic interaction studies

A combined p-glycoprotein (P-gp) & strong CYP3A inhibitor, itraconazole, increased pralsetinib exposure (1.8-fold increase in Cmax, 3.5-fold increase in AUC).

A combined P-gp and strong CYP3A inducer, rifampin, decreased pralsetinib exposure (30 % decrease in Cmax and 68% decrease in AUC).

Assessor's comments:

The SmPC recommendations on interactions were established at first MA assessment and are accepted, as there are no new data.

3.3.3. Pharmacodynamics

Mechanism of action

Pralsetinib is a tyrosine kinase inhibitor that targets oncogenic RET fusions and mutations, including V804 gatekeeper mutations associated with resistance to other therapies. RET-fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signalling pathways, leading to uncontrolled cell proliferation. Pralsetinib exhibited antitumor activity in cultured cells and animal tumour implantation models representing multiple tumour types harbouring oncogenic RET-fusions or mutations (KIF5B-RET, CCDC6-RET, RET M918T, RET C634W, as well as the V804L and V804M mutants associated with cabozantinib and vandetanib resistance). Pralsetinib was 12-, 14-, and 40-fold more potent on RET in a cellular setting compared with representatives of the janus kinase (JAK), VEGFR2, and fibroblast growth factor receptor (FGFR) families. Pralsetinib demonstrated prolonged survival in intracranial mouse models of KIF5B-RET and CCDC6-RET compared with vehicle controls. Antitumor activity correlated with pralsetinib exposures and pharmacodynamic modulation of tumour biomarkers, including direct inhibition of RET kinase activity.

Primary and secondary pharmacology

In vitro, pralsetinib inhibited several oncogenic RET fusions and mutations (CCDC6-RET, RET V804L, RET V804M, and RET M918T) with IC50 values of less than 0.5 nM. In a broad panel of purified enzyme assays, pralsetinib demonstrated selectivity for RET with 81-fold selectivity over vascular endothelial growth factor 2 (VEGFR2).

QTc

The potential for pralsetinib to prolong the QTc was evaluated as a secondary objective of Study BO42863, and was analysed for a subset of patients from all indications (i.e., patients with advanced, unresectable, RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered solid tumours). Patients were excluded from the study, according to predefined exclusion criteria, if they had a QT interval corrected for heart rate by the Fridericia method (QTcF) value of > 470 ms, uncontrolled cardiovascular disease, or poorly controlled hypertension. Cardiodynamic ECG assessments were analysed in a subset of 34 patients treated with pralsetinib 400 mg QD in Phase II of Study BO42863 (expansion [registration-enabling] phase) to evaluate the effect of pralsetinib on QTcF and other ECG parameters (ie, heart rate, PR interval, and QRS duration) with a cut-off date of 18 November 2019. Continuous 12-lead Holter ECG recordings and plasma samples were taken in triplicate at predefined time points in Cycle 1, relative to administration of pralsetinib:
Day 1 – Pre-dose (45, 30, and 15 minutes; the mean value from these 3 time points comprised the "baseline" value); post-dose (0.5, 1, 2, 4, 6, 8, and 24 hours).

Day 2 – Post-dose (24 hours).

Day 15 (Steady State) – Pre-dose (45, 30, and 15 minutes); Post-dose (0.5, 1, 2, 4, 6, 8, and 24 hours).

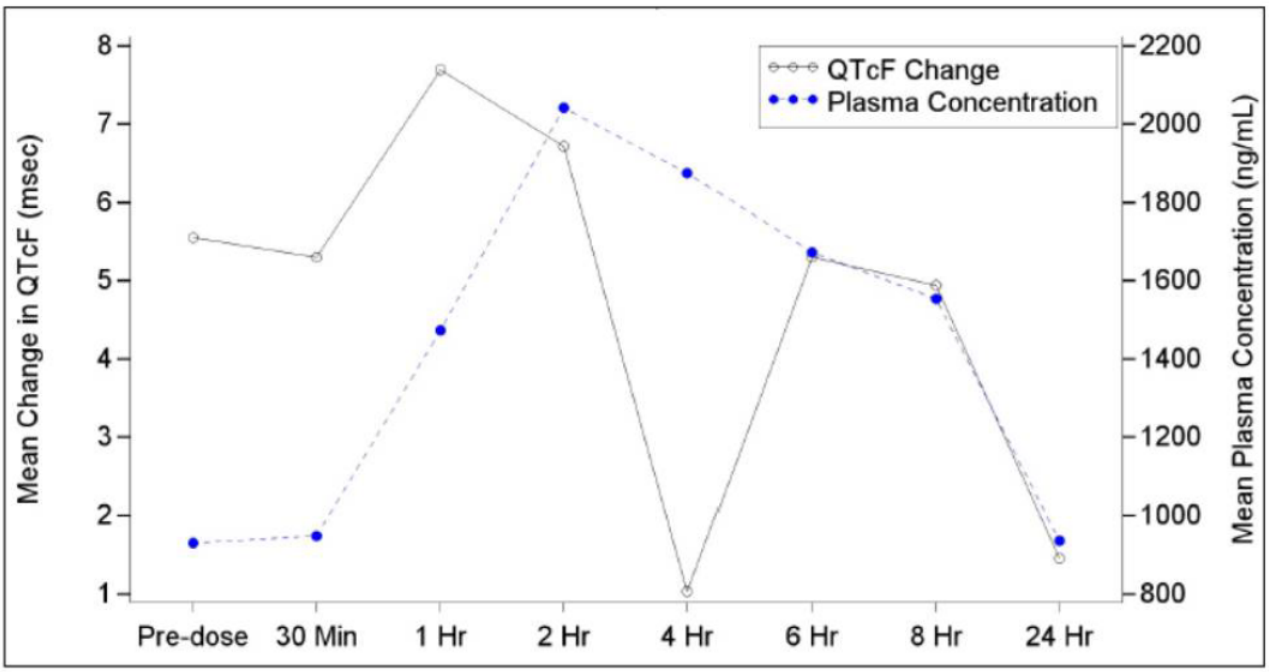
Day 16 – Post-dose (24 hours).

The primary outcome measure for cardiac safety was an analysis of the regression relationship between ΔQTcF and the plasma concentration of pralsetinib at matching times post-dose. The endpoint outcome was defined by a comparison to 20 ms of the upper bound of the 2-sided 90% CIs (equivalent to 1-sided 95% upper confidence bound) at the geometric mean Cmax for pralsetinib with the 400 mg QD dose in the subset analysed.

Pralsetinib did not result in clinically relevant or statistically significant prolongation of QTcF at steady state plasma concentrations after administration at a dose of 400 mg QD (n=34). The mean baseline QTcF (on Day 1) was 416.0 ms. On Day 15 (steady state), the mean ΔQTcF was 5.6 ms at the pre-dose time point, and above 5 ms at all post-dose time points except 4 hours (1.0 ms), 8 hours (4.9 ms), and 24 hours (pre-dose) (1.5 ms) (Figure 1). The largest mean ΔQTcF was observed at 1-hour (7.7 ms) post-dose.

No patient in the subset (n=34) had a QTcF > 500 ms. Two patients had a QTcF > 480 but ≤ 500 ms after baseline. Six patients had a QTcF > 450 but ≤ 480 ms. Four of these 6 patients had a QTcF > 450 ms but ≤ 480 ms only after baseline. Four patients had a ΔQTcF of > 30 but ≤ 60 ms. All of these changes were seen on Day 15. No patient had a ΔQTcF of > 60 ms.

Figure 1: Observed Mean Pralsetinib Concentration in Plasma and Change from Baseline in QTcF over Time after Administration of Pralsetinib 400 mg QD on C1D15 (Steady State) (Study BO42863)



Abbreviations: C1D15 = Cycle 1 Day 15; QD = once daily; QTcF = QT interval corrected for heart rate by the Fridericia method.
Note: The baseline reference time for change in QTcF was Cycle 1 Day 1.
Source: BO42863, Cardiac Safety Report, Figure 20, initial MAA 5.3.5.2 Sequence 0000.

Assessor's comments:

The Applicant has assessed the ability of pralsetinib to prolong the QT interval in a subset of 34 patients with RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered advanced solid tumours who were treated with pralsetinib at a dose of 400 mg QD in Study BO42863. The estimated mean change from baseline in QTcF was –0.9 ms (with a 2-sided 90% CI upper bound of 4.0 ms) at the observed steady state geometric mean Cmax of 2090 ng/mL for pralsetinib in the subset analysed. No effect on heart rate or cardiac conduction (PR interval and QRS duration) was observed.

The Applicant clarified that the QTc prolongation results included in the NSCLC and thyroid applications are similar with 27/528 patients (5.1%) treated at 400 mg QD experiencing QT prolongation (n=26) or long QT syndrome (n=1) in the data from the NSCLC Application and 27/532 patients (5.1%) treated at 400 mg QD experiencing grouped events of QT prolongation in the data from the Thyroid Application (Type II variation).

These findings are reflected in the SmPC sections 4.2, 4.4 and 5.1 identically for both indications.

However, it is not understood why the proposed SmPC in section 4.8 has different numbers, mentioning "QT prolongation occurred in 5.2% of 537 patients". Please clarify. **(new OC).**

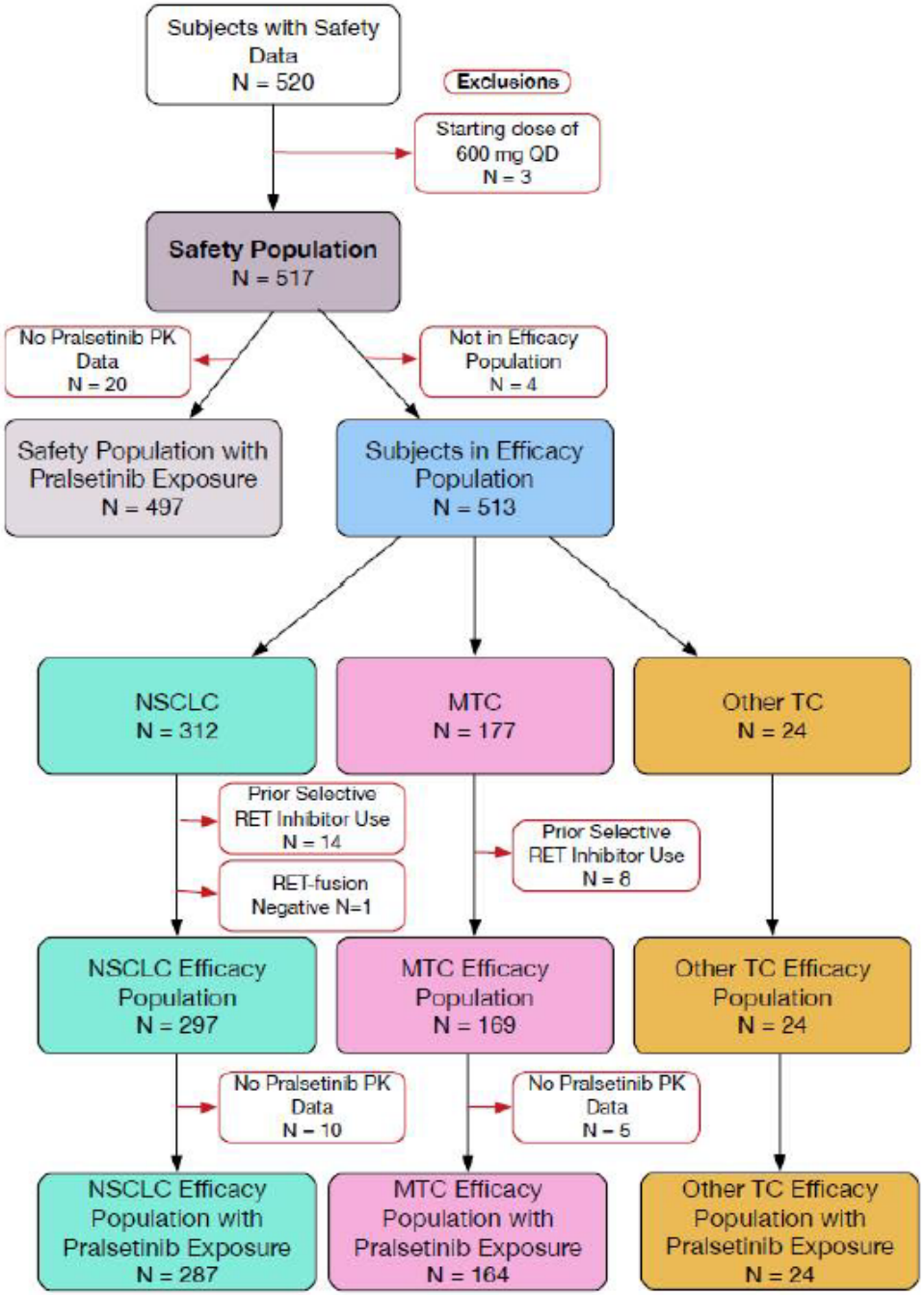
Exposure-response

The objectives of the E-R analyses were to evaluate graphically the effect of pralsetinib exposure and/or starting dose on measures of efficacy and safety as well as biomarker levels (biomarkers only in patients with RET mutation-positive MTC) from Study BO42863. These analyses were used to assess

potential relationships of systemic exposure and other covariates to the selected efficacy, safety, and biomarker measures, and to quantify the effect of pralsetinib exposure on selected measures of efficacy and safety through time-dependent E-R modeling. The E-R dataset for efficacy (E-R efficacy population) included all patients with RET-altered thyroid cancers who had efficacy data and matching pralsetinib dosing data (data cut-off date12 April 2021). The E-R dataset for safety (E-R safety population) included all patients with RET-altered thyroid cancers and RET-fusion NSCLC patients who had safety data and matching pralsetinib dosing data (cut-off date 12 April 2021).

A total of 520 patients were enrolled with safety data (cut-off date 12 April 2021), which included patients recruited after the enrolment cut-off date 23 August 2020. Three subjects who received a starting dose of 600 mg QD were excluded from the analysis (as this was greater than the RP2D), leaving 517 subjects in the E-R safety population. Out of these 517 subjects, there were 20 subjects without pralsetinib PK available, leaving 497 subjects with a matching pralsetinib Cave for the safety population (312 RET fusion-positive NSCLC patients, 177 RET mutation-positive MTC patients, and 28 other RET-altered TC patients). The E-R efficacy population excluded four of the 517 subjects in the E-R safety population because they were not part of the efficacy population. Further exclusion was made for prior selective RET-inhibitor use (n=22) and RET fusion-negative (n=1) (Figure 3), leaving a total 297 RET fusion-positive NSCLC patients and 193 RET-altered TC patients (169 MTC patients) in the E-R efficacy analysis. (Figure 3).

Figure 3: Summary of Patients in the E-R Dataset (Study BO42863)



Abbreviations: E-R = exposure-response; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s); QD = once daily; RET = rearranged during transfection; TC = thyroid cancer.

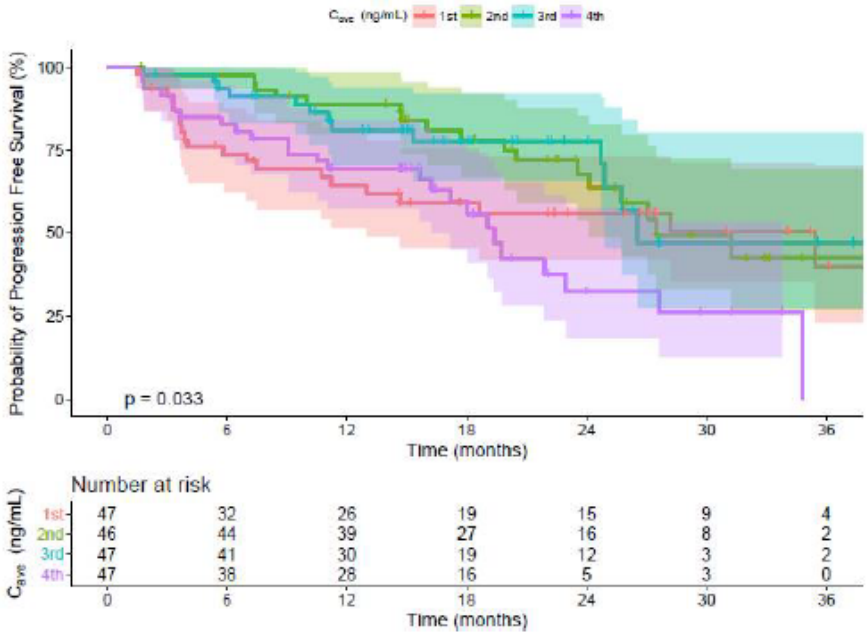
Source: E-R Report 267337A, Figure 6.

Exposure-Efficacy

Kaplan-Meier curves of the time to PFS by quartiles of Cave for patients with RET-altered thyroid cancers do not show a clear relationship between pralsetinib exposure and PFS; patients in the 1st quartile and 4th quartile of exposure appeared to have shorter PFS than patients in the 2nd and 3rd quartiles of exposure (Figure 4). Subjects in the 4th quartile of pralsetinib Cave appeared to have faster progression with median PFS occurring at 6 months compared to 12 months in the 1st quartile.

This observation from the graphical analysis is likely biased, since subjects who progressed early had less opportunity for dose reductions and/or drug holidays. Given this apparent bias, a multivariate ER model was developed using exposure (Cave) assessed in a time dependent manner. The empiric probabilities of PFS by quartiles of Cave at 12 months are provided in Table 1.

Figure 4: Kaplan-Meier Curves of Progression-free Survival by Pralsetinib C_{ave} Quartiles (Study BO42863, Patients with RET-altered Thyroid Cancers, E-R Efficacy Population)



Abbreviations: C_{ave} = average plasma concentration; E-R = exposure-response; RET = rearranged during transfection.

Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence interval, and p-value is derived from a log-rank test. Plots truncated at 36 months.

Table 1: Probability of Progression at 12 months by Quartiles of C_{ave} (Study BO42863, Patients with RET-altered Thyroid Cancers, E-R Efficacy Population)

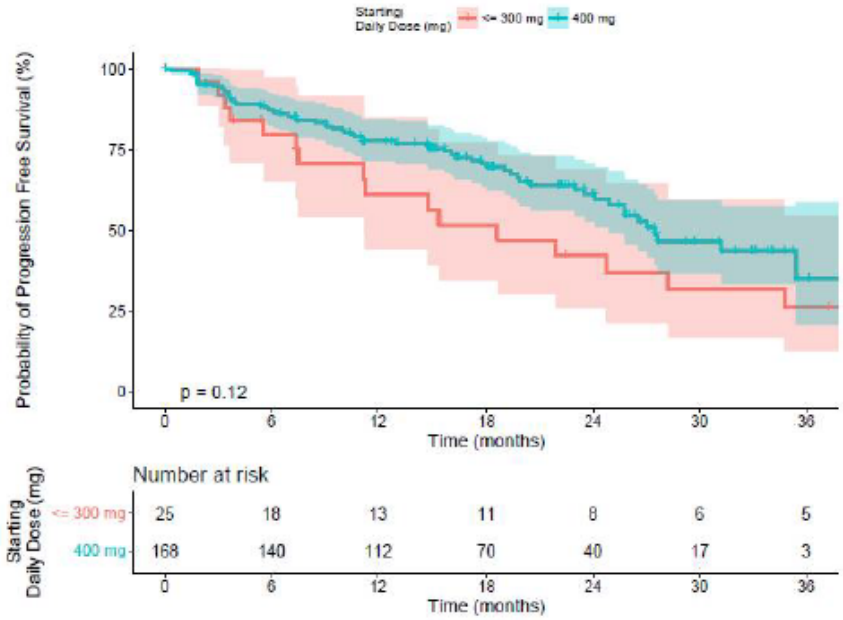
Month	C_{ave} Quartile	Probability	95% CI	Cumulative Events
12	1	0.36	0.20-0.49	16
	2	0.11	0.01-0.20	5
	3	0.19	0.06-0.30	8
	4	0.31	0.16-0.43	14

Abbreviations: C_{ave} = average plasma concentration; CI = confidence interval; E-R = exposure-response; RET = rearranged during transfection.

In the analysis of PFS versus pralsetinib starting dose, a trend but statistically significant relationship was observed when stratified by starting dose (≤ 300 mg QD versus 400 mg QD) (Figure 5). Patients who started on 400 mg QD had a longer PFS than patients who started on ≤ 300 mg QD. A total of 17 of 168 (10.1%) patients who started on a dose of 400 mg QD had progressed or died by Month 4, while 4 of 25 (16.0%) patients on a dose of ≤ 300 mg QD had progressed or died by Month 4 (p =

0.12, exact). In Figure 5, the log-rank test has a p-value of 0,12 and the 95%CI of the two groups are almost completely overlapping. Therefore, it seems that there is no statistically significant relationship with the starting dose nor a longer PFS in the 400 mg cohort.

Figure 5: Kaplan-Meier Curves of Progression-free Survival by Pralsetinib Starting Dose (Study BO42863, Patients with RET-altered Thyroid Cancers, E-R Efficacy Population)



Abbreviations: E-R = exposure-response; RET = rearranged during transfection.

Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence interval, and p-value is derived from a log-rank test. Plots truncated at 36 months.

There were statistically significant covariate relationships observed in the graphical analysis for PFS by age group, baseline Eastern Cooperative Oncology Group (ECOG) score, and prior systemic cancer therapy. Subjects ≥ 65 years appeared to progress quicker than subjects ≤ 65 years, while subjects with an ECOG score of 1 or 2 showed shorted PFS compared to subjects with a baseline ECOG score of 0. Additionally, subjects who had prior systemic cancer therapy performed worse than subjects without prior systemic cancer therapy. The use of prior systemic cancer therapy is correlated with age group and baseline ECOG score, with older subjects more likely to have a higher baseline ECOG score and history of prior systemic cancer therapy that may result in shorter PFS. No significant relationship in PFS was evident by BSA category, geographic region, race, or sex. As expected, based on patient numbers, the results of the graphical analyses of PFS were similar for patients with RET-altered thyroid cancers (n=193) and the subset of patients with RET mutation-positive MTC (n=169).

A time-dependent E-R model was developed for the E-R analysis of PFS to account for the potential bias that patients with dose interruptions or changes can have on the summary metric of Cave being used to describe the entirety of the study history in the graphical analysis of E-R.

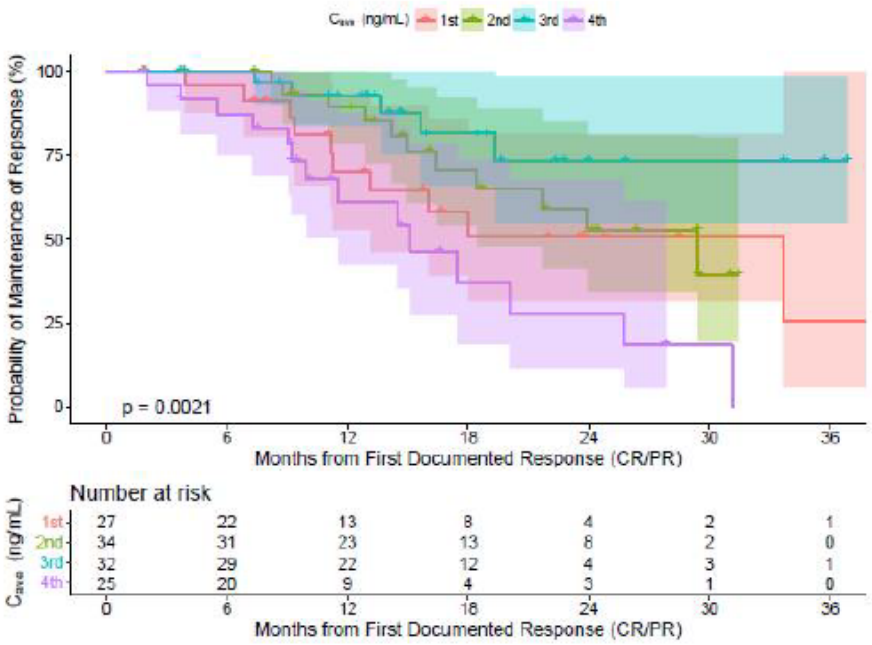
The time-varying E-R model for patients with RET-altered thyroid cancers showed improvement in PFS as exposure increased, with a corresponding hazard ratio of 0.82 (95% CI: 0.72 – 0.95, p = 0.01) for every 312.5 ng/mL increase in pralsetinib Cave. Results were similar for patients with RET-mutation-positive MTC.

In the time-dependent E-R model, there was evidence that patients with no history of prior systemic cancer therapy had a lower risk of progression compared with patients who were pre-treated with systemic cancer therapy. Results were similar for patients with RET mutation-positive MTC.

The analysis of DOR (based on Central Radiology Data and FDA censoring rules) was restricted to the subset of patients with confirmed CR or PR, resulting in a limited number of patients available in the analysis set (n=118). Kaplan-Meier curves of DOR by quartiles of Cave revealed a statistically significant relationship between DOR and quartiles of Cave (p value = 0.002) however the trend was not clear with the 4th, and 1st quartiles preforming worse (Figure 6).

In contrast, and similar to PFS, there was a clear relationship for DOR when stratified by starting dose (≤ 300 mg QD versus 400 mg QD). Patients who started on 400 mg QD tended to have longer DOR than patients who started on ≤ 300 mg QD.

Figure 6: Kaplan-Meier Curves of Duration of Response by Quartiles of C_{ave} (Study BO42863, Patients with RET-altered Thyroid Cancers With a Confirmed Response, E-R Efficacy Population)



Abbreviations: CR = complete response; E-R = exposure-response; PR = partial response; RET = rearranged during transfection.

Note: Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence interval, and p-value is derived from a log-rank test. Plots truncated at 36 months.

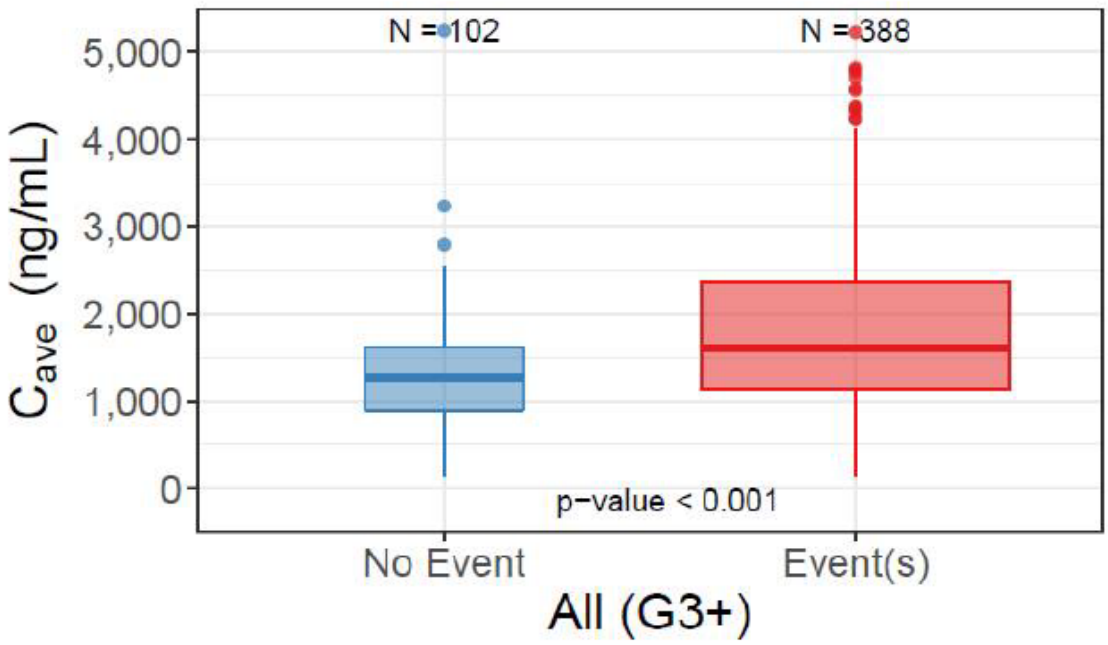
No significant relationship was evident between DOR and BSA, ECOG, geographic region, race, or sex. Marginal evidence for a relationship with prior systemic cancer therapy was observed (p = 0.044). The results of the graphical analyses of DOR were similar for patients with RET-altered thyroid cancers (n=120) and the subset of patients with RET-mutation-positive MTC (n=101).

Boxplots of BOR (as per RECIST) in the E-R efficacy population by Cave indicated no clear relationship between Cave and subjects with CR, partial response (PR) or stable disease (SD). There were too few patients with progressive disease (n=6) to draw any conclusions. The results of the graphical analyses of BOR were similar for patients with RET-altered thyroid cancers (n=187) and the subset of patients with RET-mutation-positive MTC (n=163).

Exposure-Safety

In the safety population of patients with RET-altered thyroid cancer and RET fusion-positive NSCLC in Study BO42863, 79% of patients had a Grade ≥ 3 AE, regardless of causality. Grade ≥ 3 anaemia was the post common AE investigated, with 19% of patients experiencing at least 1 event. A statistically significant trend was evident between higher pralsetinib Cave and the first occurrence of any Grade ≥ 3 AE (Figure 9). Also, patients in the 4th quartile of Cave appeared to experience a faster time to any Grade ≥ 3 AE compared with other quartiles; this result was statistically significant (Figure 10). The empiric probabilities of any Grade ≥ 3 AE by Cave quartiles at Month 12 are provided in Table 4.

Figure 9 Boxplots of Pralsetinib C_{ave} versus Any Grade ≥ 3 Adverse Event Regardless of Causality (Study BO42863, Patients with RET-altered Thyroid Cancers and RET Fusion-positive NSCLC, E-R Safety Population)



Abbreviations: C_{ave} = average plasma concentration; E-R = exposure-response; G3+ = Grade ≥ 3; RET = rearranged during transfection.

Note: The solid horizontal lines and box heights represent the median, and 25th to 75th percentiles, respectively. Dots are the outlier data (≥ 1.5 * interquartile range). Number above each box specifies the number of patients per group. P-value from Wilcoxon rank sum test. The width of the box plots is proportional to the square root of the number of observations in that box.

No statistically significant trend occurred by pralsetinib starting dose although, between Months 1 and 36 of treatment, patients with a starting dose of 400 mg QD (N=475) tended to have a shorter time to any Grade ≥ 3 AE compared with patients with a starting dose of ≤ 300 mg QD (N=42) (Figure 11). A statistically significant covariate relationship was evident for age group with subjects ☐ 65 years having a shorter time to Grade ≥3 events. Kaplan-Meier curves of time to first occurrence of any Grade ≥ 3 AE showed no statistically significant relationship by BSA category, geographic region, race, disease type (NSCLC vs. TC), baseline ECOG score, or sex

Assessor's comments:

In the E-R graphical analysis of Study BO42863 in patients with RET-altered thyroid cancers, relationships were observed between increasing pralsetinib exposure (Cave and/or starting dose) and longer PFS, longer DOR, and disease control and clinical benefit responses as well as safety events (any Grade ≥ 3 AE, regardless of causality, Grade ≥ 3 anaemia and pneumonia, Grade ≥ 3 lymphopenia, decreases from baseline for haemoglobin and ANC values), with greater effects being observed with the 400 mg QD dose than with a dose of ≤ 300 mg QD.

3.3.4. PK/PD modelling

A pooled population PK analysis of data from healthy volunteers, patients with RET-altered thyroid cancers and patients with NSCLC was conducted to quantify variability and the effects of intrinsic and extrinsic factors on the PK of pralsetinib.

For PFS, the HR for Cave was 0.78 which indicated an improvement in PFS as exposure increased in the RET mutation-positive MTC population. No prior systemic cancer therapy was as a significant covariate with a HR of 0.41.

For all grade 3+ AEs in the safety population, the HR for Cave was 1.14 indicating increased risk of events as exposure increased. Age group ≥65y was a significant covariate with a HR of 1.69.

For grade 3+ anaemia in the safety population, the HR for Cave was 1.30 indicating increased risk of events as exposure increased. No covariates were significant.

For grade 3+ pneumonia in the safety population, the HR for Cave was 1.23 indicating increased risk of events as exposure increased. Baseline ECOG score 1 or 2 was a significant covariate with HR 2.02.

For grade 3+ hypertension in the safety population, no relationship to pralsetinib exposure was shown. Age group ≥65y was identified as a significant covariate with HR 2.20.

For grade 3+ lymphopenia in the safety population, the HR for Cave was 1.23 indicating increased risk of events as exposure increased. Non-white race was identified as a significant covariate with a HR of 0.09.

Only 10 subjects experienced at least one grade 3+ pneumonitis AEs in the safety dataset. No model was applied.

3.3.5. Discussion on clinical pharmacology

The basic pharmacokinetic properties of pralsetinib were already known from the first MAA no new studies were conducted. Thus, the main subject of this assessment is PK in the target population, derived from study BO42863.

The exposure to pralsetinib at the proposed dose of 400mg was similar in patients with all thyroid cancers (MTC and thyroid) and in healthy subjects, only the intra-individual variability was generally higher (67%) in patients with all thyroid cancers than in healthy subjects.

The mechanism of action was adequately elucidated.

Exposure-response-relationship was established for both efficacy (PFS, DOR, disease control and clinical benefit responses) and safety (any Grade ≥ 3 AE, Grade ≥ 3 anaemia and pneumonia, Grade ≥ 3 lymphopenia, decreases from baseline for haemoglobin and ANC values).

No dedicated QTc study was conducted, but the Applicant has assessed the ability of pralsetinib to prolong the QT interval in a subset of 34 patients with RET-fusion NSCLC, RET-altered thyroid cancers, and other RET-altered advanced solid tumours who were treated with pralsetinib at the proposed dose of 400 mg QD in Study BO42863. The estimated mean change from baseline in QTcF was –0.9 ms (with a 2-sided 90% CI upper bound of 4.0 ms) at the observed steady state geometric mean Cmax of 2090 ng/mL for pralsetinib in the subset analysed. No effect on heart rate or cardiac conduction (PR interval and QRS duration) was observed. The Applicant clarified that the QTc prolongation results included in the NSCLC and thyroid applications are similar with 27/528 patients (5.1%) treated at 400 mg QD experiencing QT prolongation (n=26) or long QT syndrome (n=1) in the data from the NSCLC Application and 27/532 patients (5.1%) treated at 400 mg QD experiencing grouped events of QT prolongation in the data from the Thyroid Application (Type II variation).

These findings are reflected in the SmPC sections 4.2, 4.4 and 5.1 identically for both indications.

However there appears to be a discrepancy in the proposed SmPC in section 4.8 stating different numbers which needs clarification **(OC)**.

There are no data on subjects < 18 years of age and the extrapolation from adults to adolescents is solely based on the Pop-PK model. The Pop PK model was updated for RET-altered TC by excluding NSCLC data as requested. Fixing allometric exponents of weight effects to the typical values of 1 for V/F and 0.75 for CL/F (model 1) resulted in a worse model fit compared to estimated exponents (model 2). Excluding the NSCLC population from the dataset did not have large effect on the model parameters compared to the original final model based on the complete data set (report 267337). The factor of relative bioavailability incorporated in original final model seem to provide adequate adjustment for the different PK of NSCLC patients. Thus, both the final pralsetinib model (report 267337) and Model 2 is considered adequate for prediction of pralsetinib PK in RET-altered patients.

In study BLU-667-1101, 8 patients had a bodyweight <40 kg and 6 of those patients remained on the 400 mg dose throughout treatment.

For extrapolation to adolescents, simulations of exposure per weight group should be performed using a Pop PK model with fixed exponents for body weight effects on disposition parameters. A minimum weight threshold should be defined **(MO)**.

3.3.6. Conclusions on clinical pharmacology

The extrapolation from adults to adolescents is solely based on the Pop-PK model. There are no data on subjects <18 years of age. The simulations have been done based on an earlier and a newer model which need to be documented. A major objection on PK modelling to justify extrapolation to adolescents remains.

3.4. Clinical efficacy

The primary evidence of efficacy and safety of pralsetinib for this application comes from the pivotal study ARROW (hereinafter referred to as Study BO42863), an ongoing Phase I/II open-label, first-in-human (FIH) study designed to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of pralsetinib in patients with advanced, unresectable, RET fusion-positive NSCLC, RET mutation-positive MTC, and other RET-altered solid tumours (Table 1).

Table 1 Summary of Pivotal Data Included in this Application

Study Number	Study Design	Patient Population	Objectives	Dose, Duration	Number of Patients [a]	Status
BO42863 (ARROW)	Phase I/II, multicenter, open-label, dose escalation with expansion at MTD/RP2D	Phase I ≥18 years old with advanced MTC, NSCL C or other solid tumors; RET alteration required at doses > 120 mg QD Phase II ≥18 years-old with one of the following: RET fusion NSCLC treated with prior platinum therapy; platinum-naïve RET fusion NSCLC; MTC treated with cabozantinib and/or vandetanib; cabozantinib/vandetanib naïve MTC; RET fusion tumor treated with prior SoC; RET-altered tumors treated with prior selective RET TKI; and RET-mutated tumors treated with prior SoC	Phase I Identify MTD/RP2D and assess safety Phase II Efficacy (ORR and other measures of clinical benefit) and safety	Phase I BOIN dose escalation design of pralsetinib capsules administered PO with a target toxicity rate for the MTD of 30%. Cohorts of 3-6 patients (1-3 patients for the first 3 dose levels) were enrolled until 12 patients were treated and evaluable for DLT at 1 dose level Phase II Expansion cohorts defined by tumor type, prior treatments, and/or RET alteration status administered pralsetinib capsules at 400 mg QD (MTD/RP2D)	Phase I 62 enrolled Phase II 585 planned	Phase I Completed Phase II Ongoing
PK Studies						
BP42858	Open label, single center (USA), randomized, single dose, 2-way crossover study	Healthy subjects	To assess the effect of a high fat meal compared to fasting on the relative bioavailability and PK of pralsetinib using the commercial 100 mg capsule formulation	2 × 100 mg pralsetinib capsules administered in the fasting state or after the completion of a standardized high fat meal	20 subjects	Completed
BP42859	Open label, single center (USA), single dose, 2-way crossover study	Healthy subjects	To assess the bioequivalence between four 100 mg tablets and four 100 mg capsules of pralsetinib under fasting conditions	Arm A: 4 × 100 mg pralsetinib tablets Arm B: 4 × 100 mg pralsetinib capsules	90 subjects	Completed
BP42860	Open label, single center (USA), single dose study	Healthy subjects	To understand the absorption, metabolism, excretion, and mass balance of [^{14}C] pralsetinib in healthy male subjects	3 × 100 mg pralsetinib capsules plus 1 capsule containing ~10 mg (100 µCi) [^{14}C] pralsetinib	6 subjects	Completed

BP42861	Two-part, open-label, single center, fixed-sequence, 2-period study	Healthy adult subjects	Part 1: To evaluate the PK of pralsetinib in the presence and absence of itraconazole (a strong CYP3A4 inhibitor) Part 2: To evaluate the PK of pralsetinib in the presence and absence of rifampin (a strong CYP3A4 inducer)	Part 1 (Itraconazole DDI Study): **Period 1:** 2 × 100 mg pralsetinib capsules alone on Day 1 (Period 1) **Period 2:** 200 mg (10 mg/mL oral solution) itraconazole BID on Day 1 followed by 200 mg itraconazole QD on Day 2 through Day 14 with 200 mg pralsetinib single oral dose co-administered on Day 4 (Period 2) Part 2 (Rifampin DDI Study): **Period 1:** 4 × 100 mg pralsetinib capsules alone on Day 1 **Period 2:** 2 × 300 mg rifampin capsules QD on Day 1 through Day 18 with 400 mg pralsetinib single oral dose co-administered on Day 9	Part 1: 25 subjects Part 2: 25 subjects	Completed
BP42862	Open label, single center (USA), fixed sequence, 2-period study	Healthy adult subjects	To evaluate the effect of esomeprazole and gastric pH-altering on the PK of pralsetinib	**Period 1:** 4 × 100 mg pralsetinib capsules **Period 2:** 40 mg esomeprazole capsule orally QD on Day 1 to Day 6 with 400 mg pralsetinib single oral dose administered 1 hour after esomeprazole administration on Day 6	36 subjects	Completed

BID = twice daily; BOIN = Bayesian optimal interval; CNS = central nervous system; DDI = drug-drug interactions; DLT = dose limiting toxicity; MKI = multikinase inhibitor; MTD = maximum tolerated dose; NGS = next-generation sequencing; NSCLC=non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; PO = per oral; QD = once daily; QOL = quality of life; RET = Rearranged during transfection; RP2D = Recommended Phase II dose; SoC=standard of care; TKI=tyrosine kinase inhibitor

[a] As of 12 April 2021.

Assessor's comments:

The design of this multi-cohort single-arm study was not disclosed with the CHMP until enrolment was well underway (first patient enrolled in March 2017). The main purpose of the SA sought in April 2019 was to present preliminary efficacy and safety data as a way to consult upon the possibility of CMA for the 2L NSCLC cohort, as well as discussing the design of the confirmatory trial in 1L. According to the present two indications the MAH did not seek any advice.

The pivotal study BO42863 is conducted as a basket study and a single-arm trial (SAT). The phase 1 part is finalized with 62 subjects enrolled. The phase 2 part is still ongoing with 585 planned subjects. RET-mutant medullary thyroid cancer (MTC) enrolment is finalized. However, patients with RET fusion-positive solid tumours are still being enrolled.

3.4.1. Dose response study

Study BO42863 is a Phase 1/2 FIH study, of which Phase 1 (dose escalation) is now completed and Phase 2 (dose expansion) is ongoing.

Table 1 Overview of Characteristics of Study BO42863 (ARROW)

Study Identifier/Status	Number of Study Centers/Countries	Primary and Secondary Study Objectives	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
BO42863 (ARROW) Phase 1: Complete	6 centers/2 countries (North America, Europe)	Primary Objective: Determine the MTD, RP2D, safety, and tolerability Secondary Objectives: - Determine ORR by RECIST v1.1 - Assess baseline RET gene status in plasma and/or tumor tissue and correlate with measures of antineoplastic activity - Characterize PK profile of pralsetinib and correlate drug exposure with safety assessments - To characterize the pharmacodynamics of pralsetinib	Phase 1, open-label, FIH	Patients ≥18 years with unresectable advanced solid tumor (MTC or a RET-altered solid tumor) and ECOG status (0–2)	30 to 600 mg QD 100/100 mg BID 200/100 mg BID	62 patients

Assessor's comments:

The primary objective of the phase 1 trial was to determine the MTD, safety and tolerability. Sixty-two subjects were treated with 30-600 mg pralsetinib QD, 100/100 mg BID or 100/200 mg BID. The established dose for the subsequent phase 2 part of the study is 400 mg QD. This is also the approved dose for the recently approved NSCLC indication.

3.4.2. Main study

Title of Study

Study BO42863 (ARROW)

The study included a Phase 1 dose escalation part to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pralsetinib, followed by a Phase 2 expansion part to assess the clinical efficacy of pralsetinib in specific tumour types and treatment settings (measured primarily by ORR) and further define the safety and tolerability at the RP2D (Figure 1). Phase 1 ran until the RP2D was determined, at which point Phase 2 was initiated.

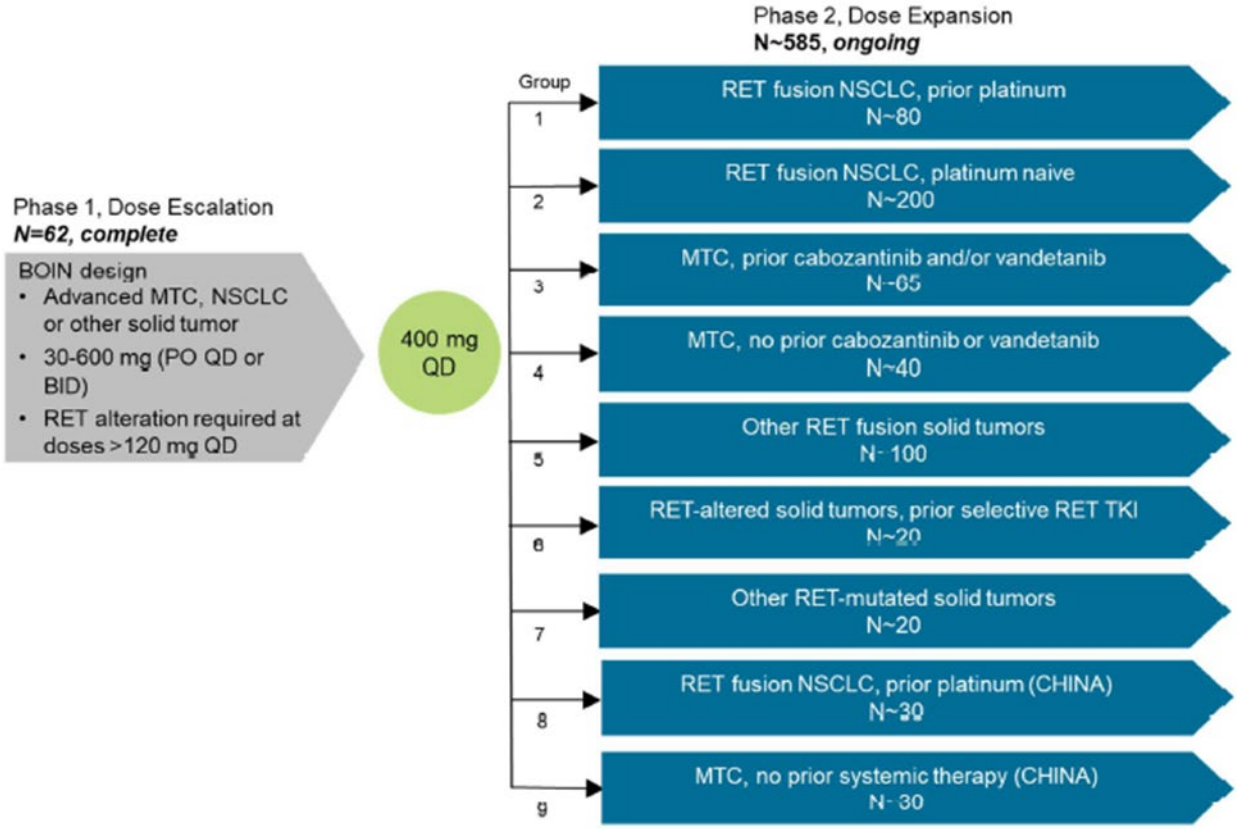
The study was designed as an open-label, single-arm trial intended to demonstrate that pralsetinib is likely to provide clinical benefit based on response rate and DOR in these populations with unmet need. Ultimately, given the high rate of durable responses observed in previously treated patients with advanced, RET-driven thyroid cancer, the population under study was expanded to include patients with MTC (Group 4) and NSCLC (Group 2) who had not previously received standard of care therapy and who could not be adequately treated with local therapy, such as surgery or radiotherapy. Enrolment groups were expanded and refined via protocol amendments.

The minimum duration of patient participation was approximately 3 months, including a screening period to assess study eligibility up to 4 weeks (28 days); a treatment period of at least 1 cycle (28 days); an EOT visit at least 14±7 days following the last dose of study drug; and a follow-up telephone contact for resolution of any AEs 30 days (+7 days) after the last dose of pralsetinib, or at the time the patient initiates another antineoplastic therapy. After C1(D1-22), patients could continue to receive pralsetinib until precluded by toxicity, noncompliance, withdrawal of consent, death, or closure of the study by the Sponsor. Patients with PD could remain on-treatment if in the opinion of the Investigator

the patient has benefited from the pralsetinib therapy, and it was clearly in the best medical interest of the patient to remain on-treatment. A patient was considered to have completed the study if he/she had completed all required visits.

Efficacy analyses (data cut-off of 12 April 2021) using BICR results were performed on patients with RET mutation-positive MTC and RET fusion-positive thyroid cancer who started treatment with pralsetinib on or before 23 August 2020 (note that all RET mutation-positive MTC patients started treatment before 23 August 2020). The cut-off was chosen to allow sufficient follow-up time to initial response. Subsequently, there has been done a new update as of 18 October 2021 for more mature endpoints. Efficacy analyses were also conducted for treatment groups of RET mutation-positive MTC patients who had previously received cabozantinib and/or vandetanib either as single agents or in combination of both, and patients with no prior systemic treatment. Patients with thyroid cancer enrolled in the exploratory Group 6 (i.e., received prior selective RET inhibitor) will be analysed separately when data are mature for this patient group and are not included in the efficacy analyses.

Figure 1 Study Schema



Abbreviations: BOIN = Bayesian optimal interval, BID = twice daily, MTC = medullary thyroid cancer, NSCLC = non-small cell lung cancer, PO = oral, QD = once daily; RET = rearranged during transfection, TKI = tyrosine kinase inhibitor

Table 1 Overview of Characteristics of Study BO42863 (ARROW)

BO42863 (EudraCT number: 2016-004390-41; NCT03037385) **Phase 2:** ongoing; data cutoff date of 12 April 2021 (patients enrolled on or before 23 August 2020)	67 centers/ 11 countries (North America, Europe, and Asia)	Primary objectives: - Determine ORR using RECIST v1.1 criteria - Further define safety and tolerability Secondary objectives: - Assess DOR, CBR, DCR, PFS, and OS - Correlate RET gene status and antineoplastic activity - Characterize PK and PD (calcitonin, CEA) - Assess brain activity in patients with NSCLC	Phase 2, open-label	Patients ≥ 18 years with measurable disease per RECIST v1.1 of - advanced RET-fusion NSCLC: previously treated (Group 1) or untreated (Group 2) with platinum-based chemotherapy - advanced MTC: treated (Group 3) or untreated (Group 4) with cabozantinib and/or vandetanib - advanced solid tumor with oncogenic RET fusion (Group 5) or mutation (Group 7) - advanced solid tumor with oncogenic RET fusion or mutation previously treated with selective RET inhibitor (Group 6) -RET-fusion NSCLC previously treated with platinum-based chemotherapy (China only; Group 8) - MTC not previously treated with systemic therapy for advanced or metastatic disease extension cohort (China only; Group 9)	400 mg QD	582 patients overall [a] 532 [a] received 400 mg QD; of these, 145 had RET mutation-positive MTC and 27 had RET fusion-positive thyroid cancer [a,b] Efficacy population: 145 with RET mutation-positive MTC and 22 with RET fusion-positive thyroid cancer [a,b]

BID = twice daily; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; FIH = first-in-human; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; PS = performance status; QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RET = rearranged during transfection; RP2D = recommended Phase 2 dose; SOC = standard of care.

a: Numbers include patients treated with pralsetinib in Phases 1 and 2. Patients who were treated at 400 mg QD in Phase 2 only were 520 patients (safety population), 138 RET mutation-positive MTC patients (safety population), 25 RET fusion-positive thyroid cancer patients (safety population), 138 RET mutation-positive MTC patients (efficacy population), and 20 RET fusion-positive thyroid cancer patients (efficacy population).

b: Patients with thyroid cancer previously treated with selective RET inhibitor are excluded (Group 6).

In Phase 2, patients will enrol into 1 of 7 groups based on their tumour type and prior therapy status (if applicable). Patients will be treated with pralsetinib at the MTD/ RP2D as determined in Phase 1 and must have at least 1 target lesion evaluable by RECIST v1.1 or RANO, with the exception of patients enrolled in Group 7:

• Group 1: NSCLC with a RET fusion previously treated with a platinum-based chemotherapy (N ~80).

• Group 2: NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug (N~200, including approximately 30 patients with prior systemic therapy).

• Group 3: MTC previously treated with cabozantinib and/or vandetanib (N ~65).

• Group 4: MTC not previously treated with cabozantinib or vandetanib (N ~40).

• Group 5: Other solid tumours with a RET fusion not eligible for any of the other groups (N ~100).

Patients should have previously received SOC appropriate for their tumour type, unless there is no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate. As the intent of this cohort is to enroll a variety of RET-fusion tumour types, Roche will notify sites if/when sufficient data are available and accrual should cease for a particular tumour type.

• Group 6: Any solid tumour with a RET alteration (fusion or mutation) previously treated with a selective RET inhibitor (N~20).

• Group 7: Other solid tumours with a RET mutation previously treated with SOC appropriate for the tumour type (N~20).

• Group 8: NSCLC with a RET fusion previously treated with a platinum-based chemotherapy (China only; N ~30)

• Group 9: MTC not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced or metastatic disease extension cohort (China only; N ~30).

Determination of RET status, as required for enrolment of all patients except those with MTC, is based on local assessment or central assessment; however, patients with MTC are not required to have RET results before enrolment. All patients enrolled in Phase 2 must submit tumour tissue (archived or new) for retrospective assessment of RET status and other pathway biomarkers. Patients enrolled into Group 6 (previous treatment with a selective RET-inhibitor) are required to have a new tumour biopsy prior to enrolment.

A total of 145 RET mutation-positive MTC patients received pralsetinib at a starting dose of 400 mg QD by 23 August 2020 (in Groups 3, 4 or 9, or in Phase 1) and are included in the efficacy analyses (Study BO42863, Report 1109798, Table 8). Of the 145 patients, 67 patients had previously received cabozantinib and/or vandetanib, including 24 patients who had previously received both cabozantinib and vandetanib. A total of 78 patients had not previously received cabozantinib and/or vandetanib, including 67 patients who had received no prior systemic treatment.

A total of 22 RET fusion-positive thyroid cancer patients received pralsetinib at a starting dose of 400 mg QD by 23 August 2020 (in Group 5 or in Phase 1) and are included in the efficacy analyses (Study BO42863, Report 1109798, Table 8). Of the 22 patients, 21 received prior systemic treatment.

Table 1 Efficacy Populations

	Efficacy Population
Patient Group	400 mg QD n (%)[a]
RET-mutant MTC	162 (100)
Prior systemic treatment	145 (27.3)
Prior cabozantinib and/or vandetanib treatment	78 (14.7)
Prior cabozantinib and vandetanib treatment	24 (4.5)
No prior cabozantinib and/or vandetanib treatment	78 (14.7)
No prior systemic treatment	67 (12.6)
RET fusion-positive thyroid cancer	27 (100%)
Prior systemic treatment	25 (92.6%)

Clinical cut-off date: 18 October 2021.
MTC = medullary thyroid cancer; QD = once daily; RET = rearranged during transfection
[a] Percentages are based on the total number of patients in each population
Source: T14_01_01_01_01_01_pop

Assessor's comments:

According to the synopsis the study was conducted in 74 centres; USA (19), China (19), France (8), Germany (5), Spain (5), Italy (4), South Korea (4), UK (3), Netherlands (2), Taiwan (2), Belgium (1), Hong Kong (1) and Singapore (1).

The phase 2 part is still ongoing with 585 planned subjects of which 138 subjects with RET-mutation positive MTC have been enrolled and finalized (Total n=145 from phase 1 and 2 treated with 400 mg QD). The pooling with patients from Phase 1 is endorsed. Patients with RET fusion-positive solid tumours (excluding NSCLC) and including RET-fusion positive thyroid cancer, cohort 5, are still being enrolled, n=22 (efficacy population). With an enrolment cut-off date of 23 august 2020 the number of subjects with RET-fusion positive thyroid cancer and treated with at least one dose pralsetinib is at submission date n=27 (safety population).

Of the 145 patients with RET-mutation positive MTC, about half of patients (n=67) were cabozantenib/vandetanib treatment-naïve (n=67). Only 78 patients received prior treatment of which 67 were previously treated with cabozantinib and /or vandetanib which are the current approved treatments in EU for locally advanced and metastatic RET mutation-positive MTC in adults. 11 patients received other systemic therapies. Of the 22 RET fusion-positive thyroid cancer patients nearly all received prior treatment (21/22).

After the requested update (CCOD 18 October 2021) there is no change to the efficacy population for RET mutant medullary thyroid cancer (MTC) patients. However, a total of 27 RET fusion-positive thyroid cancer (TC) patients received pralsetinib at a starting dose of 400 mg QD by 18 February 2021 (in Phase 1 or in Phase 2, Group 5) and are included in the updated efficacy analyses. Of the 27 RET fusion-positive TC patients 25 received prior systemic treatment (see Table 1).

At the time of the CCOD of 18 October 2021, a total of 652 patients had been screened for inclusion; of which, 65 were screen failures. Of these, 29/65 patients did not meet the inclusion criteria, 31/65 patients met one or more exclusion criteria, 4/65 patients withdrew consent and 1/65 medullary thyroid cancer (MTC) patient did not have a RET mutation.

Methods

Study participants

Inclusion Criteria

Patients meeting the following criteria will be eligible for participation in the study:

1. Patient is ≥ 18 years of age.

2. Diagnosis during dose escalation (Phase 1) – Pathologically documented, definitively diagnosed non-resectable advanced solid tumour.

• All patients treated at doses > 120 mg per day must have MTC, or a RET-altered solid tumour per local assessment of tumour tissue and/or blood.

• Phase 1 enrichment patients must have MTC or a RET-altered solid tumour per local assessment of tumour tissue and/or blood.

3. Diagnosis during dose expansion (Phase 2) – All patients (with the exception of patients with MTC enrolled in Groups 3, 4, and 9) must have an oncogenic RET fusion or mutation (excluding

synonymous, frameshift, and nonsense mutations) solid tumour, as determined by local testing of tumour or circulating tumour nucleic acid in blood; as detailed below.

• Group 1 – patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion previously treated with a platinum-based chemotherapy.

• Group 2 – patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant

and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug.

• Group 3 – patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was previously treated with cabozantinib and/or vandetanib.

• Group 4 – patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was not previously treated with cabozantinib or vandetanib.

• Group 5 – patients must have a pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic RET fusion, have previously received SOC appropriate for their tumour type (unless there is no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate), and must not eligible for any of the other groups.

• Group 6 – patients must have a pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic RET fusion or mutation, previously treated with a selective TKI that inhibits RET, such as selpercatinib.

• Group 7: patients must have a pathologically documented, definitively diagnosed advanced solid tumour with an oncogenic RET mutation previously treated with SOC appropriate for the tumour type and not eligible for any of the other groups.

• Group 8: patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion that was previously treated with a platinum-based chemotherapy (China only).

• Group 9: patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced or metastatic disease (China only).

4. Patients must have non-resectable disease. Prior to Protocol Amendment 9, patients must have progressed following standard therapy or have not adequately responded to standard therapy, or the patient must be intolerant to, or the Investigator has determined that treatment with standard therapy is not appropriate, or there must be no accepted standard therapy for their disease.

5. Dose expansion (Phase 2) patients in all groups (except Group 7) must have measurable disease per RECIST v1.1 (or RANO, if appropriate for tumour type).

6. Patient agrees to provide tumour tissue (archived, if available or a fresh biopsy) for RET status confirmation and is willing to consider an on-treatment tumour biopsy, if considered safe and medically

feasible by the treating Investigator. For Phase 2, Group 6, patients are required to undergo a pre-treatment biopsy to define baseline RET status in tumour tissue.

7. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.

8. Patient provides informed consent to participate in the study.

Exclusion Criteria

Patients meeting any of the following criteria will not be eligible for participation in the

study:

1. Patient's cancer has a known primary driver alteration other than RET. For example, NSCLC with a targetable mutation in EGFR, ALK, ROS1, or BRAF; colorectal with an oncogenic KRAS, NRAS, or BRAF mutation. Investigators should discuss enrolment with Sponsor regarding co-mutations.

2. Patient has any of the following within 14 days prior to the first dose of study drug:

a. Platelet count < 75 × 109/L.

b. Absolute neutrophil count (ANC) < 1.0 × 109/L.

c. Hemoglobin < 9.0 g/dL (red blood cell transfusion and erythropoietin may be used to reach at least 9.0 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug.

d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present.

e. Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease.

f. Estimated (Cockroft-Gault formula) or measured creatinine clearance < 40 mL/min.

g. Total serum phosphorous > 5.5 mg/dL.

3. Patient has a QTcF > 470 msec. Patient has a history of prolonged QT syndrome or Torsades de pointes. Patient has a familial history of prolonged QT syndrome.

4. 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 (e.g., Type II second degree heart block or third-degree heart block).

5. Patient has central nervous system (CNS) metastases or a primary CNS tumour that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease. If a patient requires corticosteroids for management of CNS disease, the dose must have been stable for the 2 weeks preceding C1D1.

6. Presence of clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

7. Patient received the following anticancer therapy:

a. Any systemic anticancer therapy (except for immunotherapy or other antibody therapies) and all forms of radiotherapy, within 14 days or 5 half-lives prior to the first dose of study drug. Pralsetinib may be started within these washout periods if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.

b. Any immunotherapy or other antibody therapy within 28 days prior to the first dose of study drug (immune related toxicities must have resolved to < Grade 2 prior to starting pralsetinib).

8. Dose expansion patients in Groups 1-5 and 7 (Phase 2): patient has previously received treatment with a selective RET inhibitor such as selpercatinib.

9. Patient received neutrophil growth factor support within 14 days of the first dose of study drug.

10. Patient requires treatment with a prohibited medication or herbal remedy (as specified in Appendix 2) that cannot be discontinued at least 2 weeks before the start of study drug administration. pralsetinib may be started within 14 days or 5 half-lives of prior therapy if considered by the Investigator to be safe and within the best interest of the patient, with prior Sponsor approval.

11. Patient has had a major surgical procedure within 14 days of the first dose of study drug (procedures such as central venous catheter placement, tumour needle biopsy, and feeding tube placement are not considered major surgical procedures).

12. Patient has a history of another primary malignancy that has been diagnosed or required therapy (except maintenance anti-hormonal therapy) within the past year. The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, curatively treated localized thyroid cancer, and completely resected carcinoma in situ of any site.

13. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.

14. Women 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.

Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 90 days after the last dose of study drug. Refer to Section 9.6.1 for acceptable methods of contraception.

15. Pregnant females, as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy, obtained within 7 days prior to the first dose of study drug. Females with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Sponsor, after pregnancy has been ruled out. Females of non-childbearing potential (postmenopausal for more than 1 year; bilateral tubal ligation; bilateral oophorectomy; hysterectomy) do not require a serum β-hCG test.

16. If female, patient is breastfeeding.

17. Patient has prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's or Sponsor's opinion, could affect the safety of the patient; alter the absorption, distribution, metabolism, or excretion of the study drug; or impair the assessment of study results.

Confirmatory studies planned:

AcceleRET-MTC (CO42865): a multi-center, open-label, randomized phase 3 study to evaluate the efficacy and safety of pralsetinib compared with SOC treatment (cabozantinib or vandetanib) for adult patients and adolescents (n=20) with advanced and metastatic RET-mutant MTC who have not previously received an SOC MKI therapy (n=198).

TAPISTRY (BO41932) is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations. Cohort K will be evaluating pralsetinib in patients with RET fusion-positive solid tumors (excluding NSCLC). This cohort will enroll up to 40 RET fusion-positive thyroid cancer patients.

Assessor's comments:

The incl/excl. criteria clearly define a newly diagnosed or pre-treated population with stage IV RET-mutation positive MTC (group 3 and 4) and pre-treated stage IV RET fusion-positive thyroid cancer patients (group 5) in good condition, ECOG PS 0-1. As the inclusion criteria for Group 5 also included patients where there was no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate, 1/22 patients with RET fusion-positive thyroid cancer patients was treatment-naïve. After the efficacy update it is 2/27 patients. Moreover, after the ECOD of 18 February 2021 another treatment-naïve patient was enrolled and was therefore, excluded from the efficacy population. All 3 treatment-naïve patients who had advanced anaplastic thyroid cancer, with poor prognosis were by the Investigator determined that no other appropriate therapy was available at the time of enrolment in the study. Efficacy analyses for the RET fusion-positive thyroid cancer patients treated at 400 mg QD are presented for this study both for all patients (n=27) and for patients with prior systemic treatment (n=25). The MAH confirms that the proposed indication is for patients with prior systemic treatment.

All patients should be ≥18 years of age. However, this criterion is not reflected in the proposed new indications. To justify the inclusion of adolescent patients, adult data have been extrapolated to this patient group and these data will subsequent be confirmed with data from 20 adolescent patients to be enrolled across the AcceleRET MTC Phase 3 study (CO42865) and the pralsetinib cohort in the BO41932 global basket trial (TAPISTRY) as per agreed Paediatric Investigation Plan (PIP).

According to the RET-mutation positive MTC patients only the pre-treated patients (group 3, n=67) are reflected in the proposed indication.

The MAH commits to providing the primary and final analysis of AcceleRET-MTC study post-approval and both the primary and final analysis for Cohort K of the TAPISTRY study. Cohort K of the TAPISTRY study is evaluating pralsetinib in RET fusion-positive solid tumours (excluding NSCLC) and includes RET fusion-positive thyroid cancer patients as a subgroup within this cohort.

The MAH has provided a discussion on the feasibility of the studies AcceleRET-MTC and TAPISTRY with an assumption of the number of patients being recruited in the studies:

AcceleRET-MTC (CO42865): Based upon the countries and associated country-specific recruitment rates, considering the number of sites and enrolment timelines and the Sponsor's due diligence to select sites with paediatric capabilities and work with sites to effectively recruit adolescent patients, the modelling indicates that 132 sites (30 countries) can complete randomization of 198 patients in approximately 60 months. Last patient enrolled projected by July 2027.

TAPISTRY (BO41932): To confirm the efficacy and safety of pralsetinib in the treatment of adult and paediatric patients 12 years of age and older with RET fusion-positive TC, the MAH will submit the final report of integrated studies BO41932 (TAPISTRY) and BO42863 (ARROW) to provide a more precise estimation of the BICR-assessed overall response rate and duration of response in at least 50 patients. As of the 18 October 2021 CCOD, 30 RET fusion-positive thyroid cancer patients treated with 400 mg QD had been enrolled in ARROW of which 27 had a prior systemic treatment. To meet the patient numbers for the integrated analysis proposed in the specific obligation, an additional 23 patients will be recruited into cohort K of the TAPISTRY study.

The MAH provided information on the histological types of the RET-fusion positive thyroid cancer patients (Table 1). As of the clinical cut-off date (CCOD) of 18 October 2021, the MAH has recruited differentiated, poorly differentiated, and anaplastic RET fusion-positive thyroid cancers.

The MAH has been asked to reword the indications where prior treatments should be explicitly explained. The MAH suggests to supplement with "not previously treated with a RET inhibitor" as its omission may lead to the use of pralsetinib following treatment with selpercatinib and as the MAH points out there is presently no pre-clinical or clinical data to suggest that patients who previously received selpercatinib may benefit form pralsetinib treatment.

However, before the extension of indication to adolescents based on PK bridging using the Final Pop PK model can be accepted, the MAH is requested to provide model predicted exposure metrics by weight group for simulated adolescent TC patients (see pharmacologic OC)

To be consistent with the wording of indication in NSCLC "local advanced" and "metastatic" should instead be "advanced" which the MAH has accepted. The wording of indications is subsequently as follows:

*"Adult**s** ~~and paediatric patients 12 years of age and older~~ with ~~locally~~ advanced ~~or metastatic~~ RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib **and not previously treated with a RET inhibitor**."*

*"Adult**s** ~~and paediatric patients 12 years of age and older~~ with ~~locally~~ advanced ~~or metastatic~~ RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib **and not previously treated with a RET inhibitor**."* **(New MO).**

The MAH justifies that the clarification on exclusion on previous same-class (RET inhibitors) treatments is necessary upon risk of use of pralsetinib after selpercatinib. It is agreed with the MAH that there is no clinical data to suggest retreatment with same class products in this setting is justified, but overall, it is still considered that the proposed new indications are too extense upon such clarification, thus the MAH has been encouraged to reconsider deleting the wording "and not previously treated with a RET inhibitor" However, the MAH still deems the wording on the exclusion of previous RET inhibitors necessary to be included in the proposed indications to avoid any potential misinterpretations by prescribers. This is accepted.

Treatments

Efficacy analyses were conducted for patients with RET-altered thyroid cancer treated in the phase 2 part of the study with pralsetinib at 400 mg QD who began treatment on or before 23 August 2020 to allow sufficient follow-up time to initial response. All patients in the efficacy population were enrolled consecutively.

Dose modification for AEs: pralsetinib dose reductions to below 100 mg QD were not permitted. If a patient required dose reduction below these dose levels, study treatment was to be discontinued.

Pralsetinib may increase the plasma concentration of co-administered sensitive cytochrome P450 2C9 (CYP2C9) substrates. Medications that are sensitive CYP2C9 substrates with known drug-drug interaction potential were to be used with caution.

Medications and treatments other than those specified above, including palliative and supportive care for disease-related symptoms, were permitted during the study.

Antiemetic and antidiarrheal treatments could be used at the Investigator's discretion and in accordance with the local guidelines after documented nausea, vomiting, or diarrhoea occurred without medications having been used. Prophylaxis for nausea, vomiting, or diarrhoea could be instituted beginning on C2D1 in patients who experienced these toxicities during Cycle 1, and during Cycle 1 for patients who had experienced nausea, vomiting, or diarrhoea.

Assessor's comments:

The patients were treated with pralsetinib 400 mg QD until disease progression or unacceptable toxicity and the treatment should be discontinued in patients who were unable to tolerate 100 mg QD. This is reflected in the SmPC. Recommended dose modifications for adverse reactions were described. This was also described for concomitant use with strong cytochrome P-450 (CYP)3A4 inhibitors or combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors. Supportive medications were allowed at the Investigator's discretion.

Objectives

Please see outcomes/endpoints.

Outcomes/endpoints

The study objectives and endpoints are presented in Table 2.

This study had 2 parts: the first part was a Phase I study and the second part was a Phase II study. Phase I patients treated at the maximum tolerated dose (MTD)/RP2D were pooled with Phase II patients for Phase II objectives/endpoints accordingly.

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Phase I	
Primary	
To determine the MTD and RP2D of pralsetinib	MTD and RP2D of pralsetinib
To determine the safety and tolerability of pralsetinib	Overall safety profile of pralsetinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, changes in vital signs, ECG, and safety laboratory tests

Secondary	
To determine the ORR	ORR by RECIST v1.1 for all pralsetinib treated patients according to patients' disease type and/or RET-altered status if applicable, and/or prior treatment status, if appropriate
To assess baseline RET gene status in plasma and/or tumor tissue and correlate with measures of antineoplastic activity	RET gene status and correlation between RET gene status and ORR, CBR, DOR, PFS, OS, and DCR, and other measures of antineoplastic activity (in plasma and/or tissue) in all patients according to their disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate
To characterize the PK profile of pralsetinib and correlate drug exposure with safety assessments	PK parameters of interest: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}24h}$, C_{24}, Vz/F, $t_{½}$, CL/F, and R
To characterize the pharmacodynamics of pralsetinib	Pharmacodynamic parameters: changes in tumor/blood including, but not limited to, changes in blood calcitonin and CEA (MTC patients), and changes in tumor biomarker levels (DUSP6 and SPRY4) (all patients)
Phase II [a]	
Primary	
To determine the ORR	ORR by RECIST v1.1 criteria by patients' disease type, and/or RET-altered status if applicable, and/or prior treatment status if appropriate
To further define the safety and tolerability of pralsetinib	Overall safety profile of pralsetinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, changes in vital signs, ECGs, and safety laboratory tests
Secondary	
To assess additional measures of clinical benefit	DOR, CBR, DCR, PFS, and OS in all patients by disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate
To assess baseline RET gene status in plasma and/or tumor tissue and correlate with measures of antineoplastic activity	RET gene status and correlation between RET gene status and ORR, CBR, DOR, PFS, OS, and DCR, and other measures of antineoplastic activity (in plasma and/or tissue) in all patients, including patients treated at the MTD/RP2D in Phase I according to their disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate
To characterize the PK profile of pralsetinib and correlate drug exposure with safety assessments (including changes in ECG intervals) and efficacy	Potential effects of pralsetinib were evaluated as change from predose (C1D1) baseline ECG parameters (heart rate, PR, QRS, and QTcF) to postdose (C1D15), paired with blood samples for

	PK assessment. For the purpose of QT assessment, concentration-response analysis of the regression relationship between ΔQTcF and the postdose plasma concentration of pralsetinib was conducted [b] PK parameters as described above in Phase I
To characterize the pharmacodynamics of pralsetinib	Pharmacodynamic parameters as described above in Phase I
To assess brain activity	To assess brain activity in patients with NSCLC

AE=adverse events; AUC=area under the concentration-time curve; CEA=carcinoembryonic antigen; CL/F=apparent oral clearance; C_{max}=maximum plasma concentration; DCR=disease control rate; DOR=duration of response; DUSP6=dual specificity phosphatase 6; ECG=electrocardiogram; MTC=medullary thyroid cancer; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; QTcF=QT interval of the 12-lead electrocardiogram corrected for heart rate by Fridericia's formula; R=accumulation ratio; RECIST=Response Evaluation Criteria in Solid Tumors; RET=rearranged during transfection; RP2D=recommended Phase II dose; SAE=serious adverse event; SPRY4=sprout receptor tyrosine kinase signaling antagonist 4; $t_{½}$=terminal elimination half-life; t_{last}=time of last quantifiable plasma drug concentration; t_{max}=time to maximum plasma drug concentration; Vz/F=apparent volume of distribution.

[a] Phase I patients treated at the RP2D were pooled with Phase II patients for the Phase II objectives.

[b] Complete results of this endpoint are available in a separate document (BO42863, Cardiac Safety Report).

Source: Study BO42863, Report 1109798, Table 1.

Addition: CBR=clinical benefit rate.

Assessor's comments:

The objectives for the phase 2 part of the study are endorsed.

The primary endpoint for efficacy analyses was ORR (RECIST v1.1) by BICR assessment which is endorsed as primary endpoint for this SAT.

The following secondary endpoints were evaluated: duration of response (DoR), clinical benefit rate (CBR), duration of clinical response (DCR), progression-free survival (PFS), overall survival (OS). DoR is defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurs first. CBR was calculated as the proportion of patients reaching CR, PR, or stable disease lasting 16 or more weeks. DCR is defined as the proportion of patients with a confirmed CR/PR, or SD, per RECIST v1.1. The secondary endpoints are considered relevant and are as such endorsed.

Sample size

Phase 2 (Dose-expansion at the MTD/RP2D)

Group 3: The sample size of approximately 65 MTC patients previously treated with cabozantinib and/or vandetanib will provide > 90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.2 versus the alternative ORR=0.4.

Group 4: The sample size of approximately 40 MTC patients not previously treated with cabozantinib or vandetanib will be enrolled for exploratory analysis.

Group 5: The sample size of approximately 100 patients who have solid tumours with a RET fusion previously treated with SOC, have previously received SOC appropriate for their tumour type (unless there is no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate), and must not eligible for any of the other groups. This sample size will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.1 versus the alternative ORR=0.3.

Group 9: The sample size of approximately 30 MTC patients that were not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for the advanced or metastatic disease will be enrolled by assuming the observed ORR from 27% to 50% based on the preliminary data.

Assessor's comments:

The study is an early phase study and the sample size for the different patient groups were decided to rule out response rates that were too low to further pursue the development of the product in that patient group.

Randomisation

This a non-randomised phase 1/2 study.

Blinding (masking)

As the study was initially conducted in patients who had already received or who were otherwise inappropriate candidates for standard of care treatments, the study was designed as an open-label, single arm trial intended to demonstrate that pralsetinib is likely to provide clinical benefit based on response rate and DOR in these populations with unmet need.

An Independent Data Monitoring Committee (IDMC) was established to monitor safety and study conduct. The IDMC operated according to the rules established in the iDMC Charter. The IDMC reviewed unblinded safety summaries and summaries of key efficacy endpoints prepared by an independent data coordinating center (IDCC). Members of the IDMC were external to the Sponsor.

Assessor's comments:

The study is open label, single arm trial. The MAH established an IDMC to monitor safety and study conduct. This is agreed.

Statistical methods

Analysis populations

Safety Population: All patients who were exposed to at least 1 dose of pralsetinib, regardless of starting dose or cancer diagnosis as of 12 April 2021. Patients were analyzed based on the initial dose prescribed on D1, regardless of study phase. Prior selective RET inhibitor treated patients (i.e., Group 6 patients) were not included in any safety subgroups defined by tumour type, but were included in the overall safety population;

Efficacy Population: Patients were analysed based on the initial dose prescribed on D1, regardless of study phase. Prior selective RET inhibitor treated patients (i.e., Group 6 patients) were explored separately and were not included in any efficacy subgroups defined by tumour type, but were included in the overall efficacy population;

RET-altered Measurable Disease Population: Efficacy population patients who have measurable (target) disease per RECIST v1.1 (or Response Assessment in Neuro-Oncology, if appropriate for tumour type) at baseline according to BICR and sufficient evidence of a RET alteration. The RET-altered Measurable Disease Population will be the primary population for analysis of ORR, best overall response (BOR), clinical benefit rate (CBR), disease control rate (DCR), and DOR. Prior selective RET inhibitor treated patients will be explored separately and will not be included in any defined efficacy subgroups.

Response-evaluable Population: All efficacy population patients who had measurable (target) disease per RECIST v1.1 at baseline, at least 1 evaluable postbaseline disease response assessment performed as per BICR, and had no major protocol violations. The response-evaluable population was the predefined sensitivity analysis for ORR, DOR, CBR, and DCR.

Additionally, for Phase 1 analyses as of data cut-off of 18 November 2019 reported in CSR 1, the following analysis population was defined:

Dose-determining Population: All patients in the dose escalation part of the study (Phase 1) who received at least 75% (21 days) of pralsetinib and completed C1 through C1D28 or experienced a DLT (Protocol v13.0 Section 11.2).

Patients enrolled after the cut-off date of 23 August 2020 are not included in the primary efficacy analyses. The MAH has provided an update of the efficacy dataset with the clinical cutoff date (CCOD) of 18 October 2021 (enrolment cut-off date [ECOD] of 18 February 2021) as requested. The new efficacy dataset will include all patients who started treatment with pralsetinib before 18 February 2021 (i.e., the efficacy population).

Table 1 Analysis population, patients treated at 400 mg QD

	RET-mutant MTC (N)	RET-fusion Thyroid (N)
Safety Population[a]	145	30
6 Months Population[b]	145	27
Efficacy Population[c]	145	27

Clinical cutoff date: 18 October 2021

[a] Patients who have received at least 1 dose of treatment

[b] Patients who received at least 6 months of treatment or discontinued from treatment prior to 6 months (ecod 18 April 2021)

[c] Patients who are dosed on or prior to the ecod (18 February 2021)

Assessor's comments:

Only participants enrolled up to the cut-off date of 23 Aug 2020 are included in this application. This was performed, according to the MAH, to allow sufficient follow-up time from initial response among

responders allowing for at least two assessments. After this date more patients have been enrolled in the study. Immaturity of the data from ARROW is reflected in the selection of the efficacy population and limited information from time-to-event endpoints. Considering the single-arm design of the study, a complete update of the efficacy dataset with a later data cut-off has been considered needed before a final B/R assessment can be carried out. The MAH has as requested provided outputs using data from the new clinical cut-off date (CCOD) of 18 October 2021. An overview table (Table 1) is presented showing the number of patients in the RET-mutant medullary thyroid cancer (MTC) and RET fusion-positive thyroid cancer populations treated at 400 mg QD. All RET-mutant MTC patients treated at 400 mg QD were enrolled before the 18 February 2021, therefore the safety population (all recruited patients) and the population consisting of all patients treated for at least 6 months or who discontinued treatment prior to 6 months is the same as the efficacy population. No RET fusion-positive thyroid cancer patients were enrolled between 18 February 2021 (ECOD for the efficacy population) and 18 April 2021 (the ECOD for the 6 months population). Therefore, the number of patients who received at least 6 months of treatment (or discontinued from treatment prior to this) is the same as the number of patients in the efficacy population.

The MAH defined several study populations for the primary efficacy analysis. The primary endpoint ORR and the secondary endpoints BOR, CBR, DCR and DOR will be primarily tested using the RET-altered Measurable Disease Population. This population only includes treated subjects with measured disease at baseline according to BIRC. The remaining endpoints will be primarily tested using all recruited patients who received at least one treatment dose. Sensitivity analysis were performed using the response-evaluable population, defined as the subset of patients with measurable disease without major protocol violations.

The exclusion of patients without measurable disease at baseline from the primary analysis for the response-based endpoints (ORR, BOR, CBR, DCR) is not agreed. Those patients should have been considered non-evaluable and included in the denominator. Since those endpoints were calculated using the efficacy population (CSR, Table 10 page 116), further analyses are not requested. The definition of the efficacy population is endorsed.

Table 2 Efficacy Endpoints and Analysis Population

	RET-altered Measurable Population	Efficacy Population	Response Evaluable Population
ORR, BOR, CBR, DCR, DOR	X	X	X
Intracranial ORR, BOR, CBR, DCR, DOR*	X	X	X
PFS, and intracranial PFS*		X	
OS		X	
EORTC QoL		X	
Bowel function movement		X	

* RET-fusion NSCLC CNS metatstases sub-population and other solid tumor if applicable.

Source: SAP version 5.0 page 37.

Primary efficacy endpoint ORR

The primary efficacy endpoint of ORR is defined as the proportion of patients with a confirmed response (complete response [CR] or partial response [PR] for at least two assessments with at least 28 days apart and no disease progression [PD] in between) before PD and/or other anticancer therapy. ORR and its two-sided 95% CI, which is based on the exact binomial distribution (Clopper-Pearson), will be presented.

Secondary endpoints CBR and DCR

They will be analysed as described for ORR.

Assessor's comments:

The ORR and its two-sided 95 % CI was calculated using the Clopper-Pearson method, which is agreed. The same method was used for CBR and DCR.

Secondary endpoint PFS

PFS will be analyzed using Kaplan-Meier (KM) methods, the estimated median with two-sided 95% CI and 25th and 75th percentiles will be provided. The confidence interval calculation is based on identity (i.e. linear) transformation. PFS at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24-, 30-month etc.

every 6-month after 12-month) will be computed, along with the standard errors using Greenwood's formula (Klen, 2003). PFS will also be displayed with KM plots.

PFS analysis will be conducted based on BICR data and investigator assessment.

Table 8 Duration of Response and Progression Free Survival Censoring Rules

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

Source: SAP version 5.0 page 47.

Secondary endpoint DOR

Patients without confirmed CR or PR will be excluded from this analysis. The DOR analysis will be conducted based on BICR data and different censoring rules specified in Table 8.

Duration of response will be analysed using KM methods and will include the estimated median with two-sided 95% CI and 25th and 75th percentiles. DOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-,

24-, 30-month etc.) will be computed, along with the standard errors using Greenwood's formula (Klen, 2003). Additionally, the proportion of patients with DOR of at least 3, 6, 9, 12, 18, 24, and 30 months will be summarized regardless of censoring status.

The DOR analysis will also be produced based on investigator assessment as a supportive analysis for RET-mutation MTC, RET-thyroid, and DOR across RET alteration status and disease types.

Secondary endpoint OS

OS will be analysed and summarized in a same manner as for PFS. Patients who are still alive or lost to follow-up will be censored at the last known alive date.

Assessor's comments:

The time to event endpoints PFS, DOR and OS were calculated using the Kaplan-Meier method. This is endorsed. The implemented censoring rules for the EMA submission (EMA censoring rules) for PFS and DOR, and the censoring rules for OS are agreed.

It is worth noticing that the interpretation of the time to event endpoints (PFS, DOR and OS) is hampered by the lack of a control arm and therefore the time to event endpoints are only considered exploratory.

Changes from the planned analyses

At the time of database lock (11 June 2021) SAP v4.0 (dated 17 December 2020) was effective. However, post database lock the SAP was updated to include changes to the safety AE reporting methodology as a result of feedback from the EMA.

Changes from the planned analyses in protocol to SAP version 1.0

- Efficacy Population is not used in this SAP and analyses since Safety Population is applied for overall population and each pre-specified subgroup. The definition for efficacy population for each pre-specified subgroup is same as the definition based on Safety Population.
- NSCLC patients tested with oncomine diagnostic target test (ODxTT) is added as an ODxTT sub-population in this SAP. RET-fusion positive NSCLC with measurable (target) lesions in CNS/brain patients, including brainstem and cerebellum, and without radiotherapy and radiosurgery 2 months before study drug, will be included into CNS metastases sub-population.
- Patients are grouped based on different grouping rules respectively. For example, the grouped starting dose will be based on patients' starting treatment dose.
- CNS metastases activity analysis is added as an exploratory analysis. The exploratory analysis on medical history, prior or concomitant medication, and time to event for pneumonitis, pneumonia, and hypertension are added, respectively.
- TEAE, related TEAE, SAE, and related SAE will be analysed by 1) prior PD-1/PD-L1 status for RET-fusion NSCLC patients treated at 400 mg QD, 2) by selected subgroups, RET-fusion NSCLC, MTC, others, and all Safety Population treated at 400 mg QD.

Changes from SAP version 1.0 to SAP version 2.0

- The definition for Efficacy Population is added to the SAP. The Efficacy Population is defined as a subset of the Safety Population who were dosed on or before July 11, 2019. This modification

was based on feedback received from FDA to allow enough follow-up time from initial response among responders.

- CNS metastases activity analysis is using only lesions in CNS/brain. The CNS ORR which is based on CNS/brain lesions will be provided. However, the analysis for PFS and DOR which are based on CNS/brain lesions are removed.
- The analysis of DOR across RET alteration status, and tumour types, i.e. RET-fusion NSCLC, RET-fusion PTC, MTC, and others, are added as a supportive analysis.
- Three AESI categories, pneumonia AESI, pneumonitis AESI, and tumour lysis syndrome AESI are added. The additional analyses for the AESIs are defined.
- One grouped term neutropenia, which include neutropenia and neutrophil count decreased, is also added. The analyses for grouped neutropenia will follow the same analysis method for AESIs. The exploratory time to event analyses for a single PT hypertension will also be provided.
- The summary analyses of demographics, medical history, prior and concomitant medication, prior anticancer therapies, dose modification will be provided for the AESIs.
- The laboratory parameter creatinine will be graded with NCI CTCAE version 5.0 to correct the grading error for this specific laboratory test used in CTCAE version 4.03.
- Changes from SAP version 2.0 to SAP version 3.0
- The RET-fusion NSCLC subpopulation and corresponding analyses are removed. RET fusion NSCLC will not split into different categories based on patients' prior therapy(ies).
- The dose-determing population, and DLT related analyses are removed.
- The prior radioactive iodine (RAI) and prior lenvatinib and/or sorafenib are added as two additional categories in prior antineoplastic therapy for RET-fusion thyroid patients.
- The primary analysis population for MTC has been changed from MTC to RET-mutation MTC. The detailed analyses for RET-mutation MTC has been added for primary analysis, secondary analysis endpoints, and safety analysis endpoints.
- The primary analysis population for PTC has been changed from RET-fusion PTC to RET-fusion thyroid. The detailed analysis for RET-fusion thyroid has been added for primary analysis, secondary analysis endpoints and safety analysis endpoints.
- One grouped term thrombocytopenia, which include thrombocytopenia and platelet count decreased, is added. The analysis for grouped thrombocytopenia will follow the same analysis method for AESIs and grouped neutropenia.
- The mitogen-activated protein kinases pathway expression signature analysis is removed from this version. The detailed analysis was documented in SAP Version 2.0.
- The C634X are combined with other genotypes, such as C609, C611, C618, C620, C630 of RET into cysteine rich domain.
- The summary analyses of circulating plasma concentrations of calcitonin and CEA are added for RET-mutation MTC patients. In addition, the BRR analyses based on calcitonin and CEA are also provided, respectively.
- The history CNS metastases are added into baseline characteristics analysis.

- Grouped anaemia are added into grouped AE analysis and time to onset of grouped anaemia is also added into time to onset analysis.
- The analysis for bowel movement function is added.
- The description about table/listing/figure formats is removed.

Changes from SAP version 3.0 to SAP version 4.0

- The objectives/endpoints/sample size section has been updated according to PA 13.
- The actual enrolment cut-off date has been removed.
- The primary efficacy endpoint ORR and the secondary efficacy endpoint CBR, DCR, and DOR will be analysed based on RET-altered Measurable Disease Population. The ORR and DOR will be conducted based on Efficacy Population as sensitivity analysis. Other efficacy endpoints will be based on Efficacy Population.
- The RET-fusion NSCLC subpopulation and corresponding analyses are added back to have comprehensive analysis plan.
- The subgroup, RET-altered thyroid patients, has been added into Section 3.6.4. The safety analyses will also be provided for RET-altered thyroid patients.
- The primary efficacy endpoints by RET gene status (hereditary, sporadic, others) for RET-mutation MTC patients has been added.
- The prior line of therapy has been added into baseline characteristics analysis. The primary analysis endpoint by the prior line of therapy will be provided. The derivation of prior line of therapy is also documented in Appendix.
- The RET gene status for MTC has been added into baseline characteristics analysis. The primary analysis endpoint by RET gene status for RET-mutation MTC will be provided. The derivation of RET gene status is also documented in Appendix.
- The definition of RET-fusion NSCLC CNS metastases population has been updated to include more details. In addition, the RET-fusion NSCLC CNS metastases activity analysis has been moved from Additional Exploratory Analysis to the Secondary
- Efficacy Analysis. The CNS metastases activity for other tumour types other than NSCLC has been added into Additional Exploratory Analysis section (Section 4.6.3).
- The AESI pneumonia, tumour lysis syndrome has been removed from AESI section. The updated AESI hypertension and new AESI hepatotoxicity have been added.

Changes from SAP version 4.0 to SAP version 5.0

- Number of protocol amendment when EORTC QLQ-C30 was introduced was corrected in section 4.6.3.1
- Clarification added in section 4.6.2.1 on the censoring rules for the start of a new antineoplastic/non-protocol treatment for PFS and DOR.
- All AE analyses will be done after adjacent AEs have been linked. Section 4.7.1.1 was updated to provide a more detailed explanation on how linked AEs will be reported.

- The AESI of Pneumonia and tumour lysis syndrome have been added back.
- Time to improvement has been removed from section 4.7.2
- Return to Baseline will no longer be consider when analysing Time to Resolution/Return to Baseline, therefore the name of the endpoint was also changed to Time to Resolution.
- Data imputation guidelines for new anticancer therapy date imputation have been added in section 7.1.5.

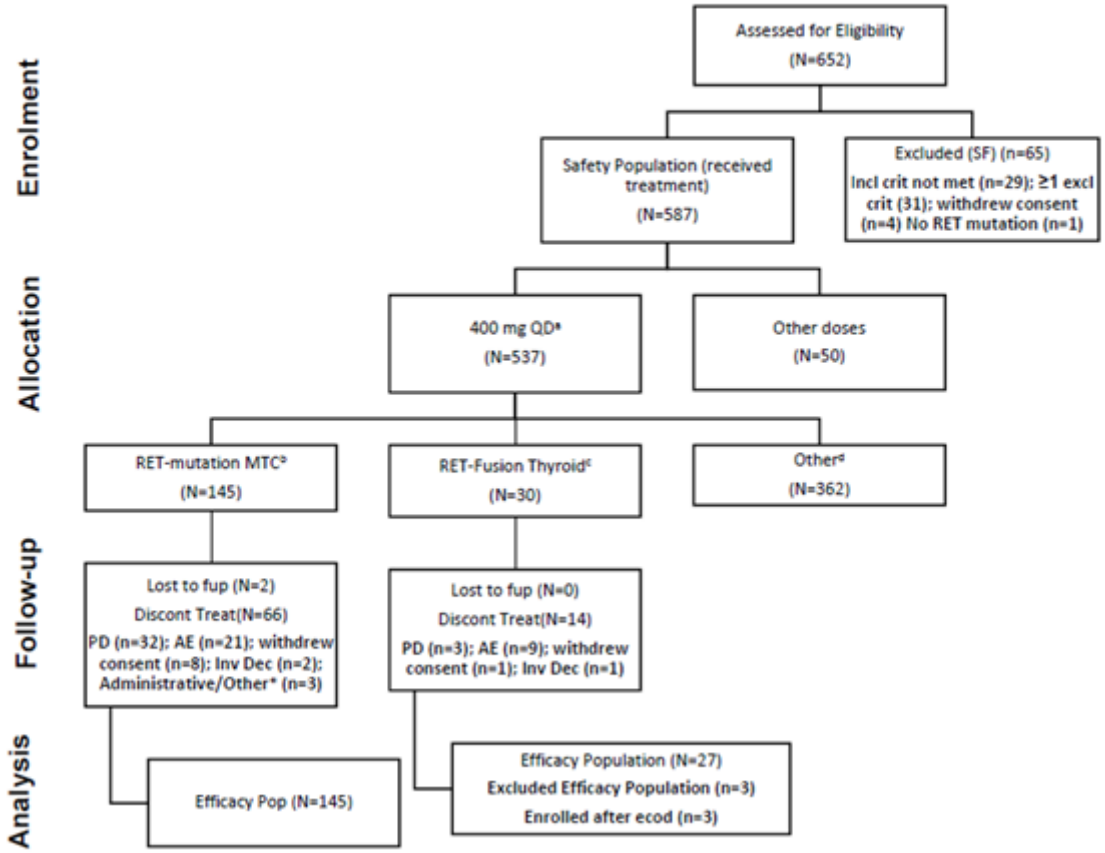
Assessor's comments:

The current version of the SAP is version 5.0 dated 9 August 2021. However, at the time of database lock (11 June 2021) SAP v4.0 (dated 17 December 2020) was effective. The changes made from version 1 to version 4 are related to the evolution of the study from exploratory to pivotal study. The changes made from version 4 to 5 are related to reporting of AE events and do not affect the interpretation of the results.

Results

Participant flow

Figure 1 Participant Flow



Assessor's comments:
The MAH has provided a flow diagram with the enrolment cut-off date as of 18 Feb 2021.

Recruitment

Date First Subject Enrolled: 17 March 2017 (First patient enrolled to data cut-off)

Data Cut-off Date: 12 April 2021

Database lock: 11 June 2021

Subjects in the pivotal study were enrolled and treated at 74 study centres in USA (19), China (19), France (8), Germany (5), Spain (5), Italy (4), South Korea (4), UK (3), Netherlands (2), Taiwan (2), Belgium (1), Hong Kong (1) and Singapore (1).

Conduct of the study

Protocol amendments

The original Protocol for Study BO42863 (dated 8 November 2016) was amended 13 times: 5 were global and 8 were country-specific amendments. The study methodology presented below is in accordance with the latest global Protocol Amendment 13 (dated 8 July 2020).

Table 6 Major Changes of Global Protocol Amendments

Amendment Number	Date	Summary of Major Changes
1	9 January 2017	The inclusion criteria now include only patients with unresectable disease; The exclusion criteria now exclude patients with NSCLC with a targetable mutation in EGFR, ALK, or ROS1; An enrollment stopping rule was incorporated that terminated further enrollment to the study if there was an excess of permanent treatment discontinuations due to study drug-related AEs; Strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, as well as inducers of CYP3A4 and strong dual P-gp and CYP3A4 inhibitors were included in the list of prohibited medications; An ECG measurement was added at Day 1 and Day 15, 4 hours post-dose.
2	2 February 2018	Exclusion criterion 1 was revised to exclude NSCLC patients with known BRAF mutations.

4.1	25 July 2018	Based on the favorable tolerability and encouraging efficacy observed in Phase 1, the sample size of Phase 2 was increased; A summary of Phase 1 was added, including determination of the MTD, overall safety, and preliminary efficacy for Phase 1; The overall enrollment for Phase 2 was increased to further evaluate the safety, efficacy, and PK of pralsetinib in RET-altered patients treated at the MTD/RP2D; Group 6 was added in Phase 2 to assess pralsetinib safety and efficacy in patients previously treated with a selective RET inhibitor; The allowed ECOG performance status was changed to be 0 to 1; Quality of life assessments added.
7	12 December 2018	Phase 2: Definitions of Groups 1 to 4 were adjusted to reflect previous treatment with approved standard of care agents. Group 5 was split into new Group 5 and new Group 7 to reflect that solid tumor patients with RET fusions and RET mutations may be distinct clinical and/or regulatory populations; Phase 2: Sample size was 80 patients in Group 1, 40 patients in Group 2, 60 patients in Group 3, and 40 patients in Group 5 to test the efficacy hypotheses for each group (increasing the study's total sample size to 360 patients); Phase 2: Safety Review Committee was added; Two new exclusion criteria were added to exclude patients with Grade 2 or serum phosphorus at baseline or with clinically significant interstitial lung disease or interstitial pneumonitis and exclusion criterion 7 was revised to clarify the washout period duration; The dose and administration section was split into subsections for Phase 1 and 2 and additional details/guidance on AE management and dose adjustments in Phase 2 were provided; Clarification that dose re-escalation after dose modification for AEs was discouraged and any exceptions to this rule were clarified.

9	3 July 2019	The study phase was updated from "1" to "1/2" to better describe the study design with the increased patient population and hypothesis testing; The study design was better described with the increased patient population and hypothesis testing; The Phase 2 Group 2 sample size was increased to 200 patients due to the encouraging initial data in treatment-naïve RET fusion-positive NSCLC patients, to allow for enrollment of RET fusion-positive NSCLC patients with no prior treatment (increasing the study's total sample size to 527 patients). Prior platinum chemotherapy in the neoadjuvant and adjuvant setting was permitted in this group if the last dose of platinum was ≥4 months before the first dose of study drug; Stopping rules were updated to account for increased sample size; Dose modification for Grade ≥3 pneumonitis was modified (patients had to be permanently discontinued from study treatment, unless the Investigator discussed with the Sponsor and believed the risk-benefit justified retreatment); Clarification was added that patients enrolled in Phase 1 and treated at the RP2D were pooled together with the appropriate Phase 2 groups for analyses; Statistics section was updated to align with the SAP.
13	8 July 2020	• Group 5: To more accurately characterize the activity of pralsetinib across various RET fusion-positive solid tumor types, the sample size of Group 5 has increased from N ~ 40 to N ~ 100 patients. (increasing the study's total sample size to 647 patients). As the intent of this cohort is to enroll a variety of RET-fusion tumor types, it is also clarified that Blueprint will notify sites if/when sufficient data are available and accrual should cease for a particular tumor type. Additionally, to ensure enrollment of a population with unmet medical need, patients should have previously received SOC appropriate for their tumor type, unless there is no accepted standard therapy for the tumor type or the Investigator has determined that treatment with standard therapy is not appropriate. Finally, given the primary endpoint of ORR, it is now required that subjects in Group 5 must have at least 1 target lesion evaluable by RECIST v1.1. • Phase 2 secondary objective in NSCLC patients and exploratory objective in patients with tumor types other than NSCLC have been updated to assess brain metastases activity in patients with measurable (target by RECIST v1.1) lesions in the brain by BICR (brain metastases sub-population) and assess the time to intracranial progression in all patients.

		• An additional analysis population, the RET-altered Measurable Disease Population, has been added to provide an assessment of the activity of pralsetinib in a mechanistically-relevant population. New language clarifies that this will be the primary analysis population for ORR, DOR, CBR and DCR, while the remaining efficacy endpoints will be examined using the Efficacy Population. • Subgroup analyses will be completed for Groups 2 and 4, consisting of: 1) patients enrolled prior to Protocol Amendment 9 (who were not candidates for standard therapies and thus may have had a poor prognosis) and 2) those enrolled on or after Protocol Amendment 9 (possibly a more typical first-line population). This will allow examination of the activity of pralsetinib in more typical first-line populations of patients with NSCLC and MTC. • Pharmacodynamic parameters of pralsetinib will include changes in tumor/blood including, but not limited to, changes in blood calcitonin and CEA and biochemical response rate (MTC patients only). • Group 2: The primary intent of this cohort is to assess the activity of pralsetinib in the treatment-naïve patients with NSCLC; therefore, text was added to clarify that this group will include no more than 30 patients with prior systemic therapy. • Updated study visit frequency after Cycle 17. All study visits after Cycle 17 will occur at every 4 cycles (16 weeks) (e.g. Cycle 21, Cycle 25…); study visit frequency and imaging was aligned within the Schedule of Assessments table. • Adjusted pralsetinib dose modification recommendations for treatment related Grade 1 and Grade 2 pneumonitis.

Table 1 Summary of Patient Enrollment by protocol number, RET-altered Thyroid Patients, Safety Population, 400 mg QD

Protocol Version	RET-mutant MTC (N=145)	RET fusion-positive TC (N=30)
Protocol Amendment 1.1	7 (4.8%)	3 (10.0%)
Protocol Amendment 2	27 (18.6%)	0
Protocol Amendment 2.1	9 (6.2%)	0
Protocol Amendment 3	2 (1.4%)	0
Protocol Amendment 4.1	23 (15.9%)	3 (10.0%)
Protocol Amendment 5	3 (2.1%)	0
Protocol Amendment 6	4 (2.8%)	1 (3.3%)
Protocol Amendment 7	31 (21.4%)	6 (20.0%)
Protocol Amendment 8	13 (9.0%)	0
Protocol Amendment 9	9 (6.2%)	9 (30.0%)
Protocol Amendment 10	6 (4.1%)	0
Protocol Amendment 11	2 (1.4%)	1 (3.3%)
Protocol Amendment 12	9 (6.2%)	1 (3.3%)
Protocol Amendment 13	0	6 (20.0%)

MTC=medullary thyroid cancer; TC=thyroid cancer.
Source: t_enroll_pv_RAT_SE_400_18Oct2021_42863.

Table 2. Overview of Analysis Population - RET fusion-positive thyroid cancer patients treated at 400 mg QD (CCOD of 18 October 2021)

	All Patients		Prior Systemic Treatment	
	In Population N(%)	Excluded N(%)	In Population N(%)	Excluded N(%)
Safety Population	30 (100)	0	27 (100)	0
Efficacy Population	27 (90)	3 (10)	25 (93)	2 (7)
RET-altered Measurable Disease Population	24 (80)	6 (20)	22 (81)	5 (19)

Assessor's comments:

The original Protocol for Study BO42863 (dated 8 November 2016) was amended 13 times. Changes for the target populations of MTC and TC are regarding groups 3, 4, 5 and 9. The MAH has provided a list of protocol amendments and how many patients were affected of those. Protocol amendment

v7 and protocol amendment v13 were the only protocol versions to include updates to the inclusion/exclusion criteria for cohorts 3, 4, 5 and 9 (Table 1). The amendment v7 rational section in protocol amendment v13 (RET-mutant MTC population): "The medullary thyroid cancer (MTC) groups (Groups 3 and 4) were updated to reflect previous treatment with one of the approved MKIs (cabozantinib and/or vandetanib) and not any MKI." A total of 70 (48%) patients were enrolled using protocol amendment v7 or a later version. The amendment v13 rational section in protocol amendment v13 (Group 5 patients): "Additionally, to ensure enrolment of a population with unmet medical need, patients should have previously received SOC appropriate for their tumour type, unless there is no accepted standard therapy for the tumour type or the Investigator has determined that treatment with standard therapy is not appropriate." Only 6 (20%) patients were enrolled after protocol amendment v13. The mentioned protocol amendments are not considered to endanger the integrity of the results. Changes for group 5 (solid tumours including RET fusion-positive TC) were done as of 8 July 2020 just before the data cut-off as of 23 Aug 2020. These changes were done to ensure enrolment of a population with unmet medical need. The MAH has provided an overview table (Table 2) regarding the RET fusion-positive thyroid cancer patients in terms of the number of patients excluded from the ORR analysis. Three patients were excluded from the efficacy population as these patients received their first treatment after the 18 February 2021 (the ECOD for the CCOD of 18 October 2021). A further three patients were excluded from the RET-altered measurable disease population as they did not have measurable (target) disease at baseline according to BICR. Hence, the ORR for the RET fusion-positive thyroid cancer patients was analysed including the patients without measurable disease in the denominator (ITT) for the efficacy population.

The consequences for the changes for group 4 (MTC patients not pre-treated with SOC) were a division of the patients included in 2 groups: 1) patients not candidates for SOC and 2) patients from a more typically first-line population. Upon request of the completed subgroup analyses the MAH has clarified that the mention of Group 4 patients in this context was a typo and will be corrected in protocol amendment 14, which is currently being finalized. The subgroup analyses were only performed for NSCLC patients.

Protocol deviations

At the time of the latest clinical cut-off date (CCOD 18 October 2021), a total of 39/145 (26.9%) **RET-mutant MTC patients** treated at 400 mg QD had at least one important/major protocol deviation. More than 1 important protocol deviation was reported in 10 individual patients.

- 13 patients had at least 1 important protocol deviation relating to Study Conduct/Procedures, Screening: 10 patients had no brain scan performed at screening as sites had not realized it had been introduced with protocol amendment 4.1; in 1 case AST was not tested at screening; 1 patient was not given the Dosing Diary; in 1 case pre-dose ECG not done due to subject's delay.

- 11 patients had at least 1 important protocol deviation relating to Study Conduct/Procedures, Study Assessment: 4 patients had one visit conducted via telemedicine due to covid-19 restrictions and assessments were missed; 4 patients had incomplete imaging at screening; 1 patient forgot to have tumour assessment; 1 patient had tumour assessment out of window; 1 patient diary lost.

- 7 patients had at least 1 important protocol deviation relating to dose administration: in 2 cases patients were dispensed an insufficient number of pills; in 2 cases the Investigator didn't follow the protocol guidance for dose reduction/interruption; in 2 cases the wrong kit was dispensed by the site pharmacy; in 1 case 2 doses were missed due to site error on IMP re-supply.

- 5 patients had at least 1 important protocol deviation relating to safety reporting/follow-up: delay in reporting SAE as required per protocol
- 3 patients had at least 1 important protocol deviation relating to Informed Consent, Presence/Absence: latest version of the ICF not signed by patients
- 2 patients had at least 1 important protocol deviation relating to Informed Consent, Signature/Date: in 1 case site staff did not sign ICF; in 1 case patient's signature missing on some pages of ICF
- 2 patients had at least 1 important protocol deviation relating to Informed Consent, Version: patients re-consented with wrong ICF version
- 2 patients had at least 1 important protocol deviation relating to Safety, Recording: in 1 case the Investigator did not follow protocol guidance regarding dose modification following AE hypocalcaemia; in 1 case the Investigator did not follow protocol guidance regarding dose modification following AE neutrophil count decreased.
- 1 patient had at least 1 important protocol deviation relating to Informed Consent: wrong version of the Informed consent signed
- 1 patient had at least 1 important protocol deviation relating to Investigational product, Handling/Storage/Retention: patient Dosing Diary not given to patient
- 1 patient had at least 1 important protocol deviation relating to Study Conduct/Procedures, Inclusion/Exclusion Criteria: first treatment prior to enrollment confirmation
- There were 2 major deviations related to medical review: 2 patients had an alternate driver mutation (KRAS G60D in 1 case and KRAS G12A in the other case).

Table 1 Summary of Protocol Deviations – RET fusion-positive Thyroid Cancer Patients (Efficacy Population)

Protocol: BO42863
Data cutoff date: 18 Oct 2021

Table 14.1.9.1.4.5 Protocol Deviation
Efficacy Population - RET-fusion Thyroid Patients

	400 mg QD		All Doses	
Category Sub-Category	Overall (N=27) n (%)	Prior Systemic Treatment (N=25) n (%)	Overall (N=29) n (%)	Prior Systemic Treatment (N=26) n (%)
Patients with at Least One Important/Major Deviation	9(33.3)	9(36.0)	10(34.5)	9(34.6)
Important	9(33.3)	9(36.0)	10(34.5)	9(34.6)
Informed Consent, Presence/Absence	4(14.8)	4(16.0)	4(13.8)	4(15.4)
Study Conduct/Procedures, Study Assessment	4(14.8)	4(16.0)	4(13.8)	4(15.4)
Study Conduct/Procedures, Screening	1(3.7)	1(4.0)	2(6.9)	1(3.8)
Major	0	0	0	0
Medical Review 1 [1]	0	0	0	0

[1] Major protocol deviation leading to exclusion from Response Evaluable Population.

Assessor's comments:

The MAH has updated the reported important protocol deviations. At the time of the latest clinical cut-off date (CCOD 18 October 2021), a total of 39/145 (26.9%) RET-mutant MTC patients treated at 400 mg QD had at least one important/major protocol deviation. More than 1 important protocol deviation was reported in 10 individual patients. An updated list regarding the MTC patient group has also been provided. No further important protocol deviations were reported for the patient who had incomplete images at screening, indicating that subsequent tumour assessments were complete. The AEs that were managed by the Investigators based on their own risk assessment and not according to the protocol resolved and the Investigators were reminded of the importance of following the guidance.

The MAH has provided an updated list of reported important protocol deviations (Table 1) and has clarified that the important protocol deviations reported for RET-fusion positive thyroid cancer patients were not considered having a significant effect on the safety or efficacy outcomes of the study.

Baseline data

	Overall (N=145) n (%)	Prior Systemic Treatment (N=78) n (%)	Prior Cabo. /Vand. Treatment (N=67) n (%)	Prior Cabo. And Vand. Treatment (N=24) n (%)	No Prior Cabo./Vand. Treatment (N=78) n (%)	No Prior Systemic Treatment (N=67) n (%)
History of CNS/Brain Metastases	13 (9.0)	7 (9.0)	7 (10.4)	3 (12.5)	6 (7.7)	6 (9.0)
RET-altered Mutation Status (continued)						
Cysteine rich domain[5]	42 (29.0)	17 (21.8)	15 (22.4)	5 (20.8)	27 (34.6)	25 (37.3)
V804X[6]	3 (2.1)	2 (2.6)	2 (3.0)	2 (8.3)	1 (1.3)	1 (1.5)
Other	8 (5.5)	4 (5.1)	4 (6.0)	1 (4.2)	4 (5.1)	4 (6.0)

Table 2 Demographics and Baseline Disease Characteristics, RET mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant MTC			RET Fusion-positive TC	
	Overall (N=145)	Prior Cabo and/or Vand (N=67)	No prior Systemic Treatment (N=67)	Overall (N=27)	Prior Systemic Treatment (N=25)
Age (years)					
Median	57.0	59.0	55.0	61.0	60.0
Range	18, 83	25, 83	18, 81	23, 84	23, 74
Sex (n (%))					
Female	52 (35.9)	23 (34.3)	24 (35.8)	17 (63.0)	16 (64.0)
Male	93 (64.1)	44 (65.7)	43 (64.2)	10 (37.0)	9 (36.0)
Race (n (%))					
Asian	43 (29.7)	3 (4.5)	37 (55.2)	9 (33.3)	8 (32.0)
Black	1 (0.7)	0	1 (1.5)	1 (3.7)	1 (4.0)
White	89 (61.4)	55 (82.1)	27 (40.3)	17 (63.0)	16 (64.0)
Unknown	11 (7.6)	8 (11.9)	2 (3.0)	0	0
Other	1 (0.7)	1 (1.5)	0	0	0
BMI (kg/m^2)					
Median	24.03	23.07	24.30	24.06	24.06
Range	14.0, 46.5	14.7, 36.5	15.0, 46.5	14.9, 31.9	14.9, 31.9
Histology Type (n (%))					
Medullary	145 (100)	67 (100)	67 (100)	0	0
Papillary	0	0	0	24(88.9)	23(92.0)
Follicular	0	0	0	0	0
Anaplastic	0	0	0	1(3.7)	1(4.0)
Other	0	0	0	2(7.4)	1(4.0)
ECOG (n (%))					
0	63 (43.4)	18 (26.9)	38 (56.7)	11(40.7)	11(44.0)
1	79 (54.5)	46 (68.7)	29 (43.3)	16(59.3)	14(56.0)
2	3 (2.1)	3 (4.5)	0	0	0
Most Common Target/Non-Target Lesion Location[1]					
Liver	73 (50.3)	38 (56.7)	29 (43.3)	7(25.9)	7(28.0)
Mediastinal Adenopathy	71 (49.0)	28 (41.8)	35 (52.2)	16(59.3)	15(60.0)
Lung	68 (46.9)	31 (46.3)	28 (41.8)	23(85.2)	22(88.0)

TNM Stage at Screening [2]					
Stage II	0	0	0	2(7.4)	2(7.4)
Stage IV	49 (33.8)	28 (41.8)	15 (22.4)	15(55.6)	14(56.0)
Stage IVA	11 (7.6)	4 (6.0)	7 (10.4)	1(3.7)	1(4.0)
Stage IVB	16 (11.0)	9 (13.4)	5 (7.5)	4(14.8)	3(12.0)
Stage IVC	69 (47.6)	26 (38.8)	40 (59.7)	5(18.5)	5(20.0)
RET-altered Mutation Status	145 (100)	67 (100)	67 (100)		
RET - mutation	92 (63.4)	46 (68.7)	37 (55.2)		
M918T	42 (29.0)	15 (22.4)	25 (37.3)		
Cysteine rich domain[3]	3 (2.1)				
V804X[4]		2 (3.0)	1 (1.5)		
Other					
RET - fusion				0	0
KIF5B				17(63.0)	15(60.0)
CCDC6				6(22.2)	6(24.0)
NCOA4				4(14.8)	4(16.0)
Other	8 (5.5)	4 (6.0)	4 (6.0)		
History of CNS Metastases n (%)	13 (9.0)	7 (10.4)	6 (9.0)	10(37.0)	10(40.0)

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021

Notes: BMI=Body mass index, calculated as (weight in kg)/(height in meter)^2; Cabo= Cabozantinib; Vand= Vandetanib, Black = Black or African American.

[1] Target/Non-target lesion location is based on central image data.

[2] TNM = Tumor, Node, Metastasis

[3] Cysteine rich domain includes patients with single nucleotide variants of or short indels that include but are not limited to the following residues: C609, C611, C618, C620, C630 and/or C634 of RET.

[4] V804X includes patients with a RET-mutation status of V804M and/or V804L.

Source: T14_01_03_01_01_04_dm_mtc_400mg ; T14_01_03_01_04_05_dm_eff_thyr ; T14_01_04_01_01_04_bdc_mtc_400mg; T14_01_04_01_04_05_bdc_eff_thyr

Assessor's comments:

The MAH has provided an updated overview of the baseline characteristics for the 2 indication groups (efficacy population) (Table 2).

The patients with RET-mutant MTC (N=145) were predominantly White (61.4%) or Asian (29.7%), male (64.1%), and had a median age of 57 years. All patients had Stage IV disease and most had ECOG status of 0 (63 patients [43.4%]) or 1 (79 patients [54.5%]). Liver (50.3%) was the most common target/non-target lesion location at baseline based on central image data, followed by mediastinal adenopathy (48.3%) and lung (46.9%). Thirteen patients (9.0%) had a history of CNS metastases; of these, 9 patients (6.2%) had CNS metastases identified by BICR as target/non-target lesion at baseline.

The patients with RET fusion-positive thyroid cancer (N=27) were either White (63.0%) or Asian (33.3%), predominantly female (63.0%), and had a median age of 61 years. At baseline, 24 patients (88.9%) had PTC, 1 patient (3.7%) had anaplastic thyroid cancer and 2 patients had "other" (both were poorly differentiated thyroid cancer) histology type (7.4%). Twenty-five (92.6%) had Stage IV disease, and two patients had Stage II disease (these patients were <55 years and had metastatic disease according to the 8th edition AJCC TNM staging for DTC) at baseline. All

patients had ECOG status of 0 (11 patients [40.7%]) or 1 (16 patients [59.3%]). Lung (85.2%) was the most common target/non-target lesion location at baseline based on central image data, followed by mediastinal adenopathy (16 patients [59.3%]). Ten patients (37.0%) had a history of CNS metastases; of these, 6 patients (22.2%) had CNS metastases identified by BICR as target/non-target lesion at baseline.

In the MTC population 67/145 have been treated with prior cabozantinib or vandetanib of which 24 have been treated with both regimens. 11 received other systemic therapies. 67/145 were treatment-naïve. In the TC group 25/27 have been treated with prior systemic treatment. The baseline characteristics for the previous treated and the treatment-naïve populations are reflected in the SmPC.

Numbers analysed

Table 1 Patient disposition, RET-mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant MTC			RET Fusion-positive TC	
	Overall (N=145)	Prior Cabo and/or Vand (N=67)	No prior Systemic Treatment (N=67)	Overall (N=27)	Prior Systemic Treatment (N=25)
Discontinued from Treatment	66 (45.5)	42 (62.7)	19 (28.4)	14 (51.9)	12 (48.0)
Continuing on Treatment	79 (54.5)	25 (37.3)	48 (71.6)	13 (48.1)	13 (52.0)
Discontinued from Study	48 (33.1)	31 (46.3)	13 (19.4)	13 (48.1)	11 (44.0)
Continuing Study Follow-up	97 (66.9)	36 (53.7)	54 (80.6)	14 (51.9)	14 (56.0)
Reasons For Discontinuation of Treatment					
Disease Progression	32 (22.1)	25 (37.3)	5 (7.5)	3 (11.1)	3 (12.0)
Adverse Event(s)	21 (14.5)	10 (14.9)	8 (11.9)	9 (33.3)	7 (28.0)
Withdrew Consent	8 (5.5)	5 (7.5)	3 (4.5)	1 (3.7)	1 (4.0)
Administrative/Other	3 (2.1)	1 (1.5)	2 (3.0)	0	0
Investigator's Decision	2 (1.4)	1 (1.5)	1 (1.5)	1 (3.7)	1 (4.0)
Reasons For Discontinuation of Study					
Death	27 (18.6)	17 (25.4)	8 (11.9)	10 (37.0)	8 (32.0)
Withdrew Consent	12 (8.3)	7 (10.4)	3 (4.5)	3 (11.1)	3 (12.0)
Disease Progression	3 (2.1)	2 (3.0)	1 (1.5)	0	0
Adverse Event(s)	2 (1.4)	2 (3.0)	0	0	0
Lost to Follow-up	2 (1.4)	1 (1.5)	1 (1.5)	0	0
Investigator's Decision	1 (<1)	1 (1.5)	0	0	0
Initiation of Another Antineoplastic Therapy	1 (<1)	1 (1.5)	0	0	0

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021

Notes: Cabo=Cabozantinib; Vand=Vandetanib.

Source: T14_01_02_01_04_05_ds_eff_thyr. T14_01_02_01_01_04_ds_mtc_400mg.

Assessor's comments:

The MAH has provided an overview of the patient disposition of the 2 indication groups each divided into the overall group and prior/no prior treatment groups (Table 1).

Out of the 145 MTC patients, a total of 66 patients (45.5%) discontinued from treatment and 48 patients (33.1%) discontinued from the study. Death (27 patients [18.6%] was the main reason for study discontinuation, followed by withdrawal of consent (12 patients [8.3%]), disease progression (3 patients [2.1%]), AEs, lost to follow-up (2 patients [1.4%] each), investigator's decision, and initiation of another antineoplastic therapy (1 patient [<1%] each). Disease progression (32 patients [22.1%]) was the main reason for treatment discontinuation, followed by AEs (21 patients [14.5%]), withdrawal of consent (8 patients [5.5%]), administrative/other (3 patients [2.1%]) and investigator's decision (2 patients [1.4%]). At the CCOD, 79 patients (54.5%) remained on study treatment.

Out of the 27 RET-fusion positive patients fourteen patients (51.9%) discontinued from treatment and 13 patients (48.1%) discontinued from the study, with death (10 patients [37.0%]) as the main reasons for study discontinuation, followed by withdrawal of consent (3 patients [11.1%]). AEs were the main reason for treatment discontinuation (9 patients [33.3%]), followed by disease progression (3 patients [11.1%]), withdrawal of consent and investigator's decision (1 patient [3.7%]). At the time of CCOD, 13 patients (52.0%) remained on study treatment.

Outcomes and estimation

Primary efficacy endpoint: Overall response rate

Table 3 Summary of Best Overall Response, RET-mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant MTC			RET Fusion-positive TC	
	Overall (N=145)	Prior Cabo and/or Vand (N=67)	No prior Systemic Treatment (N=67)	Overall (N=27)	Prior Systemic Treatment (N=25)
ORR (confirmed CR or PR), n (%)[a]	90 (62.1)	35 (52.2)	48 (71.6)	21 (77.8)	21 (84.0)
95% CI[b]	(53.6, 70.0)	(39.7, 64.6)	(59.3, 82.0)	(57.7, 91.4)	(63.9, 95.5)
CR, n (%)	9 (6.2)	2 (3.0)	4 (6.0)	4 (14.8)	4 (16.0)
PR, n (%)	81 (55.9)	33 (49.3)	44 (65.7)	17 (63.0)	17 (68.0)
SD, n (%)	42 (29.0)	27 (40.3)	13 (19.4)	5 (18.5)	4 (16.0)
PD, n (%)	5 (3.4)	2 (3.0)	2 (3.0)	0	0
Not evaluable, n (%)	8 (5.5)	3 (4.5)	4 (6.0)	1 (3.7)	0

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021

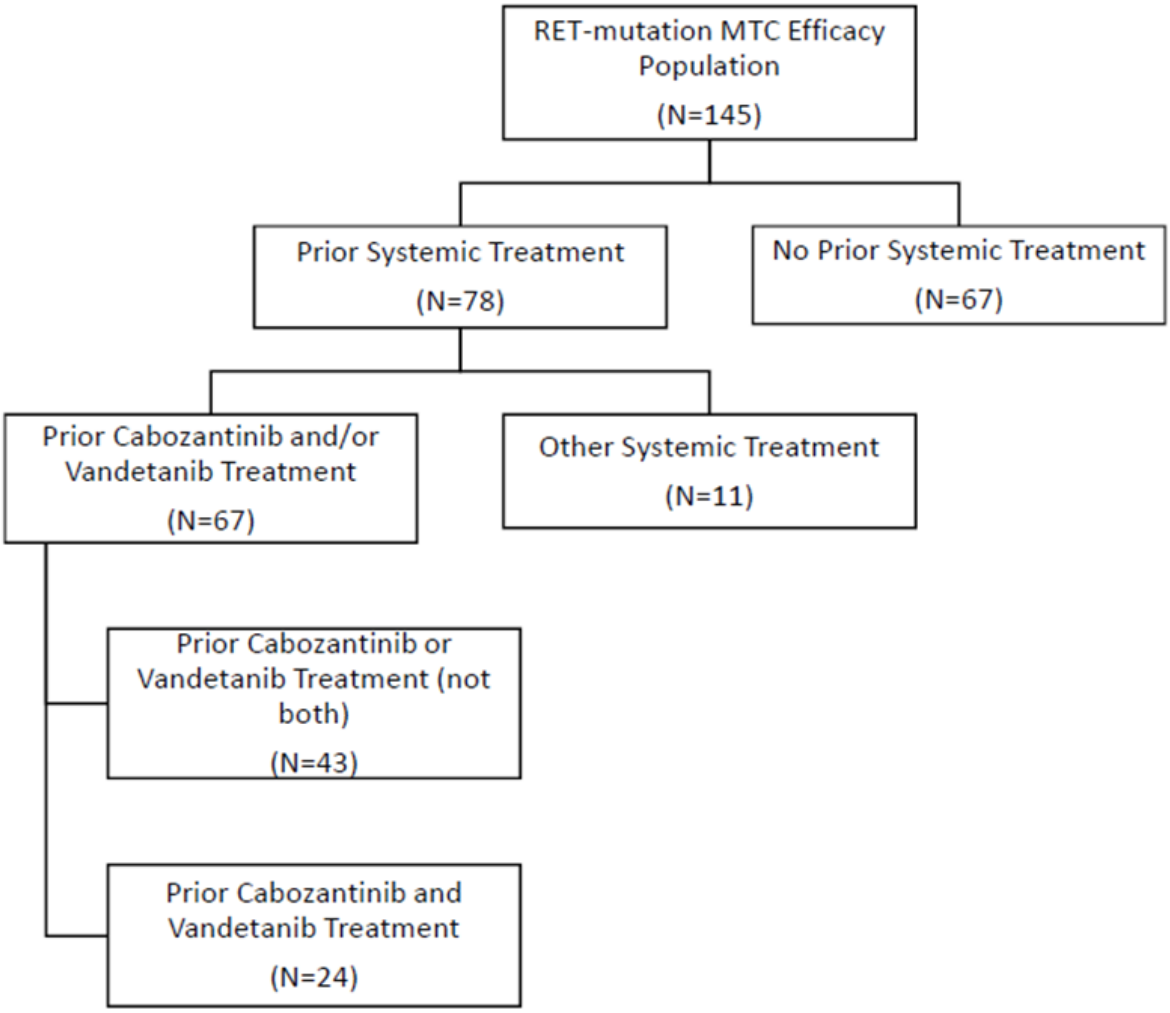
Cabo=cabozantinib; CI=confidence interval; CR=complete response; MTC=medullary thyroid cancer; ORR=overall response rate; PD=progressive disease; PR=partial response; RET=rearranged during transfection; SD=stable disease; Vand=vandetanib.

a The proportion of patients with BOR of confirmed CR or PR.

b Two-side 95% confidence interval (CI) based on exact binomial distribution using Clopper-Pearson method.

Source: T14_02_01_01_04_03_br_cr_mtc; T14_02_01_01_04_05_br_cr_thyr

Figure 1 Flowchart: RET-mutation MTC - Efficacy population treated at 400 mg QD



Assessor's comments:

Overall, the confirmed ORR for MTC patients at the CCOD of 18 October 2021 was 62.1% (90/145; 95% CI 53.6, 70.0) by BIRC assessment. For the treatment-naïve patients it was 71.6% (48/67; 95% CI 59.3, 82.0) with falling ORR according to prior treatment with cabo and/or vand, 52.2% (35/67; 95% CI 39.7, 64.6) . The majority of the BoR overall were PRs (55.9%), followed by SD (29.0). Nine (6.2%) reached CR. Five (3.4%) of the patients had progressed at the time of DCO. It should be noted, that SD was confirmed when lasting at least 16 weeks. The ORR observed with pralsetinib in ths population is indeed compelling despite small numbers of patients and might be considered of relevance and even higher than ORRs reported with TKIs in the subgroup of patients with RET mutations (32% with cabozantinib and 56.5% with vandetanib). However, only 5 (3 in the pre-treated groups) of the MTC patients (none of the TC patients) have progressed at the DCO.

According to the SAP, patients without disease assessments would be imputed as 'not evaluable (NE)'. As of the clinical cut-off date (CCOD) of 18 October 2021, a total of 8 patients in the RET mutant MTC efficacy population treated at 400 mg QD had a BOR of NE. As of the CCOD of 18 October 2021, 1 patient in the RET fusion-positive thyroid cancer efficacy population treated at 400 mg QD was imputed as NE. The MAH has as requested provided narratives for the patients classified as NE. These are endorsed.

The MAH has clarified the definitions of best overall response of NE (not evaluable): patients who did not have post baseline assessments. This also includes patients with no lesions (either target and non-target) at baseline, as assessed by BIRC. Non-measurable disease: patients who did not have target lesions at baseline as assessed by the BIRC. The MAH has also clarified the response status of 16 MTC patients of whom 8 patients had a BOR of NE with 12 patients having non-measurable disease. Four patients had both BOR of NE and non-measurable disease.

However, the target patient population is the population previous treated with tyrosine kinase inhibitors (n=67). The MAH has clarified the confusing numbers of patients previous or not previous treated with Cabozantinib and/or Vandetanib by providing a new figure (Figure 1). The missing 11 patients had a prior systemic treatment other than Cabozantinib or Vandetanib and were analysed as part of the overall efficacy population and also as part of the "No Prior Cabo/Vande treatment" population (n=78). Among the previous treated patients fourty-three had prior cabo or vand while twenty-four had prior cabo and vand.

Assessor's comments:

Overall, the confirmed ORR for TC patients at the CCOD of 18 October 2021 was 77.8% (21/27; 95% CI 57.7, 91.4). For the pre-treated patients, which is the target population it was 84.0% (21/25; 95% CI 63.9, 95.5). The majority of the BOR overall were PRs (63.0%) followed by SD (18.5%).

Secondary efficacy endpoint: Duration of response

Summary of Duration of Response (MTC):

Table 4 Summary of Time to Response and Duration of Response, RET mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant Positive MTC			RET Fusion-positive TC	
	Overall	Prior Cabo and/or Vand	No prior Systemic Treatment	Overall	Prior Systemic Treatment
Number of confirmed responders	90	35	48	21	21
Time to first response (months)					
Mean (SD)	5.66 (4.387)	4.99 (3.986)	6.06 (3.649)	2.57 (1.577)	2.57 (1.577)
Median (min–max)	4.29 (1.7-27.3)	3.71 (1.8-20.2)	5.57 (1.8-18.6)	1.84 (1.7-7.9)	1.84 (1.7-7.9)
DOR KM estimates (months)					
Median (95% CI)[a]	29.5 (24.0, NR)	25.8 (18.0, NR)	NR	23.6 (15.1, NR)	23.6 (15.1, NR)
Patients with event, n (%)	29 (32.2)	18 (51.4)	8 (16.7)	8 (38.1)	8 (38.1)
Patients censored, n (%)	61 (67.8)	17 (48.6)	40 (83.3)	13 (61.9)	13 (61.9)
Follow-up DOR KM estimates (months)					
Median (95% CI)[a]	22.1 (18.2, 25.9)	27.6 (23.7, 31.5)	16.5 (13.1, 20.0)	17.7 (13.0, 29.7)	17.7 (13.0, 29.7)

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021
Cabo=Cabozantinib; CI=confidence interval; DOR=duration of response; KM=Kaplan-Meier; NR=not reached; SD=standard deviation; Vand=Vandetanib.
Patients with confirmed CR/PR are included in the analysis.
a The 95% CI is based on Greenwood formula.
Source: T14_02_03_01_02_04_04_dor_ret_cr_ema_mtc_400mg; T14_02_03_01_02_04_05_dor_ret_cr_ema_thyr.

Assessor's comments:

Duration of response are analysed for patients with confirmed CR or PR. As median DOR was not reached the MAH has provided a new update where median time to first response in the 90 RET-mutant MTC patients overall with a confirmed response was 4.29 months (range: 1.7 - 27.3). Median DOR was 29.5 months (95% CI: 24.0, NR), with 61 (67.8%) patients censored and 29 (32.2%) patients with an event (Table 4). Median response follow-up time was 22.1 months (95% CI: 18.2, 25.9). Median DOR was 25.8 months (95% CI: 18.0, NR) in RET-mutant MTC patients with prior cabozantinib and/or vandetanib treatment and Median DOR was not reached in RET-mutant MTC patients with no prior systemic treatment. Median time to first response in the 21 RET fusion-positive thyroid cancer patients overall with a confirmed response was 1.84 months (range: 1.7-7.9), and median response follow-up time was 17.7 months (95% CI: 13.0, 29.7). Median DOR was

23.6 months (95% CI: 15.1, NR), with 13 patients (61.9%) censored and 8 patients (38.1%) with an event (Table 4).

Clinical benefit rate (CBR) by central radiology assessment per RECIST 1.1: The MAH has not provided updated data as of 18 October 2021.

Disease control rate by central radiology assessment per RECIST 1.1: The MAH has not provided updated data as of CCOD 18 October 2021.

Progression free survival (PFS):

Table 5 Summary of Progression Free Survival, RET-mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant Positive MTC			RET Fusion-positive TC	
	Overall (N=145)	Prior Cabo and/or Vand (N=67)	No prior Systemic Treatment (N=67)	Overall (N=27)	Prior Systemic Treatment (N=25)
PFS KM estimates (months)					
Median (95% CI)[a]	31.2 (25.8, NR)	25.8 (19.7, 35.0	NR (27.5, NR)	25.4 (13.0, -)	25.4 (17.0, -)
Patients with event, n (%)	57 (39.3)	35 (52.2)	17 (25.4)	12 (44.4)	10 (40.0)
Patients censored, n (%)	88 (60.7)	32 (47.8)	50 (74.6)	15 (55.6)	15 (60.0)
Follow-up PFS KM estimates (months)					
Median (95% CI)[a]	25.9 (22.3, 29.5)	30.8 (28.6, 33.4)	22.0 (19.1, 25.9)	21.2 (18.3, 31.5)	21.2 (18.3, 31.5)

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021

Cabo=Cabozantinib; CI=confidence interval; KM=Kaplan-Meier; NR=not reached; PFS=progression free survival; Vand=Vandetanib.

[a] The 95% CI is based on Greenwood formula.

Source: T14_02_02_01_02_04_04_pfs_ret_cr_ema_mtc_400mg ; T14_02_02_01_02_04_05_pfs_ret_cr_ema_thyr

Assessor's comments:

Overall, 57 (39.3%) of 145 patients with RET-mutant MTC had a PFS event at the CCOD of 18 October 2021. Median PFS (KM estimate) was 31.2 months (95% CI: 25.8, NR). Median follow-up time was 25.9 months (95% CI: 22.3, 29.5) (Table 5). Median PFS was shorter in the 67 patients with prior cabozantinib and/or vandetanib treatment (25.8 months [95% CI: 19.7, 35.0]). Median follow-up time was 30.8 months (95% CI: 28.6, 33.4). Median PFS was not reached for the 67 patients with no prior systemic treatment. Median follow-up time was 22.0 months (95% CI: 19.1, 25.9). The MAH has not provided an updated KM curve.

As of the clinical cut-off date (CCOD) of 18 October 2021 a total of 88 patients were censored. The MAH has clarified that all censored patients had no documented progressive disease (PD) at the time of the CCOD. Hence, the remaining patients are still in risk of an event.

According to the EMA censoring rules listed in the Table 8 in the SAP v 5.0, patients with no baseline assessments and alive after 2 scheduled assessments, and patients without experienced progression nor death were to be censored. The number of PFS events for 18 October 2021 clinical cut-off date for the RET-mutant medullary thyroid cancer (MTC) patients is 57. The MAH has clarified why there can be seen differences in the number of events as there is made an distinguish between the number of "Death without progressive disease (PD) before the 1st Scheduled Assessment" and the number of "Death without PD before the 2nd Scheduled Assessment".

Overall, 12 (44.4%) of 27 patients with RET fusion-positive thyroid cancer had a PFS event (Table 5). Median PFS (KM estimate) was 25.4 months (95% CI: 17.0, NR). Median follow-up time was 21.2 months (95% CI: 18.3, 31.5). The median PFS and median follow-up time is the same for the patients with prior systemic treatment. The MAH has not provided an updated KM curve.

Overall survival (OS):

Table 6 Summary of Overall Survival, RET-mutant MTC and RET fusion-positive TC patients, efficacy population treated at 400 mg QD

	RET-mutant Positive MTC			RET Fusion-positive TC	
	Overall (N=145)	Prior Cabo and/or Vand (N=67)	No prior Systemic Treatment (N=67)	Overall (N=27)	Prior Systemic Treatment (N=25)
OS KM estimates (months)					
Median (95% CI)[a]	NR (NR, NR)	NR (36.9, NR)	NR (NR, NR)	25.4 (17.7, NR)	NR (17.7, NR)
Deaths, n (%)	28 (19.3)	18 (26.9)	8 (11.9)	10 (37.0)	8 (32.0)
Patients censored, n (%)	117 (80.7)	49 (73.1)	59 (88.1)	17 (63.0)	17 (68.0)
Follow-up OS KM estimates (months)					
Median (95% CI)[a]	27.1 (25.2, 29.6)	31.0 (27.4, 32.4)	22.7 (22.0, 24.8)	21.6 (15.7, 32.5)	21.6 (15.7, 32.5)

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021.
Cabo=Cabozantinib; CI=confidence interval; KM=Kaplan-Meier; NR=not reached; OS=overall survival; Vand=Vandetanib.
[a] The 95% CI is based on Greenwood formula.
Source: T14_02_04_01_04_04_ovs_ret_mtc_400mg; T14_02_04_01_04_05_ovs_ret_thyr

Assessor's comments:

Overall, 28/145 patients (19.3%) with RET-mutant MTC treated at 400 mg had died. KM estimate for median OS was not reached and median follow up time was 27.1 months (95% CI: 25.2, 29.6) (Table 6).

Overall, 10/27 patients (37.0%) with RET-fusion positive thyroid cancer had died. KM estimate for median OS (KM estimate) was 25.4 months (95% CI: 17.7, NR) and median follow up was 21.6

months (95% CI: 15.7, 32.5). Only 8/25 patients (32.0%) with prior systemic treatment had died. KM estimate for median OS was not reached and median follow up time was the same as for the overall population.

Overall, PFS and OS preliminary results seem encouraging, but a firm conclusion over the long-term benefit from pralsetinib for the intended population cannot be drawn due to the lack of a control arm.

Ancillary analyses

Subgroup analyses of mTTR and DOR:

mTTR and DOR by age group:

Overall, median time to first response as per EMA censoring rule was slightly shorter in RET mutation-positive MTC patients treated at 400 mg QD who were ≥65 years old (3.75 months [range: 1.9-11.5]) compared to those who were <65 years old (4.63 months [range: 1.6-27.3]). Median DOR was 25.8 months (95% CI: 19.4, 33.7) for patients <65 years old, and was not reached for patients who were ≥65 years.

The number of patients, who were <65 years, reaching a DOR ≥9 months, ≥12 months, ≥18 months and ≥24 months was 58 (75.3%), 44 (57.1%), 23 (29.9%) and 10 (13.0%), respectively. The number of patients, who were ≥65 years, reaching a DOR ≥9 months, ≥12 months, ≥18 months and ≥24 months was 8 (72.7%), 6 (54.5%), 4 (36.4%) and 2 (18.2%), respectively.

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: >=65 Years old

	Overall (N=11)	Prior Systemic Treatment (N=5)	Prior Cabo./Vand. Treatment (N=4)	Prior Cabo. And Vand. (N=2)	No Prior Cabo./Vand. Treatment (N=7)	No Prior Systemic Treatment (N=6)
Time to Response						
Time (Days) to First Response (CR/PR)						
n	11	5	4	2	7	6
Mean (StdDev)	162.7 (91.97)	159.2 (112.89)	170.8 (126.90)	138.0 (41.01)	158.1 (77.32)	165.7 (81.85)
Median	114.0	113.0	138.0	138.0	114.0	143.0
Min, Max	58, 349	58, 349	58, 349	109, 167	74, 281	74, 281
Time (Months) to First Response (CR/PR)						
n	11	5	4	2	7	6
Mean (StdDev)	5.35 (3.022)	5.23 (3.709)	5.61 (4.169)	4.53 (1.347)	5.20 (2.540)	5.44 (2.689)
Median	3.75	3.71	4.53	4.53	3.75	4.70
Min, Max	1.9, 11.5	1.9, 11.5	1.9, 11.5	3.6, 5.5	2.4, 9.2	2.4, 9.2

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: >=65 Years old

	Overall (N=11)	Prior Systemic Treatment (N=5)	Prior Cabo./Vand. Treatment (N=4)	Prior Cabo. And Vand. (N=2)	No Prior Cabo./Vand. Treatment (N=7)	No Prior Systemic Treatment (N=6)
Duration of Response Follow-up Time Kaplan-Meier Estimates (Months) [1]						
Median (95% CI) [2]	19.6 (15.8, 26.4)	15.8 (1.8, 29.5)	15.8 (1.8, 15.8)	- (1.8, -)	22.7 (16.7, 29.5)	21.2 (16.7, 26.4)
25th, 75th Percentiles	16.7, 26.4	15.8, 29.5	8.8, 15.8	1.8, -	19.6, 26.4	18.2, 24.6
Duration of Response Kaplan-Meier Estimates (Months)						
Median (95% CI) [2]	- (9.2, -)	- (5.6, -)	11.5 (5.6, -)	5.6 (-, -)	- (9.2, -)	- (9.2, -)
25th, 75th Percentiles	9.2, -	8.5, -	5.6, -	5.6, 5.6	9.2, -	9.2, -
Min, Max	1.8, 29.5^	1.8, 29.5^	1.8, 15.8^	1.8, 5.6	7.4, 29.5^	7.4, 26.4^

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: >=65 Years old

	Overall (N=11)	Prior Systemic Treatment (N=5)	Prior Cabo./Vand. Treatment (N=4)	Prior Cabo. And Vand. (N=2)	No Prior Cabo./Vand. Treatment (N=7)	No Prior Systemic Treatment (N=6)
Duration of Response (DOR), n (%)						
<6 months	2 (18.2)	2 (40.0)	2 (50.0)	2 (100)	0	0
<3 months	1 (9.1)	1 (20.0)	1 (25.0)	1 (50.0)	0	0
>=3 months to <6 months	1 (9.1)	1 (20.0)	1 (25.0)	1 (50.0)	0	0
>=6 months	9 (81.8)	3 (60.0)	2 (50.0)	0	7 (100)	6 (100)
>=9 months	8 (72.7)	3 (60.0)	2 (50.0)	0	6 (85.7)	5 (83.3)
>=12 months	6 (54.5)	2 (40.0)	1 (25.0)	0	5 (71.4)	4 (66.7)
>=18 months	4 (36.4)	1 (20.0)	0	0	4 (57.1)	3 (50.0)
>=24 months	2 (18.2)	1 (20.0)	0	0	2 (28.6)	1 (16.7)
Patients with Event, n (%)	4 (36.4)	2 (40.0)	2 (50.0)	1 (50.0)	2 (28.6)	2 (33.3)
Patients Censored, n (%)	7 (63.6)	3 (60.0)	2 (50.0)	1 (50.0)	5 (71.4)	4 (66.7)
Discontinued from Study	1 (9.1)	1 (20.0)	1 (25.0)	1 (50.0)	0	0
<6 months	1 (9.1)	1 (20.0)	1 (25.0)	1 (50.0)	0	0
>=6 months	0	0	0	0	0	0

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: <65 Years old

	Overall (N=78)	Prior Systemic Treatment (N=36)	Prior Cabo./Vand. Treatment (N=30)	Prior Cabo. And Vand. (N=12)	No Prior Cabo./Vand. Treatment (N=48)	No Prior Systemic Treatment (N=42)
Time to Response						
Time (Days) to First Response (CR/PR)						
n	78	36	30	12	48	42
Mean (StdDev)	167.3 (130.58)	145.5 (143.96)	134.0 (88.23)	165.9 (110.15)	188.1 (148.27)	186.0 (116.43)
Median	130.5	113.0	113.0	166.5	169.0	169.5
Min, Max	50, 830	53, 830	54, 393	55, 393	50, 830	50, 565
Time (Months) to First Response (CR/PR)						
n	78	36	30	12	48	42
Mean (StdDev)	5.50 (4.290)	4.78 (4.730)	4.40 (2.899)	5.45 (3.619)	6.18 (4.871)	6.11 (3.825)
Median	4.29	3.71	3.71	5.47	5.55	5.57
Min, Max	1.6, 27.3	1.7, 27.3	1.8, 12.9	1.8, 12.9	1.6, 27.3	1.6, 18.6

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: <65 Years old

	Overall (N=78)	Prior Systemic Treatment (N=36)	Prior Cabo./Vand. Treatment (N=30)	Prior Cabo. And Vand. (N=12)	No Prior Cabo./Vand. Treatment (N=48)	No Prior Systemic Treatment (N=42)
Duration of Response Follow-up Time Kaplan-Meier Estimates (Months) [1]						
Median (95% CI) [2]	14.7 (12.9, 21.9)	24.0 (22.0, 29.4)	24.4 (18.9, 29.4)	24.0 (16.1, -)	11.0 (9.2, 13.0)	9.5 (7.6, 12.9)
25th, 75th Percentiles	9.2, 24.4	16.6, 33.7	16.6, 29.4	16.1, -	7.4, 14.7	7.4, 13.4
Duration of Response Kaplan-Meier Estimates (Months)						
Median (95% CI) [2]	25.8 (19.4, -)	25.8 (18.4, 33.7)	25.8 (18.0, -)	18.0 (12.9, 29.4)	33.7 (24.0, 33.7)	- (16.5, -)
25th, 75th Percentiles	16.5, 33.7	15.1, 33.7	15.1, -	12.9, 29.4	24.0, 33.7	16.5, -
Min, Max	1.8^, 36.9^	7.7, 36.9^	8.8, 36.9^	8.8, 29.4	1.8^, 33.7	1.8^, 28.5^

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.2.3.1-2.4.4a Summary of Time to Response and Duration of Response by Age Group per EMA Censoring Rule, Central Radiology Assessment per RECIST v1.1
Efficacy Population - RET-mutation MTC Confirmed Response Patients Treated at 400 mg QD

Age Group: <65 Years old

	Overall (N=78)	Prior Systemic Treatment (N=36)	Prior Cabo./Vand. Treatment (N=30)	Prior Cabo. And Vand. (N=12)	No Prior Cabo./Vand. Treatment (N=48)	No Prior Systemic Treatment (N=42)
Duration of Response (DOR), n (%)						
<6 months	10 (12.8)	0	0	0	10 (20.8)	10 (23.8)
<3 months	3 (3.8)	0	0	0	3 (6.3)	3 (7.1)
>=3 months to <6 months	7 (9.0)	0	0	0	7 (14.6)	7 (16.7)
>=6 months	68 (87.2)	36 (100)	30 (100)	12 (100)	38 (79.2)	32 (76.2)
>=9 months	59 (75.6)	33 (91.7)	29 (96.7)	11 (91.7)	30 (62.5)	26 (61.9)
>=12 months	45 (57.7)	30 (83.3)	26 (86.7)	9 (75.0)	19 (39.6)	15 (35.7)
>=18 months	24 (30.8)	19 (52.8)	16 (53.3)	4 (33.3)	8 (16.7)	5 (11.9)
>=24 months	11 (14.1)	9 (25.0)	8 (26.7)	1 (8.3)	3 (6.3)	2 (4.8)
Patients with Event, n (%)	21 (26.9)	17 (47.2)	14 (46.7)	8 (66.7)	7 (14.6)	4 (9.5)
Patients Censored, n (%)	57 (73.1)	19 (52.8)	16 (53.3)	4 (33.3)	41 (85.4)	38 (90.5)
Discontinued from Study	2 (2.6)	1 (2.8)	1 (3.3)	1 (8.3)	1 (2.1)	1 (2.4)
<6 months	1 (1.3)	0	0	0	1 (2.1)	1 (2.4)
>=6 months	1 (1.3)	1 (2.8)	1 (3.3)	1 (8.3)	0	0

Source: Listing 16.3.4.1.2
Notes: Patients with confirmed CR/PR are included in the analysis. Cabo., Cabozantinib; Vand., Vandetanib.
[1] Duration of response follow-up is based on reverse Kaplan-Meier method, with censoring at date of death or disease progression.
[2] The 95% CI is based on Greenwood formula.
^, ongoing at time of data cut

Assessor's comments:

Subgroup analyses regarding mTTR and DOR by age group for MTC patients ≥65 years (N=11) and <65 years (N=78) showed a mTTR slightly shorter for the older group (3.75 months compared to 4.29 months in the younger group). However, the CI intervals are very broad.

The number of patients reaching a DOR ≥9 months, ≥12 months, ≥18 months and ≥24 months were also slightly higher in the younger than in the older group.

The MAH has not provided updated subgroup analyses.

mTTR and DOR by prior lines of therapy:

Table 1 Summary of Time to Response and Duration of Response by prior lines of treatment, RET-mutant MTC, overall efficacy population treated at 400 mg QD

	Overall	0 lines	1 line	≥2 lines
Number of patients	90	48	21	21
Time to first response (months)				
Mean (SD)	5.66 (4.387)	6.06 (3.649)	5.73 (6.625)	4.67 (3.009)
Median (min–max)	4.29 (1.7-27.3)	5.57 (1.8-18.6)	3.68 (1.8- 27.3)	3.71 (1.7- 12.9)
DOR KM estimates (months)				
Median (95% CI)[a]	29.5 (24.0, NR)	NR (NR, NR)	24.0 (15.1, NR)	29.4 (18.0, 33.7)
Patients with event, n (%)	29 (32.2)	8 (16.7)	10 (47.6)	11 (52.4)
Patients censored, n (%)	61 (67.8)	40 (83.3)	11 (52.4)	10 (47.6)
Follow-up DOR KM estimates (months)				
Median (95% CI)[a]	22.1 (18.2, 25.9)	16.5 (13.1, 20.0)	30.4 (23.2, 33.9)	31.5 (27.1, 40.4)

Clinical cutoff date: 18 October 2021; Enrolment cutoff date: 18 February 2021
CI=confidence interval; DOR=duration of response; KM=Kaplan-Meier; NR=not reached; SD=standard deviation.
Patients with confirmed CR/PR are included in the analysis.
[a] The 95% CI is based on Greenwood formula.
Source: T14_02_03_01_02_04_04_dor_ret_cr_ema_mtc_400mg; T14_02_03_01_02_04_04f_dor_pact_cr_ema_eff_mtc_400mg.

Assessor's comments:

As requested, the MAH is providing an overview table for time to response and duration of response for the RET-mutant medullary thyroid cancer (MTC) efficacy population by prior lines of treatment, as of the CCOD of 18 October 2021 (Table 1).

For the RET-mutant MTC patients, this subgroup analysis showed a shorter median time to first response in patients with prior line(s) of systemic therapy (1 line and ≥2 lines), 3.7 and 3.7 months, respectively compared to those who were treatment-naïve (5.6 months). Median DOR was not reached for the treatment-naïve patients, and was slightly longer in patients with ≥2 prior lines of systemic therapy (29.4 months [95% CI: 18.0, 33.7]) compared to those with 1 prior line of systemic therapy (24.0 months (95% CI: 15.1, NR]).

Summary of main study

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

Summary of Efficacy for trial BO42863 (ARROW)

Title: A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumours.			
Study identifier	BLU-667-1101, BO42863 (ARROW)		
Design	Phase 1/2, multicentre, open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		The study is ongoing Not applicable The study is ongoing
Hypothesis	Exploratory: efficacy and safety of pralsetinib in RET-mutant MTC and RET fusion-positive thyroid cancer.		
Treatments groups	RET-mutation MTC patients		Pralsetinib 400 mg QD until a discontinuation criterion was met, 145 objects randomized.
	RET-fusion TC patients		Pralsetinib 400 mg QD until a discontinuation criterion was met, 22 subjects randomized.
Endpoints and definitions	Primary endpoint	ORR	Proportion of patients achieving with a confirmed response of complete response (CR) or partial response (PR) per RECIST v1.1 by blinded independent central review (BICR)
	Secondary endpoint	DOR	Time from first documentation of response per RECIST v1.1 by BICR until progressive disease (PD) or death
		CBR	Clinical Benefit Rate
		DCR	Duration of Clinical Response
		PFS	Time from first dose until PD per RECIST v1.1 by BICR or death of any cause
		OS	First dose until death Time from of any cause
Database lock	Data Cut-off (DCO) Date: 18 October 2021 Database lock: 11 June 2021		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary efficacy analysis set is constituted by patients with measurable disease at baseline by RECIST v1.1 per BICR and with at least 24 weeks of tumour assessment as of the data cut-off date		
Descriptive statistics and estimate variability	Treatment group	RET-mutant MTC	RET-fusion positive TC
	Number of subjects	145	27
	ORR (confirmed), number of subjects (rate)	90 (62.1%)	21 (77.8%)
	95% CI a	53.6, 70.0	57.7, 91.4
	Median DOR in responders, months	29.5	23.6
	95% CI b	24.0, not reached	15.1, not reached
	Median PFS, months	25.9	21.2
	95% CI b Median OS, months	22.3, 29.5 27.1	18.3, 31.5 21.6
	95% CI b	25.2, 29.6	15.7, 32.5

Effect estimate per comparison	Not applicable
Notes	an Exact 2-sided 95% CI based on exact binomial distribution (Clopper-Pearson). b 95% CI generated using the Greenwood formula.

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

N/A

Clinical studies in special populations

Assessor's comments:

The MAH is asked to include the table with number of patients per age group **(OC).**

Supportive study

The MAH has provided data from additional 62 patients from the phase 1 part of the pivotal phase 1/2 study with only a few patients having thyroid cancer. These patients are included in the efficacy analysis.

3.4.3. Discussion on clinical efficacy

The applicant is seeking an extension of indication for pralsetinib as monotherapy for adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) and RET fusion-positive thyroid cancer, in both cases that had already received prior treatment with tyrosine kinase inhibitors and had not been previously treated with a RET inhibitor. Clinical data to support this indication come from cohorts of the pivotal phase I/II, open-label, multi-cohort, single-arm BO42863 study (ARROW).

The MAH has updated the Pop PK for RET-altered TC by excluding NSCLC data as requested and has submitted simulations for extrapolation to adolescents performed with the Final Pop-PK model as an addendum to the final model report. As there is no data available for adolescent patients, this exercise is considered as a full extrapolation.

Design and conduct of clinical studies

The Applicant received SA from CHMP in April 2019. The design of this multi-cohort single-arm study was not disclosed with the CHMP until enrolment was well underway (first patient enrolled in March 2017). The main purposes for that advice were consulting on the possibility of CMA for the 2L NSCLC cohort (based on preliminary efficacy and safety data), and discussing the design of the confirmatory trial for NSCLC in 1L. Advice for the currently sought indications for thyroid cancer was not requested.

ARROW included a dose-escalation phase I to determine the MTD and RP2D of pralsetinib, followed by a phase II expansion with diverse RET-altered cancer cohorts, among them NSCLC (1L/2L), medullary thyroid cancer (MTC), and other tumours. Although the cohorts of interest for the proposed indications are Groups 3, 4, 5 and 9 from the phase II, it was considered acceptable to pool patients from phase I who had similar disease characteristics and had been treated at the RP2D (400 mg QD) in the main efficacy dataset.

The cut-off for the submitted efficacy dataset is 12 April 2021, but only patients with sufficient follow-up, defined as those who started treatment on or before 23 august 2020, were included. Due to many excluded patients, immaturity of the results and missing overview tables that made the assessment difficult the MAH was requested to update efficacy data. Hence, there has been provided an update of the efficacy dataset with the clinical cut-off date (CCOD) of 18 October 2021 (enrolment cut-off date [ECOD] of 18 February 2021). The new efficacy dataset includes all patients who started treatment with pralsetinib before 18 February 2021 (i.e., the efficacy population). There is no change to the efficacy population for RET mutant medullary thyroid cancer (MTC) patients. A total of 27 RET fusion-positive thyroid cancer (TC) patients received pralsetinib at a starting dose of 400 mg QD by 18 February 2021 (in Phase 1 or in Phase 2, Group 5) and are thus included in the updated efficacy analyses.

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

The overall primary and secondary objectives from the extension phase II of ARROW seem appropriate to ascertain the efficacy and safety of pralsetinib in the intended indication. ORR and DOR, as assessed by BICR, are acceptable measures of anti-tumour activity for multikinase inhibitors in a phase I/II trial for a rare population.

The uncontrolled nature of this SAT is a clear limitation to interpretation of efficacy data, particularly since historical comparisons are complicated: established treatments of MKIs for advanced MTC (cabozantinib and vandetanib) and for advanced DTC (sorafenib and lenvatinib) have shown important ORR, DOR, PFS and OS benefits in RCTs against placebo in MTC and DTC patients with documented radiographic progression.

145 patients with RET-mutation positive MTC were included and fulfilled the efficacy dataset requirement (started treatment on or before 18 February 2021) with about half of patients (n=67) being treatment-naïve. Only 67 patients received prior treatment with cabozantinib and/or vandetanib which are the current approved treatments in EU for locally advanced and metastatic RET mutation-positive MTC in adults. Of the 27 RET fusion-positive thyroid cancer patients nearly all had received prior treatment (25/27). Most protocol deviations were minor.

Efficacy data and additional analyses

Pivotal study ARROW was initiated in March 2017 and is still ongoing (around 585 patients are planned to be enrolled). In line with the proposed indications, the MAH has categorised data from these patients included within the nine cohorts into broad groupings, i.e. RET-mutant MTC (n=145) and RET fusion-positive thyroid cancer (n=27), and new datasets have been defined.

RET-mutant MTC

The total number of patients supporting the claimed indication in RET-mutant MTC population was 145. 67 patients received prior treatment with cabozantinib and/or vandetanib (of which 24 patients received prior treatment with both) and 67 were treatment-naïve. 11 patients had prior systemic treatment with other medicinal products. At the new data cut-off, with an estimated median follow-up time of 22.1 months, 90 out of the 145 patients from the efficacy dataset had achieved confirmed response by BICR, attaining ORR of 62.1% (95% CI 53.6, 70.0). Response were durable, with a median duration of 29.5 months (95% CI 24.0, NR). Median PFS was 31.2 months, and median OS has not been reached.

Prior cabozantinib/vandetanib treatment

Results for the pre-treated patient group (n=67) showed an ORR of 52.2% (95% CI 39.7, 64.6); CR was obtained in 3.0% of the patients and PR was obtained in 49.3% of them. Overall, ORR results in the subgroup analysis for the MKI Progressive MTC patients were considerably lower than those reached for the general MTC population.

Even though response rates observed with pralsetinib in this population are promising and even higher than ORRs reported with multikinase inhibitors in the subgroup of patients with RET mutations (32% with cabozantinib and 56.5% with vandetanib) it is unknown whether this ORR can be translated into a clinical benefit in terms of PFS. Therefore, a major therapeutic advantage must be demonstrated over existing therapies in terms of a confirmatory Phase III study (AcceleRET-MTC), that will be provided as a specific obligation (SOB).

Cabozantinib/vandetanib treatment naïve

Sixty-seven patients included were treatment-naïve. In this group the ORR was 71.6% (95% CI 59.3, 82.0); CR was obtained in 6.0% of the patients and PR was obtained in 65.7%. Patients reached SD were 19.4%. Overall, ORR results in the subgroup analysis for the prior treatment-naïve MTC patients are higher than those reached for the general analysis of the MTC population.

RET-fusion positive TC

The total number of patients supporting the claimed indication in RET-fusion positive TC population was 27. Twenty-five (25) of them were previously treated and 2 was treatment naïve. At data cut-off, with an estimated median follow-up time of 17.7 months, 21/27 patients from the efficacy dataset had achieved confirmed response by BICR, attaining ORR of 84.0% (95% CI 63.9, 95.5); CR was seen in 16.0% of the patients and PR in 68.0% of them. Median DOR was 23.6 months (95% CI 15.1, NR), median PFS was 21.2 months, and median OS has not been reached.

Assessment of paediatric data on clinical efficacy

Pralsetinib is also intended to be used in adolescent patients (i.e. ≥12 years) with RET mutation-positive MTC and RET fusion-positive thyroid cancer, but no adolescent patients were recruited in pivotal trial ARROW. EMA decision of 9 July 2021 on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for pralsetinib (EMEA-002575-PIP02-20) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. To justify the inclusion of adolescent patients, adult data have been extrapolated to this patient group and these data will be subsequently confirmed with data from 20 adolescent patients to be enrolled across the AcceleRET-MTC Phase 3 study (CO42865) and the pralsetinib cohort in the BO41932 global basket trial (TAPISTRY) as agreed per the Paediatric Investigation Plan (PIP).

Gavreto should not be used in children below 12 years of age. Safety and efficacy in children below 12 years of age have not been established.

The MAH proposes the use of Gavreto in patients from 12 years old with RET-mutant MTC and RET fusion-positive thyroid cancer. However, there are no data in patients below 18 years of age. The safety and efficacy of Gavreto in children aged 12 to 18 years of age is supported by extrapolation of evidence from clinical trials in adults to the paediatric population, based on population pharmacokinetic data demonstrating similar drug exposure in adults and paediatric patients.

The MAH has updated the Pop PK for RET-altered TC by excluding NSCLC data as requested and has submitted simulations for extrapolation to adolescents performed with the Final Pop PK model as an addendum to the final model report. However, the major objection on PK is not considered solved and extrapolation to adolescents is not considered sufficiently justified at the moment.

Additional efficacy data needed in the context of a conditional MA

The data submitted to support the efficacy of pralsetinib in the treatment of RET-mutant MTC and RET fusion-positive thyroid cancer patients are not considered comprehensive and further data will be submitted post approval.

The MAH will submit the results from study AcceleRET-MTC (CO42865), a multi-center, open-label, randomized phase 3 study to evaluate the efficacy and safety of pralsetinib compared with SOC treatment (cabozantinib or vandetanib) for adult patients and adolescents (n=20) with advanced and metastatic RET-mutant MTC who have not previously received a multikinase inhibitor therapy (n=198). The final CSR is expected by January 2028.

The rarity of RET-fusion positivity in thyroid cancer makes the conduct of a randomized controlled trial in this patient population not feasible. The MAH will perform an integrated efficacy analysis of RET fusion-positive solid tumour patients (excluding NSCLC) from the BO42863 (ARROW) and BO41932 (TAPISTRY) studies to provide additional data to support conversion to full approval. TAPISTRY (BO41932) is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies in patients with unresectable, locally advanced or metastatic solid tumours determined to harbour specific oncogenic genomic alterations. It is anticipated that this integrated analysis will include at least 90 RET fusion-positive solid tumour patients with at least 8 months follow up, with at least 40 patients coming from BO42863 (ARROW) and at least 50 patients coming from BO41932 (TAPISTRY). One of the cohorts (K) in BO41932 is evaluating pralsetinib in RET fusion-positive solid tumours (excluding NSCLC) and expected to enroll up to 40 RET fusion-positive thyroid cancer patients. The final integrated analysis report will be available by June 2025.

3.4.4. Conclusions on the clinical efficacy

Results from the relevant cohorts of study ARROW are considered compelling and of clinical relevance in the applied indications, with important response rates in the range of 62-78% across the sought indications and their subgroups. Such responses were durable with mDOR between 23.6 and 29.5 months. Uncertainties are still present due to the lack of direct controls and population heterogeneity of the database, but these will be addressed with the studies imposed as specific obligations.

The following measures are considered necessary to address issues related to clinical efficacy:

- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with advanced RET-mutant MTC, the MAH should submit the results of study CO42865 (AcceleRET-MTC) a randomised, open-label, Phase 3 study of pralsetinib versus standard of care in patients who have not received a multikinase inhibitor therapy for the treatment of advanced RET-mutant MTC.

- In order to further confirm the efficacy and safety of pralsetinib in the treatment of adult patients with advanced RET-fusion positive thyroid cancer, the MAH should submit the results of an integrated efficacy analysis of study BLU-667-1101, a Phase 1/2 Study of pralsetinib in patients with thyroid cancer, NSCLC and other advanced solid tumours and cohort K from the Phase II study BO41932 (TAPISTRY), evaluating pralsetinib in patients with RET fusion-positive solid tumours (excluding NSCLC)

3.5. Clinical safety

Introduction

The assessment of safety for Study BO42863 (CCOD: 12 April 2021 and with a new update CCOD: 18 October 2021) includes data for RET mutation-positive MTC patients (n=145) who started treatment

with pralsetinib 400 mg QD, and data for RET fusion-positive thyroid cancer patients (n=30) who started treatment with pralsetinib 400 mg QD. Data from RET mutation-positive MTC patients and RET fusion-positive thyroid cancer patients were pooled and are presented as RET-altered thyroid cancer. In addition, an updated safety analysis at the time of the CCOD is included for all patients who started treatment with pralsetinib at 400 mg QD in Study BO42863, regardless of indication (n=537).

Safety data presentation: The safety population includes all patients who received at least one dose of pralsetinib, regardless of starting dose. Patients were grouped based on the initial dose prescribed on Day 1, regardless of study phase.

Patient exposure

Table 1 Summary of Studies Contributing to Safety Evaluation

Study No	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
Study BO42863	Phase I/II, open-label, multicenter, dose-escalation, first-in-human study with expansion into Phase II at the MTD/RP2D	Patients ≥18 years with advanced, unresectable, RET-altered NSCLC, MTC, or other RET-altered solid tumors	582 patients overall 532 patients received 400 mg QD 145 patients with RET mutation-positive MTC 27 patients with RET fusion-positive thyroid cancer	Phase I: BOIN dose-escalation design of pralsetinib capsules administered PO with a target toxicity rate for the MTD of 30%. Cohorts of 3-6 patients (1-3 patients for the first 3 dose levels) were enrolled until 12 patients were treated and evaluable for DLT at 1 dose level Phase II: Expansion cohorts defined by tumor type, prior treatments, and/or RET alteration status administered pralsetinib capsules at 400 mg QD (MTD/RP2D)

BOIN=Bayesian optimal interval; DLT=dose limiting toxicity; MTC=medullary thyroid cancer; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; PO=per oral; RET=rearranged during transfection; QD=once daily; RP2D=recommended Phase II dose

Table 25 Summary of Study Treatment (Safety Population, 400 mg QD)

Parameter	RET Mutation-positive MTC Patients N = 145	RET Fusion-positive Thyroid Cancer Patients N = 27	RET-altered Thyroid Cancer Patients N = 172
Duration of treatment (weeks)[a]			
Mean (StdDev)	80.30 (44.197)	61.96 (42.346)	77.42 (44.299)
Median (Min, Max)	80.00 (1.4, 169.9)	61.57 (<1, 162.0)	77.14 (<1, 169.9)
Duration of treatment (months)[b]			
Mean (StdDev)	18.47 (10.164)	14.25 (9.739)	17.81 (10.188)
Median (Min, Max)	18.40 (<1, 39.1)	14.16 (<1, 37.3)	17.74 (<1, 39.1)
Cumulative dose (mg)[c]			
Mean (StdDev)	177802.1 (106494.71)	128814.8 (96054.49)	170112.2 (106172.98)
Median (Min, Max)	175600.0 (4000, 473600)	114000.0 (1600, 421200)	169300.0 (1600, 473600)
Average daily dose (mg)[d]			
Mean (StdDev)	340.8 (70.98)	325.0 (83.97)	338.3 (73.13)
Median (Min, Max)	379.1 (114, 402)	336.5 (126, 400)	375.4 (114, 402)
Dose intensity (mg/day)[e]			
Mean (StdDev)	322.2 (78.33)	305.9 (93.30)	319.7 (80.78)
Median (Min, Max)	342.3 (88, 400)	324.3 (116, 400)	335.6 (88, 400)
Relative dose intensity (%)			
Mean (StdDev)	80.6 (19.58)	76.5 (23.32)	79.9 (20.20)
Median (Min, Max)	85.6 (22, 100)	81.1 (29, 100)	83.9 (22, 100)
Relative dose intensity (n [%])			
<75%	58 (40.0%)	11 (40.7%)	69 (40.1%)
75% to <90%	22 (15.2%)	5 (18.5%)	27 (15.7%)
90% to <120%	65 (44.8%)	11 (40.7%)	76 (44.2%)
120% to <150%	0	0	0
≥150%	0	0	0

MTC = medullary thyroid cancer; StdDev = standard deviation

[a] Duration of Treatment(Weeks) is defined as (treatment end date - treatment start date + 1) / 7.

[b] Duration of Treatment(Months) is defined as (treatment end date - treatment start date + 1) / 30.4375.

[c] Cumulative Dose (mg) is defined as the sum of all dose actually taken.

[d] Average Daily Dose (mg): cumulative dose / number of days actually dosed.

[e] Dose Intensity (mg/day): cumulative dose / treatment duration (days).

[f] Relative Dose Intensity: dose intensity / planned dose intensity * 100. Planned dose intensity is based on initial assigned daily dose.

Source: T14_01_08_01_01_07_treat_rat

Assessor's comments:

Overall 532/582 enrolled patients in BO42863 (phase I+II) were treated with 400 mg pralsetinib QD (the safety pool). The safety population included 145 MTC patients and 30 TC patients (n=175). The median duration of treatment for the MTC and TC patients was 18.4 and 14.16 months, respectively (CCOD: 12 April 2021). The average daily dose for the whole group was median 375 mg. The safety database in the two claimed indications is considered of limited extent.

Adverse events

Common AEs

Table 1 Adverse Events Occurring in ≥10% of Patients (Any Grade, any population) by Intensity by Preferred Term (Safety Population, Treated at 400 mg QD

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Preferred Term	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
Patients with AE by Highest NCI CTCAE Grade	175 (100)	122 (69.7)	23 (13.1)	536 (99.8)	343 (63.9)	92 (17.1)
Anaemia	93 (53.1)	39 (22.3)	0	275 (51.2)	118 (22.0)	0
Aspartate aminotransferase increased	86 (49.1)	8 (4.6)	0	263 (49.0)	36 (6.7)	0
Constipation	77 (44.0)	1 (<1)	0	233 (43.4)	3 (<1)	0
Alanine aminotransferase increased	62 (35.4)	6 (3.4)	0	197 (36.7)	26 (4.8)	0
Hypertension	72 (41.1)	42 (24.0)	0	185 (34.5)	95 (17.7)	0
Diarrhoea	65 (37.1)	7 (4.0)	0	176 (32.8)	16 (3.0)	0
White blood cell count decreased	62 (35.4)	16 (9.1)	0	151 (28.1)	34 (6.3)	0
Pyrexia	48 (27.4)	4 (2.3)	0	148 (27.6)	7 (1.3)	0
Fatigue	53 (30.3)	6 (3.4)	0	146 (27.2)	14 (2.6)	0
Neutrophil count decreased	41 (23.4)	12 (6.9)	0	138 (25.7)	56 (10.4)	0
Cough	44 (25.1)	2 (1.1)	0	135 (25.1)	3 (<1)	0
Blood creatinine increased	49 (28.0)	0	0	134 (25.0)	3 (<1)	0
Hypocalcaemia	69 (39.4)	13 (7.4)	0	125 (23.3)	20 (3.7)	0
Neutropenia	40 (22.9)	18 (10.3)	0	123 (22.9)	61 (11.4)	0
Dyspnoea	35 (20.0)	5 (2.9)	0	109 (20.3)	12 (2.2)	2 (<1)
Nausea	33 (18.9)	1 (<1)	0	101 (18.8)	1 (<1)	0
Decreased appetite	37 (21.1)	2 (1.1)	0	100 (18.6)	7 (1.3)	0
Headache	43 (24.6)	0	0	95 (17.7)	3 (<1)	0
Hyperphosphataemia	54 (30.9)	0	0	95 (17.7)	1 (<1)	0
Oedema peripheral	39 (22.3)	1 (<1)	0	91 (16.9)	1 (<1)	0
Pneumonia	31 (17.7)	18 (10.3)	3 (1.7)	91 (16.9)	50 (9.3)	8 (1.5)

Blood creatine phosphokinase increased	29 (16.6)	14 (8.0)	0	89 (16.6)	41 (7.6)	0
Asthenia	28 (16.0)	5 (2.9)	0	87 (16.2)	9 (1.7)	1 (<1)
Dry mouth	28 (16.0)	0	0	87 (16.2)	0	0
Hypokalaemia	27 (15.4)	6 (3.4)	0	86 (16.0)	21 (3.9)	0
Dysgeusia	32 (18.3)	0	0	85 (15.8)	0	0
Lymphocyte count decreased	43 (24.6)	24 (13.7)	0	81 (15.1)	46 (8.6)	0
Dizziness	29 (16.6)	2 (1.1)	0	80 (14.9)	3 (<1)	0
Urinary tract infection	27 (15.4)	11 (6.3)	0	79 (14.7)	24 (4.5)	0
Hypoalbuminaemia	29 (16.6)	0	0	78 (14.5)	0	0
Back pain	18 (10.3)	1 (<1)	0	77 (14.3)	6 (1.1)	0
Vomiting	24 (13.7)	2 (1.1)	0	76 (14.2)	6 (1.1)	0
Hypophosphataemia	13 (7.4)	6 (3.4)	0	68 (12.7)	35 (6.5)	0
Hyponatraemia	19 (10.9)	9 (5.1)	0	66 (12.3)	24 (4.5)	0
Lymphopenia	30 (17.1)	21 (12.0)	0	65 (12.1)	45 (8.4)	0
Platelet count decreased	18 (10.3)	5 (2.9)	0	64 (11.9)	17 (3.2)	0
Blood alkaline phosphatase increased	13 (7.4)	1 (<1)	0	62 (11.5)	8 (1.5)	0
Myalgia	34 (19.4)	0	0	62 (11.5)	0	0
Pneumonitis	20 (11.4)	6 (3.4)	0	59 (11.0)	15 (2.8)	1 (<1)
Blood bilirubin increased	20 (11.4)	1 (<1)	0	58 (10.8)	8 (1.5)	0
Abdominal pain	23 (13.1)	1 (<1)	0	57 (10.6)	6 (1.1)	0
Arthralgia	34 (19.4)	1 (<1)	0	57 (10.6)	3 (<1)	0
Disease progression	9 (5.1)	1 (<1)	8 (4.6)	56 (10.4)	8 (1.5)	42 (7.8)
Pain in extremity	20 (11.4)	0	0	56 (10.4)	1 (<1)	0
Leukopenia	16 (9.1)	3 (1.7)	0	55 (10.2)	13 (2.4)	0
Dysphonia	25 (14.3)	0	0	45 (8.4)	0	0
Upper respiratory tract infection	21 (12.0)	1 (<1)	0	45 (8.4)	3 (<1)	0
Rash	21 (12.0)	0	0	50 (9.3)	0	0
Stomatitis	19 (10.9)	1 (<1)	0	35 (6.5)	6 (1.1)	0
Gastrooesophageal reflux disease	18 (10.3)	0	0	34 (6.3)	0	0

Clinical cut-off date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a

patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: Table 14.3.2.103.1.6, Table 14.3.2.104.1.7.

Table 2 Grouped terms (Safety Population, Treated at 400 mg QD) (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Grouped terms	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Anemia	93 (53.1)	39 (22.3)	0	282 (52.5)	120 (22.3)	0
Neutropenia	80 (45.7)	30 (17.1)	0	248 (46.2)	113 (21.0)	0
Thrombocytopenia	30 (17.1)	5 (2.9)	0	105 (19.6)	26 (4.8)	0
Pneumonitis	20 (11.4)	6 (3.4)	0	67 (12.5)	18 (3.4)	2 (<1)
Pneumonia	38 (21.7)	21 (12.0)	4 (2.3)	112 (20.9)	64 (11.9)	10 (1.9)
Hypertension	75 (42.9)	42 (24.0)	0	189 (35.2)	95 (17.7)	0
Hemorrhage	38 (21.7)	7 (4.0)	0	111 (20.7)	21 (3.9)	2 (<1)
QT prolongation	12 (6.9)	1 (<1)	0	28 (5.2)	2 (<1)	0

Clinical cut-off date: 18 October 2021.

Notes: If a patient experienced more than 1 event in a given grouped term category, that patient is counted once for the category. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: Table 14.3.2.138.1.7, Table 14.3.2.138.1.6.

Assessor's comments:

As expected, all patients experienced an AE (Table 1). Grade 3 or higher AEs constituted around 80% of AEs in the overall patient population (n=537) and the subgroup of patients with RET-altered TC (n=172). The most common any Grade AE (PT occurring in ≥10%) was anaemia (53.1%), AST increased (49.1%), constipation (44.0%), hypertension (41.1%), hypocalcaemia (39.4%), diarrhoea (37.1%), white blood cell count decreased (35.4%), ALT increased (35.4%), hyperphosphataemia (30.9%) and fatigue 30.3%). This was overall consistent with the overall safety pool except for hypertension, hypocalcaemia and hyperphosphataemia where it was seen at a higher frequency in the RET-altered patient group compared to the overall patient group. Regarding the two latter, this is probably in part due to higher incidences of hypocalcaemia and hyperphosphatemia for MTC compared to the other cancer groups in the overall population. Grouped hypertension (PTs: hypertension, blood pressure increased, and prehypertension) was seen in 42.9% in the RET-altered patient group compared to 35.2% in the overall safety population (Table 2). The MAH has discussed this higher incidence and means that it can be attributed to the increased incidence of hypertension in patients with endocrine disorders. Thyroid dysfunction, both hypo- and hyperthyroidism may increase the risk of hypertension. Another aspect, which needs to be considered, is the longer median treatment duration of RET-altered TC patients as compared to the overall safety population (22.05 months vs 14.72 months). Hypocalcaemia is a common complication following surgical

procedures of the neck, including the thyroid gland. In addition, the extent of thyroidectomy is a major risk factor for the development and incidence of both transient and permanent hypoparathyroidism, which leads to the low levels of calcium and increase of phosphorus in the blood. The majority of RET-altered TC patients had prior cancer related surgeries (27,9%), before starting pralsetinib treatment. The explanations are endorsed. However, the higher incidence of hypertension, hypocalcaemia, hyperphosphataemia and diarrhoea in the RET-altered TC group compared to the overall safety pool should be reflected in Section 4.8 of the SmPC and the MAH has on request included a sentence regarding this.

Grade ≥3 AEs

Table 28 Grade ≥3 Adverse Events Occurring in ≥10% of Patients by Preferred Term (Safety Population, Treated at 400 mg QD)

	400 mg QD			
Preferred Term	RET-altered Thyroid Cancer Patients N=172	RET Mutation-positive MTC Patients N=145	RET Fusion-positive Thyroid Cancer Patients N=27	All Patients N=532
Patients with Grade ≥3 AE	143 (83.1%)	122 (84.1%)	21 (77.8%)	429 (80.6%)
Anaemia	35 (20.3%)	28 (19.3%)	7 (25.9%)	111 (20.9%)
Hypertension	39 (22.7%)	32 (22.1%)	7 (25.9%)	89 (16.7%)
Neutropenia	17 (9.9%)	16 (11.0%)	1 (3.7%)	60 (11.3%)
Pneumonia	19 (11.0%)	17 (11.7%)	2 (7.4%)	55 (10.3%)
Neutrophil count decreased	12 (7.0%)	10 (6.9%)	2 (7.4%)	55 (10.3%)
Lymphopenia	20 (11.6%)	18 (12.4%)	2 (7.4%)	41 (7.7%)
Lymphocyte count decreased	22 (12.8%)	20 (13.8%)	2 (7.4%)	41 (7.7%)

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_109_01_04_aeptgrade_mtc_400mg_new, T14_03_02_109_01_05_aeptgrade_thyr_new, T14_03_02_109_01_06_aeptgrade_new, T14_03_02_109_01_07_aeptgrade_ra_thyr_400mg_new.

Table 1 Grade 3-4 Adverse Events Occurring in ≥2% of Patients (any population) by SOC and Preferred Term (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
System Organ Class Preferred Term	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
Blood and lymphatic system disorders						
Anaemia	39 (22.3)	0	39 (22.3)	116 (21.6)	2 (<1)	118 (22.0)
Neutropenia	17 (9.7)	1 (<1)	18 (10.3)	52 (9.7)	9 (1.7)	61 (11.4)
Lymphopenia	20 (11.4)	1 (<1)	21 (12.0)	41 (7.6)	4 (<1)	45 (8.4)
Leukopenia	3 (1.7)	0	3 (1.7)	13 (2.4)	0	13 (2.4)
Thrombocytopenia	0	2 (1.1)	2 (1.1)	5 (<1)	6 (1.1)	11 (2.0)
Gastrointestinal disorders						
Diarrhoea	7 (4.0)	0	7 (4.0)	16 (3.0)	0	16 (3.0)
General disorders and administration site conditions						
Fatigue	6 (3.4)	0	6 (3.4)	14 (2.6)	0	14 (2.6)

Pyrexia	4 (2.3)	0	4 (2.3)	7 (1.3)	0	7 (1.3)
Asthenia	5 (2.9)	0	5 (2.9)	9 (1.7)	0	9 (1.7)
Infections and infestations						
Pneumonia	15 (8.6)	3 (1.7)	18 (10.3)	45 (8.4)	5 (<1)	50 (9.3)
Urinary tract infection	11 (6.3)	0	11 (6.3)	24 (4.5)	0	24 (4.5)
Corona virus infection	7 (4.0)	1 (<1)	8 (4.6)	10 (1.9)	1 (<1)	11 (2.0)
Sepsis	2 (1.1)	3 (1.7)	5 (2.9)	11 (2.0)	6 (1.1)	17 (3.2)
Investigations						
Aspartate aminotransferase increased	7 (4.0)	1 (<1)	8 (4.6)	30 (5.6)	6 (1.1)	36 (6.7)
Alanine aminotransferase increased	6 (3.4)	0	6 (3.4)	22 (4.1)	4 (<1)	26 (4.8)
White blood cell count decreased	16 (9.1)	0	16 (9.1)	33 (6.1)	1 (<1)	34 (6.3)
Neutrophil count decreased	11 (6.3)	1 (<1)	12 (6.9)	50 (9.3)	6 (1.1)	56 (10.4)
Blood creatine phosphokinase increased	9 (5.1)	5 (2.9)	14 (8.0)	32 (6.0)	9 (1.7)	41 (7.6)
Lymphocyte count decreased	20 (11.4)	4 (2.3)	24 (13.7)	39 (7.3)	7 (1.3)	46 (8.6)
Platelet count decreased	3 (1.7)	2 (1.1)	5 (2.9)	11 (2.0)	6 (1.1)	17 (3.2)
Metabolism and nutrition disorders						
Hypophosphataemia	4 (2.3)	2 (1.1)	6 (3.4)	30 (5.6)	5 (<1)	35 (6.5)
Hyponatraemia	7 (4.0)	2 (1.1)	9 (5.1)	18 (3.4)	6 (1.1)	24 (4.5)
Hypokalaemia	4 (2.3)	2 (1.1)	6 (3.4)	16 (3.0)	5 (<1)	21 (3.9)
Hypocalcaemia	10 (5.7)	3 (1.7)	13 (7.4)	17 (3.2)	3 (<1)	20 (3.7)
Hypercalcaemia	3 (1.7)	1 (<1)	4 (2.3)	4 (<1)	1 (<1)	5 (<1)
Nervous system disorders						
Syncope	4 (2.3)	0	4 (2.3)	9 (1.7)	0	9 (1.7)
Respiratory, thoracic and mediastinal disorders						
Pneumonitis	6 (3.4)	0	6 (3.4)	12 (2.2)	3 (<1)	15 (2.8)
Pulmonary embolism	1 (<1)	0	1 (<1)	13 (2.4)	1 (<1)	14 (2.6)
Dyspnoea	5 (2.9)	0	5 (2.9)	11 (2.0)	1 (<1)	12 (2.2)
Vascular disorders						
Hypertension	42 (24.0)	0	42 (24.0)	95 (17.7)	0	95 (17.7)

Notes: Data cutoff date: 18 October 2021. Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_104_01_06_ae_grade_new, T14_03_02_104_01_07_ae_ra_thyr_400mg_grade_new

Assessor's comments:

The majority of the patients experienced grade ≥3 AEs (83.1%) (Table 28, not updated). The most common (occurring in ≥2%) were hypertension (24.0%), anaemia (22.3%), lymphocyte count decreased (13.7%), lymphopenia (12.0%), pneumonia (10.3%), neutropenia (10.3%) and hypocalcaemia (7.4%) (Table 1). As of the CCOD of 18 October 2021 the Grade ≥3 hypertension in the RET-altered patient group is now 24.0% and 17.7% in the overall safety population. The MAH explains that hypertension was managed with anti-hypertensive treatment in the majority of patients and no patient withdrew treatment permanently due to hypertension in the RET-altered TC patient group. This is comparable to overall safety population which were in general managed by standard clinical practice (dose interruptions/dose reductions and/or treatment for the event). The nature of the underlying disease, medical history with 30% of the RET-altered TC patients having hypertension and duration of treatment and follow-up in patients with thyroid cancer would help explain the lower rates in the overall safety population compared to RET-altered TC patient group.

Grade 3-4 AEs which were reported with a higher reporting rate (>2% difference) (Table 1) in the RET-altered thyroid cancer patient population as compared to the overall safety population are the preferred terms: lymphopenia (12.0% vs 8.4%), corona virus infection (4.6% vs 2.0%), white blood cell count decreased (9.1% vs 6.3%), lymphocyte count decreased (13.7% vs 8.6%), hypocalcaemia (7.4% vs 3.7%), hypercalcaemia (2.3% vs <1%), and hypertension (24.0% vs 17.7%). The corona virus infection incidence was higher because of later enrolment of RET-altered TC patients than the majority of patients in the overall safety group.

Adverse Events of Special Interest (AESI):

Table 1 Adverse Events of Interest (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175	All Patients N=537
Overall occurrence		
Pneumonia	38 (21.7)	112 (20.9)
Pneumonitis	20 (11.4)	67 (12.5)
TLS	0	0
Hypertension	75 (42.9)	189 (35.2)
Hepatotoxicity	111 (63.4)	337 (62.8)
Hemorrhagic events	38 (21.7)	111 (20.7)
QT prolongation	12 (6.9)	28 (5.2)
Related AEs		
Pneumonia	9 (5.1)	31 (5.8)
Pneumonitis	17 (9.7)	61 (11.4)
TLS	0	0
Hypertension	60 (34.3)	145 (27.0)
Hepatotoxicity	85 (48.6)	278 (51.8)
Hemorrhagic events	11 (6.3)	24 (4.5)
QT prolongation	10 (5.7)	23 (4.3)
Grade ≥3		
Pneumonia	25 (14.3)	74 (13.8)
Pneumonitis	6 (3.4)	20 (3.7)
TLS	0	0
Hypertension	42 (24.0)	95 (17.7)
Hepatotoxicity	15 (8.6)	58 (10.8)
Hemorrhagic events	7 (4.0)	23 (4.3)
QT prolongation	1 (<1)	2 (<1)
SAE		
Pneumonia	25 (14.3)	76 (14.2)
Pneumonitis	7 (4.0)	32 (6.0)
TLS	0	0
Hypertension	3 (1.7)	7 (1.3)
Hepatotoxicity	5 (2.9)	17 (3.2)

Hemorrhagic events	6 (3.4)	23 (4.3)
QT prolongation	0	2 (<1)
Related SAE		
Pneumonia	4 (2.3)	20 (3.7)
Pneumonitis	5 (2.9)	28 (5.2)
TLS	0	0
Hypertension	1 (<1)	4 (<1)
Hepatotoxicity	2 (1.1)	7 (1.3)
Hemorrhagic events	0	0
QT prolongation	0	2 (<1)
AEs leading to permanent treatment discontinuation		
Pneumonia	5 (2.9)	12 (2.2)
Pneumonitis	1 (<1)	13 (2.4)
TLS	0	0
Hypertension	0	1 (<1)
Hepatotoxicity	2 (1.1)	2 (<1)
Hemorrhagic events	0	0
QT prolongation	0	0

Clinical cutoff date: 18 October 2021.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. AEs of interest refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_127_01_07_aegrp_ra_thyr_400mg_new, T14_03_02_128_01_07_aerelgrp_ra_thyr_400mg_new, T14_03_02_129_01_07_saegrp_ra_thyr_400mg_new, T14_03_02_130_01_07_saerelgrp_ra_thyr_400mg_new, T14_03_02_136_01_07_aegrp_tox_ra_thyr_400mg_new, T14_03_02_138_01_06_aegrp_grade_new_l, T14_03_02_128_01_06_aerelgrp_new, T14_03_02_132_01_06_aegrp_grade_new, T14_03_02_129_01_06_saegrp_new, T14_03_02_130_01_06_saerelgrp_new, T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg

Assessors comment:

AESIs for Study BO42863 include the following: Pneumonia, Pneumonitis, Tumour Lysis Syndrome (TLS), Hypertension, and Hepatotoxicity. Hepatotoxicity is the most common AESI (63.4%) with the most common Serious AESI being pneumonia (14.3%) (Table 1). Other important AESI are haemorrhagic events, QT prolongation, diarrhoea, hypocalcaemia and hyperphosphataemia. It could be argued whether all potential AESIs have been addressed. Upon request the MAH has re-evaluated the criteria that have been used to define the AESIs. The MAH argues, that although diarrhoea is regarded a risk of pralsetinib and is therefore, together with hypocalcaemia and hyperphosphatemia, included within the SmPC, it needs to be considered that diarrhoea, hypocalcaemia and hyperphosphatemia are attributed to the underlying disease of thyroid cancer and its condition after surgery. Therefore, the MAH considers that diarrhoea, hypocalcaemia and hyperphosphatemia are not adverse events of special interest. This is endorsed.

Pneumonia

Table 1 Summary Characteristics of AESI of Pneumonia (Safety Population, Treated at 400 mg QD

Category	RET-altered Thyroid Cancer Patients (N=175)	All Patients (N=537)
Any Grade AE	38 (21.7)	112 (20.9)
median time to onset (weeks)	17.64	16.14
median time to resolution (weeks)	1.57	2.14
Grade ≥3	25 (14.3)	74 (13.8)
Grade 3-4	21 (12.0)	64 (11.9)
Grade 5	4 (2.3)	10 (1.9)
SAE	25 (14.3)	76 (14.2)

Clinical cutoff date: 18 October 2021.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. AEs of interest refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_127_01_07_aegrp_ra_thyr_400mg_new, T14_03_02_129_01_07_saegrp_ra_thyr_400mg_new,

,

T14_03_02_138_01_06_aegrp_grade_new_l, T14_03_02_132_01_06_aegrp_grade_new, T14_03_02_129_01_06_saegrp_new, T14_03_02_136_01_06_aegrp_tox, T14_03_02_136_01_07_aegrp_tox_ra_thyr_400mg_new, T14_05_01_101_01_07_ttoae_rt_new, T14_05_01_101_01_06_ttoae_new, T14_05_03_101_01_06_ttrae_new, T14_05_03_101_01_07_ttrae_rt_new

Table 2 AESI of Pneumonia Leading to Permanent Discontinuation of Treatment by PT and time to analysis (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Grouped term Preferred term	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)
Pneumonia	5 (2.9)	67.86	NA	12 (2.2)	29.57	1.57*
Pneumonia	4 (2.3)			11 (2.0)		
Pneumocystis jirovecii Pneumonia	1 (<1)			1 (<1)		

Clinical cutoff date: 18 October 2021.

*3 patients who discontinued treatment due to pneumonia recovered from the event. NA = not applicable.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. Grouped terms refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg, T14_05_01_102_01_15_ttoae_rt400mg_dscnt, T14_05_03_102_01_15_ttrae_rt400mg_dscnt

Assessors comment:

21.7% experienced pneumonia any grade compared with 20.9% in the overall safety pool. Patients experiencing Grade ≥3 and SAE were similar compared to the overall safety population. (Table 1). Table 2 shows the median time to onset and median time to resolution. Pneumonia reporting rate, seriousness and severity experienced by RET-altered thyroid cancer patients were similar as compared to overall safety population. At the time of the CCOD none of the pneumonia events had resolved, therefore median time to resolution could not be calculated.

Pneumonitis

Table 1 Characteristics of Pneumonitis (Safety Population, Treated at 400 mg QD)

Category	RET-altered Thyroid Cancer Patients (N=175)	All Patients (N=537)
Any Grade AE	20 (11.4)	67 (12.5)
median time to onset (weeks)	16.79	16.14
median time to resolution (weeks)	3.64	4.14
Grade ≥3	6 (3.4)	20 (3.7)
Grade 3-4	6 (3.4)	18 (3.4)
Grade 5	0	2 (<1)
SAE	7 (4.0)	32 (6.0)

Clinical cutoff date: 18 October 2021.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. AEs of interest refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_127_01_07_aegrp_ra_thyr_400mg_new, T14_03_02_129_01_07_saegrp_ra_thyr_400mg_new, T14_03_02_138_01_07_aegrp_ra_thyr_400mg_grade_new, T14_03_02_138_01_06_aegrp_grade_new_l, T14_03_02_132_01_06_aegrp_grade_new, T14_03_02_129_01_06_saegrp_new, T14_03_02_136_01_06_aegrp_tox, T14_03_02_136_01_07_aegrp_tox_ra_thyr_400mg_new, T14_05_01_101_01_07_ttoae_rt_new, T14_05_01_101_01_06_ttoae_new, T14_05_03_101_01_06_ttrae_new, T14_05_03_101_01_07_ttrae_rt_new

Table 2 Pneumonitis Leading to Permanent Discontinuation of Treatment by PT and time to analysis (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Grouped term Preferred term	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)
Pneumonitis	1 (<1)	11.71	3.14	13 (2.4)	9.43	10.00*
Pneumonitis	1 (<1)			11 (2.0)		
Interstitial lung disease	0			2 (<1)		

Clinical cutoff date: 18 October 2021.

*7 patients who discontinued treatment due to pneumonitis recovered from the event.

Note: Data cutoff date: 18 October 2021. Adverse Events (AEs) are coded using MedDRA 19.1. Grouped terms refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg, T14_05_01_102_01_15_ttoae_rt400mg_dscnt, T14_05_03_102_01_15_ttrae_rt400mg_dscnt.

Assessor's comments:

In the overall safety pool 11.4% experienced pneumonitis of any grade while it was 12.5% in the RET-altered safety group. Regarding Grade ≥3 and SAE the incidences are similar across both groups (Table 1). The treatment discontinuation rate was lower in the RET-altered TC population as compared to the discontinuation rate in the overall safety population.

It should be noted that information on the treatment given for pneumonitis is missing.

Tumour lysis syndrome (TLS):

Overall 3 patients (<1%) had an AE of TLS; no patients who received treatment at 400 mg QD had a TLS event. All events occurred during Phase 1 of the study in RET mutation-positive MTC patients, 2 patients started treatment at 300 mg pralsetinib and one with 100 mg/100 mg BID pralsetinib. Two TLS events were considered dose-limiting toxicities but did not lead to study treatment discontinuation. The other TLS event occurred after treatment was discontinued due to disease progression.

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.3.2.127.1.6 Grouped Adverse Events by Category and Preferred Term (adjacent events linked)
Safety Population - All Patients

	Starting Dose			
Category Preferred Term	<=300 mg QD (N=37) n (%)	400 mg QD (N=532) n (%)	BID [1] (N=9) n (%)	All Doses [2] (N=582) n (%)

AESI Tumour Lysis Syndrome	2 (5.4)	0	1 (11.1)	3 (<1)
Tumour lysis syndrome	2 (5.4)	0	1 (11.1)	3 (<1)

Source: Listing 16.4.1.101.1
Notes: If a patient experienced more than 1 event in a given AESI category, that patient is counted once for the category. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term. Adjacent AEs for the same preferred term are linked per patient.
[1] BID, including patients from 100 mg/100 mg BID and 200 mg/100 mg BID cohort in Study Phase 1.
[2] Including patients with 600 mg QD starting dose.

Assessor's comments:

Overall 3 patients had an TLS of any grade with all events occurring during Phase 1. No patient who received treatment at 400 mg QD had a TLS event.

Hepatotoxicity

Table 35 Grouped Hepatotoxicity AESI by Preferred Term: All Patients Treated at 400 mg QD (Safety Population)

Category Preferred Term	N=532 n (%)
AESI Hepatotoxicity	331 (62.2%)
Aspartate aminotransferase increased	257 (48.3%)
Alanine aminotransferase increased	191 (35.9%)
Hypoalbuminaemia	72 (13.5%)
Blood alkaline phosphatase increased	58 (10.9%)
Blood bilirubin increased	57 (10.7%)
Gamma-glutamyltransferase increased	35 (6.6%)
Bilirubin conjugated increased	22 (4.1%)
Transaminases increased	20 (3.8%)
Ascites	15 (2.8%)
Hyperbilirubinaemia	13 (2.4%)
Total bile acids increased	13 (2.4%)
Blood bilirubin unconjugated increased	11 (2.1%)
Hepatic function abnormal	8 (1.5%)
Hepatocellular injury	8 (1.5%)
International normalised ratio increased	5 (<1%)
Hepatic enzyme increased	3 (<1%)
Hepatic steatosis	3 (<1%)
Liver function test increased	3 (<1%)
Glutamate dehydrogenase increased	2 (<1%)
Urobilinogen urine increased	2 (<1%)
Blood fibrinogen decreased	1 (<1%)
Cholestasis	1 (<1%)
Hepatic cyst	1 (<1%)
Hepatic pain	1 (<1%)
Hepatitis acute	1 (<1%)
Hypertransaminasaemia	1 (<1%)
Jaundice	1 (<1%)
Liver disorder	1 (<1%)

Category Preferred Term	N=532 n (%)
Liver injury	1 (<1%)
Pneumobilia	1 (<1%)
Prothrombin time prolonged	1 (<1%)
Spider naevus	1 (<1%)
Thrombin time prolonged	1 (<1%)
Yellow skin	1 (<1%)

Note: If a patient experienced more than 1 event in a given AESI category, that patient is counted once for the category. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term.

Adapted from: T14_03_02_127_01_06_aegrp_new

Table 1 Characteristics of Hepatotoxicity (Safety Population, Treated at 400 mg QD)

Category	RET-altered Thyroid Cancer Patients (N=175)	All Patients (N=537)
Any Grade AE	111 (63.4)	337 (62.8)
median time to onset (weeks)	3.14	2.14
median time to resolution (weeks)	9.64	8.14
Grade ≥3	15 (8.6)	58 (10.8)
Grade 3-4	15 (8.6)	58 (10.8)
Grade 5	0	0
SAE	5 (2.9)	17 (3.2)

Clinical cutoff date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs of interest refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_127_01_07_aegrp_ra_thyr_400mg_new, T14_03_02_129_01_07_saegrp_ra_thyr_400mg_new, T14_03_02_138_01_07_aegrp_ra_thyr_400mg_grade_new, T14_03_02_138_01_06_aegrp_grade_new_l, T14_03_02_132_01_06_aegrp_grade_new, 14_03_02_129_01_06_saegrp_new, T14_03_02_136_01_06_aegrp_tox, T14_03_02_136_01_07_aegrp_tox_ra_thyr_400mg_new, T14_05_01_101_01_07_ttoae_rt_new, T14_05_01_101_01_06_ttoae_new, T14_05_03_101_01_06_ttrae_new, T14_05_03_101_01_07_ttrae_new

Table 2 AESI of Hepatotoxicity Leading to Permanent Discontinuation of Treatment by PT and time to analysis (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Grouped term Preferred term	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)
Hepatotoxicity	2 (1.1)	60.36	13.50	2 (<1)	60.36	13.50
Blood bilirubin increased	1 (<1)			1 (<1)		
Transaminases increased	1 (<1)			1 (<1)		

Clinical cutoff date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. Grouped terms refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg, T14_05_01_102_01_15_ttoae_rt400mg_dscnt, T14_05_03_102_01_15_ttrae_rt400mg_dscnt

Assessor's comments:

Half of the patients (48.3%) experiencing hepatotoxicity any grade had Aspartate aminotransferase increased and 33.7% having Alanine aminotransferase increased (Table 35, CCDO 12 April 2021). This was consistent with the overall safety group. Also, Grade ≥3 and SAE was consistent with the overall safety group (Table 1). Two patients (1.1%) of the RET-altered thyroid cancer population discontinued pralsetinib permanently due to a grouped hepatotoxicity event. No other patients in study BO42863 discontinued pralsetinib due to a hepatotoxic event; hence, the two patients are also reflected in the overall safety population. Median time to onset for those two patients was 60.4 weeks. Both patients recovered from the hepatotoxicity event after a median time of 13.5 weeks (Table 2).

Hypertension

Table 1 Summary Characteristics of AESI of Hypertension (Safety Population, Treated at 400 mg QD)

Category	RET-altered Thyroid Cancer Patients (N=175)	All Patients (N=537)
Any Grade AE	75 (42.9)	189 (35.2)
median time to onset (weeks)	2.14	2.14
median time to resolution (weeks)	3.07	3.86
Grade ≥3	42 (24.0)	95 (17.7)
Grade 3-4	42 (24.0)	95 (17.7)
Grade 5	0	0
SAE	3 (1.7)	7 (1.3)

Clinical cutoff date: 18 October 2021.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. AEs of interest refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_127_01_07_aegrp_ra_thyr_400mg_new, T14_03_02_129_01_07_saegrp_ra_thyr_400mg_new, T14_03_02_132_01_07_aegrp_ra_thyr_grade_new, T14_03_02_138_01_06_aegrp_grade_new_l, T14_03_02_132_01_06_aegrp_grade_new, 14_03_02_129_01_06_saegrp_new, T14_03_02_136_01_06_aegrp_tox, T14_03_02_136_01_07_aegrp_tox_ra_thyr_400mg_new, T14_05_01_101_01_07_ttoae_rt_new, T14_05_01_101_01_06_ttoae_new, T14_05_03_101_01_06_ttrae_new, T14_05_03_101_01_07_ttrae_new

Table 2 AESI of Hypertension Leading to Permanent Discontinuation of Treatment by PT and time to analysis (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Grouped term Preferred term	Patients who discontinued n (%)	Median Time to onset (weeks)	Median Time to resolution (weeks)	Patients who discontinued n (%)	Time to onset (weeks)	Time to resolution (weeks)
Hypertension	0	na	na	1 (<1)	5.00	1.00
Hypertension	0			1 (<1)		

Clinical cutoff date: 18 October 2021.

na = not applicable.

Note: Adverse Events (AEs) are coded using MedDRA 19.1. Grouped terms refer to grouped treatment-emergent adverse events (TEAEs). All TEAEs including treatment-emergent SAEs are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source outputs: T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg, T14_05_01_102_01_15_ttoae_rt400mg_dscnt, T14_05_03_102_01_15_ttrae_rt400mg_dscnt

Assessor's comments:

As mentioned earlier there was seen more patients with hypertension in the RET-altered group (42.9% than in the overall safety group (35.2%). Grade ≥3 AE were higher in the RET-altered thyroid cancer population compared to the overall safety population, 24.0% vs 17.7%, respectively. Seriousness of hypertension events were similar between the RET-altered thyroid cancer population

and the overall safety population (Table 1). No patient of the RET-altered thyroid cancer population discontinued pralsetinib permanently due to a grouped hypertension event (Table 2).

Assessor's comments:

There is no section on ADRs. The MAH is requested to provide an updated ADR table **(OC).**

Serious adverse event/deaths/other significant events

Deaths

Table 2 Overview of Safety (Safety Population, Treated at 400 mg QD)

	All Patients (N=532) n (%)	RET-altered Thyroid (N=172) n (%)	RET-mutation MTC (N=145) n (%)	RET-fusion Thyroid (N=27) n (%)
Patients with AE	531 (99.8)	172 (100)	145 (100)	27 (100)
Patients with Grade 3/4/5 AE	429 (80.6)	143 (83.1)	122 (84.1)	21 (77.8)
Patients with AE Related to Study Drug	498 (93.6)	166 (96.5)	142 (97.9)	24 (88.9)
Patients with Grade 3/4/5 AE Related to Study Drug	315 (59.2)	102 (59.3)	88 (60.7)	14 (51.9)
Patients with SAE	316 (59.4)	93 (54.1)	77 (53.1)	16 (59.3)
Patients with Grade 3/4/5 SAE	278 (52.3)	86 (50.0)	71 (49.0)	15 (55.6)
Patients with SAE Related to Study Drug	121 (22.7)	27 (15.7)	24 (16.6)	3 (11.1)
Deaths Due to AE	84 (15.8)	22 (12.8)	16 (11.0)	6 (22.2)
Deaths Due to AEs Related to Study Drug	7 (1.3)	1 (<1)	1 (<1)	0
Patients with AE by Highest NCI CTCAE Grade				
Grade 1	13 (2.4)	3 (1.7)	1 (<1)	2 (7.4)
Grade 2	89 (16.7)	26 (15.1)	22 (15.2)	4 (14.8)
Grade 3	276 (51.9)	91 (52.9)	78 (53.8)	13 (48.1)
Grade 4	69 (13.0)	30 (17.4)	28 (19.3)	2 (7.4)
Grade 5	84 (15.8)	22 (12.8)	16 (11.0)	6 (22.2)
Patients with SAE by Highest NCI CTCAE Grade				
Grade 1	3 (<1)	0	0	0
Grade 2	35 (6.6)	7 (4.1)	6 (4.1)	1 (3.7)
Grade 3	155 (29.1)	45 (26.2)	38 (26.2)	7 (25.9)
Grade 4	39 (7.3)	19 (11.0)	17 (11.7)	2 (7.4)
Grade 5	84 (15.8)	22 (12.8)	16 (11.0)	6 (22.2)
Patients with Study Drug Adjustments Due to AE	416 (78.2)	139 (80.8)	117 (80.7)	22 (81.5)
Interruption [1]	379 (71.2)	129 (75.0)	110 (75.9)	19 (70.4)
Reduction	261 (49.1)	93 (54.1)	79 (54.5)	14 (51.9)
Discontinuation	108 (20.3)	31 (18.0)	23 (15.9)	8 (29.6)
Disease Progression	16 (3.0)	1 (<1)	1 (<1)	0
Other AEs except Disease Progression	92 (17.3)	30 (17.4)	22 (15.2)	8 (29.6)
Patients with Study Drug Adjustments Due to Treatment-related AE	325 (61.1)	106 (61.6)	92 (63.4)	14 (51.9)
Interruption [1]	299 (56.2)	97 (56.4)	86 (59.3)	11 (40.7)
Reduction	247 (46.4)	85 (49.4)	73 (50.3)	12 (44.4)
Discontinuation	40 (7.5)	9 (5.2)	7 (4.8)	2 (7.4)
Disease Progression	0	0	0	0
Other AEs except Disease Progression	40 (7.5)	9 (5.2)	7 (4.8)	2 (7.4)

Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Adjacent AEs for the same preferred term are linked per patient.
[1] Dose interruptions include doses interrupted due to an adverse event and missed due to an adverse event.
Source: Study BO42863, Report 1109798, Table 24; T14 03 01 101 01 06 aeall new

General physical health deterioration	2 (1.2)	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	5 (2.9)

Table 1 Overview of Deaths

	RET-altered Thyroid Cancer Patients N=175 n (%)	All Patients N=537 n (%)
Total number of deaths	38 (21.7%)	169 (31.5%)
Primary cause of death		
Progressive disease	20 (11.4%)	110 (20.5%)
Unknown	2 (1.1%)	8 (1.5%)
Other	1 (0.6%)	9 (1.7%)
Adverse Event	15 (8.6%)	42 (7.8%)
Most common PT (>1%)		
Pneumonia	3 (1.7%)	8 (1.5%)
Corona virus infection	2 (1.1%)	5 (0.9%)
Pneumonia aspiration	2 (1.1%)	2 (0.4%)
Sepsis	2 (1.1%)	3 (0.6%)

Clinical cut-off date: 18 October 2021.

One patient had a fatal Adverse Event outside the reporting period and as a result the AE term is not displayed

N = number of patients exposed to Pralsetinib.

Percentages are relative to total N. Deaths where reason for death has not been reported are summarized as 'Unknown'.

Source: t_dd_orat_SE400_18Oct2021_42863

Table 1 Summary of adverse events

	All patients with starting dose of 400 mg QD (N=537) n (%)	RET-altered thyroid cancer (N=175) n (%)	RET-mutation MTC (N=145) n (%)	RET-fusion thyroid cancer (N=30) n (%)
Patients with AE	536 (99.8)	175 (100)	145 (100)	30 (100)
Patients with AE Related to Study Drug	504 (93.9)	170 (97.1)	142 (97.9)	28 (93.3)
Patients with Grade 3/4/5 AE	435 (81.0)	145 (82.9)	122 (84.1)	23 (76.7)
Patients with Grade 3/4/5 AE Related to Study Drug	326 (60.7)	107 (61.1)	91 (62.8)	16 (53.3)
Patients with SAE	329 (61.3	97 (55.4)	80 (55.2)	17 (56.7)
Patients with SAE Related to Study Drug	125 (23.3)	29 (16.6)	26 (17.9)	3 (10.0)
Deaths Due to AE	92 (17.1)	23 (13.1)	16 (11.0)	7 (23.3)
Deaths Due to AEs Related to Study Drug	7 (1.3)	1 (<1)	1 (<1)	0
Patients with AE by Highest NCI CTCAE Grade				
Grade 1	12 (2.2)	2 (1.1)	1 (<1)	1 (3.3)
Grade 2	89 (16.6)	28 (16.0)	22 (15.2)	6 (20.0)
Grade 3	272 (50.7)	91 (52.0)	77 (53.1)	14 (46.7)
Grade 4	71 (13.2)	31 (17.7)	29 (20.0)	2 (6.7)
Grade 5	92 (17.1)	23 (13.1)	16 (11.0)	7 (23.3)

Clinical cut-off date: 18 October 2021.
Sources: T14.3.1.101.1.7 and T14.3.1.101.1.6
Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment.

Adjacent AEs for the same preferred term are linked per patient.

Assessor's comments:

In the overall safety group (n=537) 7.8% died due to AEs. In the RET-altered patient group (n=175) 8.6% died due to AEs (Table 1 Overview of deaths). This is not consistent with the primary analysis (Table 2). Here it is seen that deaths due to AEs is 12.8% in the RET-altered group (n=172) and 15.8% in the overall safety group (n=532). As response to the lower incidence in deaths due to AEs in the safety update (Table 1) compared to the primary analysis (Table 2) the MAH explains that Table 2 displayed AEs, including Grade 5 AEs, derived from the adverse event eCRF (CCOD 12 April 2021) while Table 1 displayed the primary cause of death as indicated in the "end of study" eCRF

page. In cases where the primary cause of death was indicated as progressive disease and the investigator did report the progressive disease also as an AE with fatal outcome in the AE eCRF page, the death was only counted under progressive disease and not under adverse event within Table 1 (as Table 1 summarized the primary cause of death). The primary cause of death for disease progression AEs with a fatal outcome was in their vast majority indicated as progressive disease within the "end of study" eCRF page. Therefore, the reporting rate of primary cause of death being AEs in Table 1 is a fraction of AEs with fatal outcome. With the CCOD of 18 Oct 2021, 13.1% of patients experienced an AE with a fatal outcome in the RET-altered thyroid cancer population (n=175; see updated summary of adverse events, new Table 1).

In Table 1 (Overview of deaths) it is seen that more patients died due to progressive disease in the overall safety population compared to the RET-altered TC group (20.5% vs 11.4%). The reporting rate of AEs as primary cause of death in the RET-altered TC population was comparable to the overall patient population.

The MAH has upon request provided narratives for all deaths due to AEs (not shown here). 14/15 were considered not related to pralsetinib. The most common causes of a fatal AE (›1%) were pneumonia, corona virus infection, pneumonia aspiration and sepsis, apparently for both groups.

SAEs

Table 1 **Most common (≥2%) all grades, Grade 3/4 and Grade 5 Serious Adverse Events by System Organ Class and Preferred Term (Safety Population, Treated at 400 mg QD)**

	Overall (N=537)			RET-altered Thyroid (N=175)		
SOC PT	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
Infections and infestations	157 (29.2)	123 (22.9)	19 (3.5)	51 (29.1)	41 (23.4)	8 (4.6)
Pneumonia	61 (11.4)	44 (8.2)	8 (1.5)	20 (11.4)	16 (9.1)	3 (1.7)
Sepsis	20 (3.7)	16 (3.0)	3 (<1)	7 (4.0)	5 (2.9)	2 (1.1)
Urinary tract infection	20 (3.7)	19 (3.5)	0	9 (5.1)	9 (5.1)	0
Corona virus infection	17 (3.2)	11 (2.0)	5 (<1)	10 (5.7)	8 (4.6)	2 (1.1)
General disorders and administration site conditions	92 (17.1)	20 (3.7)	52 (9.7)	22 (12.6)	8 (4.6)	9 (5.1)
Disease progression	54 (10.1)	7 (1.3)	42 (7.8)	9 (5.1)	1 (<1)	8 (4.6)
Pyrexia	15 (2.8)	5 (<1)	0	5 (2.9)	3 (1.7)	0
Respiratory, thoracic and mediastinal disorders	80 (14.9)	49 (9.1)	11 (2.0)	22 (12.6)	16 (9.1)	5 (2.9)
Pneumonitis	26 (4.8)	15 (2.8)	1 (<1)	7 (4.0)	6 (3.4)	0
Dyspnoea	11 (2.0)	5 (<1)	2 (<1)	4 (2.3)	4 (2.3)	0
Pleural effusion	11 (2.0)	6 (1.1)	1 (<1)	3 (1.7)	3 (1.7)	0
Acute respiratory failure	5 (<1)	4 (<1)	1 (<1)	4 (2.3)	3 (1.7)	1 (<1)
Gastrointestinal disorders	51 (9.5)	38 (7.1)	0	18 (10.3)	13 (7.4)	0
Blood and lymphatic system disorders	46 (8.6)	41 (7.6)	1 (<1)	13 (7.4)	12 (6.9)	0
Anaemia	29 (5.4)	26 (4.8)	0	9 (5.1)	8 (4.6)	0
Nervous system disorders	31 (5.8)	17 (3.2)	2 (<1)	10 (5.7)	8 (4.6)	0
Metabolism and nutrition disorders	28 (5.2)	27 (5.0)	0	10 (5.7)	10 (5.7)	0
Hyponatraemia	8 (1.5)	8 (1.5)	0	4 (2.3)	4 (2.3)	0

Musculoskeletal and connective tissue disorders	20 (3.7)	14 (2.6)	1 (<1)	6 (3.4)	4 (2.3)	0
Vascular disorders	20 (3.7)	16 (3.0)	2 (<1)	8 (4.6)	6 (3.4)	1 (<1)
Investigations	18 (3.4)	17 (3.2)	0	5 (2.9)	5 (2.9)	0
Cardiac disorders	17 (3.2)	13 (2.4)	2 (<1)	7 (4.0)	6 (3.4)	0
Renal and urinary disorders	14 (2.6)	11 (2.0)	0	3 (1.7)	2 (1.1)	0
Hepatobiliary disorders	13 (2.4)	11 (2.0)	0	6 (3.4)	4 (2.3)	0
Injury, poisoning and procedural complications	13 (2.4)	9 (1.7)	0	6 (3.4)	5 (2.9)	0

Clinical cutoff date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_140_01_15_saept_all_ra_thyr_400_grade

Table 2 Serious Adverse Events Leading to Permanent Discontinuation of Treatment (within RET-altered thyroid population) by System Organ Class and Preferred Term (Safety Population, Treated at 400 mg QD)

	Overall (N=537)			RET-altered Thyroid (N=175)		
SOC PT	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
General disorders and administration site conditions	24 (4.5)	3 (<1)	19 (3.5)	3 (1.7)	0	3 (1.7)
Disease progression	17 (3.2)	3 (<1)	12 (2.2)	2 (1.1)	0	2 (1.1)
General physical health deterioration	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	24 (4.5)	12 (2.2)	10 (1.9)	7 (4.0)	2 (1.1)	5 (2.9)
Pneumonitis	10 (1.9)	7 (1.3)	1 (<1)	1 (<1)	1 (<1)	0
Acute respiratory failure	2 (<1)	1 (<1)	1 (<1)	2 (1.1)	1 (<1)	1 (<1)

Pneumonia aspiration	2 (<1)	0	2 (<1)	2 (1.1)	0	2 (1.1)
Respiratory failure	2 (<1)	0	2 (<1)	1 (<1)	0	1 (<1)
Acute respiratory distress syndrome	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Asphyxia	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Infections and infestations	23 (4.3)	5 (<1)	15 (2.8)	9 (5.1)	1 (<1)	8 (4.6)
Pneumonia	11 (2.0)	3 (<1)	7 (1.3)	4 (2.3)	1 (<1)	3 (1.7)
Sepsis	5 (<1)	1 (<1)	3 (<1)	2 (1.1)	0	2 (1.1)
Corona virus infection	3 (<1)	0	3 (<1)	2 (1.1)	0	2 (1.1)
Pneumocystis jirovecii pneumonia	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Septic shock	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Vascular disorders	4 (<1)	1 (<1)	2 (<1)	1 (<1)	0	1 (<1)
Jugular vein thrombosis	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Blood and lymphatic system disorders	3 (<1)	3 (<1)	0	1 (<1)	1 (<1)	0
Febrile neutropenia	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Nervous system disorders	3 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Cognitive disorder	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Gastrointestinal disorders	2 (<1)	2 (<1)	0	1 (<1)	1 (<1)	0
Large intestine perforation	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Investigations	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Blood creatine phosphokinase increased	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0

Clinical cut-off date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_142_01_15_saept_di_all_ra_thyr_400_grade

Assessor's comments:

In the RET-altered safety group 54.1% had any grade SAEs (OCCD 12 April 2021) Most common (≥2%) all grades, Grade 3/4 and Grade 5 SAEs by SOC and PT are seen in Table 1 (CCOD 18 October 2021). Of these 11.4% experienced pneumonia, 5.7% corona virus infection, 4.0% pneumonitis and 2.3% hyponatraemia. This was similar to the overall safety group except for corona virus infection and hyponatraemia, where it was 3.2% and 1.5%, respectively. The other reporting rate of SAEs were in their majority comparable between the two groups.

Pneumonia was the most common SAE (n=4; 2.3%), which led to treatment discontinuation in the RET-altered TC population. The reporting rate, however, was not different to the overall patient population (Table 2). Given the small patient numbers, a time to onset and time to resolution analysis has not been provided, as an interpretation would be not meaningful.

Laboratory findings

Haematology

Haematology parameters, for which abnormalities were reported as AE in the RET-altered thyroid cancer population treated at 400 mg QD and considered clinically meaningful are Anaemia, Lymphopenia, Leukopenia, Neutropenia, and Thrombocytopenia.

Table 1 Shift table of key haematological laboratory Treatment-emergent abnormalities worsening from baseline (Safety Population, Treated at 400 mg QD)

Parameter	RET-altered Thyroid Cancer Patients (N=175)		All Patients (N=537)	
	Worsen to G1-4 n (%)	Worsen to G3-4 n (%)	Worsen to G1-4 n (%)	Worsen to G3-4 n (%)
Decreased Hemoglobin	135 (77.1)	32 (18.3)	409 (76.2)	98 (18.2)
Decreased Lymphocytes	115 (65.7)	56 (32.0)	386 (71.9)	168 (31.3)
Decreased Leukocytes	110 (62.9)	24 (13.7)	409 (76.2)	67 (12.5)
Decreased Neutrophils	95 (54.3)	28 (16.0)	356 (66.3)	107 (19.9)
Decreased Platelets	47 (26.9)	5 (2.9)	175 (32.6)	25 (4.7)

Clinical cutoff date: 18 October 2021.

Notes: For each laboratory parameter, the percentages are based on the number of patients in each corresponding Safety Population.

Source: T14_03_04_03_01_07_hemshift_altr, T14_03_04_03_01_06_hemshift

Assessor's comments:

In Table 1, treatment-emergent shifts of key haematological abnormalities (Anaemia, Lymphopenia, Leukopenia, Neutropenia, and Thrombocytopenia) worsening from baseline are showed for the RET-

altered thyroid cancer population and the overall safety population. The worsening to G3-4 was for the RET-altered patient group is similar as compared to the overall safety pool population.

Chemistry

Chemistry parameters, for which abnormalities were reported as AE in the RET-altered thyroid cancer population treated at 400 mg QD and considered clinically meaningful are Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood creatinine increased, Blood bilirubin increased, Blood alkaline phosphatase increased, Blood albumin decreased, electrolyte disorders related to calcium, phosphate/potassium, magnesium, and sodium.

Table 2 Shift Table of key chemistry laboratory Treatment-emergent abnormalities worsening from baseline (Safety Population, Treated at 400 mg QD)

Parameter	RET-altered Thyroid Cancer Patients (N=175)		All Patients (N=537)	
	Worsen to G1-4 n (%)	Worsen to G3-4 n (%)	Worsen to G1-4 n (%)	Worsen to G3-4 n (%)
Decreased Albumin	92(52.6)	6(3.4)	262(48.8)	9(1.7)
Decreased Calcium	125(71.4)	18(10.3)	304(56.6)	27(5.0)
Decreased Magnesium	53(30.3)	0	141(26.3)	2(<1)
Decreased Phosphate	66(37.7)	16(9.1)	237(44.1)	71(13.2)
Decreased Potassium	41(23.4)	5(2.9)	128(23.8)	20(3.7)
Decreased Sodium	64(36.6)	6(3.4)	205(38.2)	39(7.3)
Increased Aspartate aminotransferase	141(80.6)	13(7.4)	424(79.0)	35(6.5)
Increased Alanine aminotransferase	97(55.4)	9(5.1)	309(57.5)	31(5.8)
Increased Blood creatinine	82(46.9)	0	233(43.4)	5(<1)
Increased Blood bilirubin	47(26.9)	4(2.3)	120(22.3)	12(2.2)
Increased Blood alkaline phosphatase	43(24.6)	2(1.1)	196(36.5)	13(2.4)
Increased Calcium	29(16.6)	7(4.0)	53(9.9)	8(1.5)
Increased Magnesium	21(12.0)	5(2.9)	74(13.8)	9(1.7)
Increased Potassium	48(27.4)	3(1.7)	138(25.7)	8(1.5)
Increased Sodium	24(13.7)	0	49(9.1)	3(<1)

Notes: Clinical cut off date: 18 Oct 2021.
For each laboratory parameter, the percentages are based on the number of patients in each corresponding Safety Population.
Source: T14_03_03_03_01_07_chemshift_altr, T14_03_03_03_01_06_chemshift

Assessor's comments:

The worsening to G3-4 was for the RET-altered patient group for decreased albumin, decreased calcium and increased calcium more than doubled compared to the overall safety pool, which again

is due to the underlying disease. This was the opposite for increased blood alkaline phosphatase and increased magnesium. The other conditions were similar between the two groups.

Upon request the MAH has made a Hy's law assessment, which included screening of patients who experienced both AST/ALT >3xULN and bilirubin >2ULN (potential Hy's law cases), those patients were further assessed for having experienced cholestasis (elevated ALP) or other causes of hyperbilirubinemia and elevated transaminases. The MAH has provided a table with those patients (not shown here). Upon review, all patients had other attributing factors which explain the elevated liver enzymes and therefore do not indicate to be true Hy's law cases. Also, no adverse event of drug induced liver injury was reported.

Vital signs

An overview of vital sign abnormalities in the RET-altered thyroid cancer population and the all patient population who started treatment with pralsetinib at 400 mg QD is presented in Table 3.

Table 3 Vital Signs Outside Normal Limits Among Patients Without Abnormality at Baseline (Safety Population, Treated at 400 mg QD)

Parameter	Direction of Abnormality	RET-altered Thyroid Cancer Patients (N=175)	All Patients (N=537)
Diastolic Blood Pressure	Low	32/161 (19.9%)	79/510 (15.5%)
Diastolic Blood Pressure	High	109/130 (83.8%)	344/393 (87.5%)
Systolic Blood Pressure	Low	5/174 (2.9%)	16/534 (3.0%)
Systolic Blood Pressure	High	100/129 (77.5%)	292/380 (76.8%)
Temperature	Low	103/109 (94.5%)	276/305 (90.5%)
Temperature	High	21/173 (12.1%)	67/529 (12.7%)
Heart Rate	Low	47/165 (28.5%)	105/506 (20.8%)
Heart Rate	High	62/163 (38.0%)	182/477 (38.2%)

Notes: Clinical cut off date: 18 Oct 2021. Table entries provide the number of patients with a post-baseline assessment abnormality in the direction specified among patients without abnormality at baseline. Abnormalities reported in patients with missing baseline values are included. Abnormality was defined as follows: Heart Rate (beats/min) low: 60, high: 100; Systolic Blood Pressure (mmHg) low: 90, high: 130; Diastolic Blood Pressure (mmHg) low: 60, high: 80; Temperature (°C) low: 36.5, high: 37.5

Source: T14_03_06_03_01_06_vs_abn_SE_18Oct2021_42863, T14_03_06_03_01_07_vs_abn_SE_400_18Oct2021_42863

Assessor's comments:

The proportion of patients with abnormal vital signs post-baseline were in general comparable between the two populations. The RET-altered TC population had a higher proportion of patients 28.5% vs 20.8%, respectively, who experienced lower heart rate during the course of treatment. However, no PT of heart rate decreased or heart rate abnormal had been reported.

ECG

Table 4 displays any ECG shifts from baseline to worst on treatment value in the RET-altered thyroid cancer population and the all patient population who started treatment with pralsetinib at 400 mg QD.

Table 4 ECG Shift from Baseline to Worst on Treatment Value (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients (N=175)			All Patients (N=537)		
	Post baseline worst value			Post baseline worst value		
Baseline	Normal	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant	Normal	Abnormal, Not Clinically Significant	Abnormal, Clinically Significant
Not Evaluable	0	1 (0.6%)	0	0	2 (0.4%)	0
Normal	41 (23.4%)	52 (29.7%)	6 (3.4%)	122 (22.7%)	156 (29.1%)	16 (3.0%)
Abnormal, Not Clinically Significant	4 (2.3%)	64 (36.6%)	5 (2.9%)	9 (1.7%)	203 (37.8%)	17 (3.2%)
Abnormal, Clinically Significant	0	0	2 (1.1%)	0	0	12 (2.2%)

Notes: Clinical cut-off date: 18 Oct 2021. Table entries provide the number of patients by baseline assessment and worst post-baseline assessment. Percentages are based on the total number of patients in each treatment group.
Baseline is defined as the last assessment prior to start of study treatment.
Source: T14_03_07_03_01_06_eg_shift_all, T14_03_07_03_01_07_eg_shift_ra_thyr_400mg

Table 2 Adverse Events related to ECG occurrences by Preferred Term (Safety Population, Treated at 400 mg QD)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
SOC Preferred Term	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Investigations						
Electrocardiogram QT prolonged	12 (6.9)	1 (<1)	0	27 (5.0)	2 (<1)	0
Electrocardiogram ST-T change	0	0	0	2 (<1)	0	0
Electrocardiogram abnormal	2 (1.1)	0	0	2 (<1)	0	0
Electrocardiogram ST segment abnormal	0	0	0	1 (<1)	0	0
Cardiac disorders						
Bradycardia	3 (1.7)	1 (<1)	0	6 (1.1)	1 (<1)	0
Sinus bradycardia	3 (1.7)	0	0	7 (1.3)	0	0
Supraventricular extrasystoles	2 (1.1)	0	0	2 (<1)	0	0
Tachycardia	2 (1.1)	0	0	10 (1.9)	0	0
Atrioventricular block complete	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0
Supraventricular tachycardia	1 (<1)	1 (<1)	0	3 (<1)	2 (<1)	0
Nodal arrhythmia	0	0	0	4 (<1)	0	0
Atrial flutter	0	0	0	2 (<1)	0	0
Extrasystoles	0	0	0	2 (<1)	0	0
Sinus tachycardia	0	0	0	2 (<1)	0	0
Atrial fibrillation	0	0	0	1 (<1)	0	0
Bundle branch block right	0	0	0	1 (<1)	0	0

Long QT syndrome	0	0	0	1 (<1)	0	0
Ventricular extrasystoles	0	0	0	1 (<1)	0	0
Ventricular pre-excitation	0	0	0	1 (<1)	0	0

Clinical cutoff date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_104_01_06_ae_grade_new, T14_03_02_104_01_07_ae_ra_thyr_400mg_grade_new

Assessor's comments:

ECG interpretation were similar in the RET-altered group compared to the overall safety pool.

Table 2 includes ECG occurrences reported as AEs. EKG QT prolonged Any Grade was seen in the RET-altered patient group compared to the overall safety pool in 6.9% vs 5.0%, respectively. Grade 3-4 AEs were seen across both groups in only 1-2 patients. There were not seen any Grade 5 AEs. Torsades des Pointes had not been reported.

Safety in special populations

Safety data by subgroups for patients with RET mutation-positive MTC whose starting dose was 400 mg QD (N=145) are discussed briefly here. Due to the low sample size, assessments were not made for RET fusion-positive thyroid cancer patients (N=30).

Age

Of note, a smaller proportion of patients were included in the ≥65 years age category (N=31) compared to those in the <65 years age category (N=114).

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.3.1.101.1.4a Summary of Adverse Events by Age Group (adjacent events linked)
Safety Population - RET-mutation MTC Patients Treated at 400 mg QD

Age Group: <65 years old

	Overall (N=114) n (%)	Prior Systemic Treatment (N=58) n (%)	Prior Cabo./Vand. Treatment (N=49) n (%)	Prior Cabo. And Vand. Treatment (N=16) n (%)	No Prior Cabo./Vand. Treatment (N=65) n (%)	No Prior Systemic Treatment (N=56) n (%)
Patients with AE	114 (100)	58 (100)	49 (100)	16 (100)	65 (100)	56 (100)
Patients with Grade 3/4/5 AE	93 (81.6)	48 (82.8)	41 (83.7)	13 (81.3)	52 (80.0)	45 (80.4)
Patients with AE Related to Study Drug	112 (98.2)	56 (96.6)	47 (95.9)	15 (93.8)	65 (100)	56 (100)
Patients with Grade 3/4/5 AE Related to Study Drug	69 (60.5)	36 (62.1)	31 (63.3)	9 (56.3)	38 (58.5)	33 (58.9)
Patients with SAE	55 (48.2)	32 (55.2)	28 (57.1)	12 (75.0)	27 (41.5)	23 (41.1)
Patients with Grade 3/4/5 SAE	50 (43.9)	28 (48.3)	25 (51.0)	11 (68.8)	25 (38.5)	22 (39.3)
Patients with SAE Related to Study Drug	16 (14.0)	9 (15.5)	7 (14.3)	2 (12.5)	9 (13.8)	7 (12.5)
Deaths Due to AE	8 (7.0)	5 (8.6)	4 (8.2)	2 (12.5)	4 (6.2)	3 (5.4)
Deaths Due to AEs Related to Study Drug	0	0	0	0	0	0
Patients with AE by Highest NCI CTCAE Grade						
Grade 1	1 (<1)	0	0	0	1 (1.5)	1 (1.8)
Grade 2	20 (17.5)	10 (17.2)	8 (16.3)	3 (18.8)	12 (18.5)	10 (17.9)
Grade 3	62 (54.4)	32 (55.2)	27 (55.1)	8 (50.0)	35 (53.8)	30 (53.6)
Grade 4	23 (20.2)	11 (19.0)	10 (20.4)	3 (18.8)	13 (20.0)	12 (21.4)
Grade 5	8 (7.0)	5 (8.6)	4 (8.2)	2 (12.5)	4 (6.2)	3 (5.4)

Age Group: <65 years old

	Overall (N=114) n (%)	Prior Systemic Treatment (N=58) n (%)	Prior Cabo./Vand. Treatment (N=49) n (%)	Prior Cabo. And Vand. Treatment (N=16) n (%)	No Prior Cabo./Vand. Treatment (N=65) n (%)	No Prior Systemic Treatment (N=56) n (%)
Patients with SAE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	5 (4.4)	4 (6.9)	3 (6.1)	1 (6.3)	2 (3.1)	1 (1.8)
Grade 3	29 (25.4)	16 (27.6)	15 (30.6)	7 (43.8)	14 (21.5)	13 (23.2)
Grade 4	13 (11.4)	7 (12.1)	6 (12.2)	2 (12.5)	7 (10.8)	6 (10.7)
Grade 5	8 (7.0)	5 (8.6)	4 (8.2)	2 (12.5)	4 (6.2)	3 (5.4)
Patients with Study Drug Adjustments Due to AE	92 (80.7)	51 (87.9)	44 (89.8)	13 (81.3)	48 (73.8)	41 (73.2)
Interruption [1]	86 (75.4)	49 (84.5)	42 (85.7)	12 (75.0)	44 (67.7)	37 (66.1)
Reduction	64 (56.1)	36 (62.1)	33 (67.3)	7 (43.8)	31 (47.7)	28 (50.0)
Discontinuation	15 (13.2)	11 (19.0)	8 (16.3)	3 (18.8)	7 (10.8)	4 (7.1)
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	15 (13.2)	11 (19.0)	8 (16.3)	3 (18.8)	7 (10.8)	4 (7.1)
Patients with Study Drug Adjustments Due to Treatment-related AE	76 (66.7)	42 (72.4)	36 (73.5)	10 (62.5)	40 (61.5)	34 (60.7)
Interruption [1]	70 (61.4)	39 (67.2)	33 (67.3)	9 (56.3)	37 (56.9)	31 (55.4)
Reduction	60 (52.6)	33 (56.9)	30 (61.2)	7 (43.8)	30 (46.2)	27 (48.2)
Discontinuation	4 (3.5)	3 (5.2)	1 (2.0)	0	3 (4.6)	1 (1.8)
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	4 (3.5)	3 (5.2)	1 (2.0)	0	3 (4.6)	1 (1.8)

Source: 16.4.1.101.1 - 16.4.1.101.8.
Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Cabo., Cabozantinib; Vand., Vandetanib.
Adjacent AEs for the same preferred term are linked per patient.
[1] Dose interruptions include doses interrupted due to an adverse event and missed due to an adverse event.

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.3.1.101.1.4a Summary of Adverse Events by Age Group (adjacent events linked)
Safety Population - RET-mutation MTC Patients Treated at 400 mg QD

Age Group: ≥65 years old

	Overall (N=31) n (%)	Prior Systemic Treatment (N=20) n (%)	Prior Cabo./Vand. Treatment (N=18) n (%)	Prior Cabo. And Vand. Treatment (N=8) n (%)	No Prior Cabo./Vand. Treatment (N=13) n (%)	No Prior Systemic Treatment (N=11) n (%)
Patients with AE	31 (100)	20 (100)	18 (100)	8 (100)	13 (100)	11 (100)
Patients with Grade 3/4/5 AE	29 (93.5)	20 (100)	18 (100)	8 (100)	11 (84.6)	9 (81.8)
Patients with AE Related to Study Drug	30 (96.8)	19 (95.0)	17 (94.4)	7 (87.5)	13 (100)	11 (100)
Patients with Grade 3/4/5 AE Related to Study Drug	19 (61.3)	14 (70.0)	13 (72.2)	5 (62.5)	6 (46.2)	5 (45.5)
Patients with SAE	22 (71.0)	16 (80.0)	14 (77.8)	6 (75.0)	8 (61.5)	6 (54.5)
Patients with Grade 3/4/5 SAE	21 (67.7)	16 (80.0)	14 (77.8)	6 (75.0)	7 (53.8)	5 (45.5)
Patients with SAE Related to Study Drug	8 (25.8)	5 (25.0)	5 (27.8)	1 (12.5)	3 (23.1)	3 (27.3)
Deaths Due to AE	8 (25.8)	6 (30.0)	6 (33.3)	3 (37.5)	2 (15.4)	2 (18.2)
Deaths Due to AEs Related to Study Drug	1 (3.2)	1 (5.0)	1 (5.6)	0	0	0
Patients with AE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	2 (6.5)	0	0	0	2 (15.4)	2 (18.2)
Grade 3	16 (51.6)	11 (55.0)	9 (50.0)	3 (37.5)	7 (53.8)	5 (45.5)
Grade 4	5 (16.1)	3 (15.0)	3 (16.7)	2 (25.0)	2 (15.4)	2 (18.2)
Grade 5	8 (25.8)	6 (30.0)	6 (33.3)	3 (37.5)	2 (15.4)	2 (18.2)

Age Group: ≥65 years old

	Overall (N=31) n (%)	Prior Systemic Treatment (N=20) n (%)	Prior Cabo./Vand. Treatment (N=18) n (%)	Prior Cabo. And Vand. Treatment (N=8) n (%)	No Prior Cabo./Vand. Treatment (N=13) n (%)	No Prior Systemic Treatment (N=11) n (%)
Patients with SAE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	1 (3.2)	0	0	0	1 (7.7)	1 (9.1)
Grade 3	9 (29.0)	7 (35.0)	5 (27.8)	1 (12.5)	4 (30.8)	2 (18.2)
Grade 4	4 (12.9)	3 (15.0)	3 (16.7)	2 (25.0)	1 (7.7)	1 (9.1)
Grade 5	8 (25.8)	6 (30.0)	6 (33.3)	3 (37.5)	2 (15.4)	2 (18.2)
Patients with Study Drug Adjustments Due to AE	25 (80.6)	17 (85.0)	15 (83.3)	5 (62.5)	10 (76.9)	8 (72.7)
Interruption [1]	24 (77.4)	17 (85.0)	15 (83.3)	5 (62.5)	9 (69.2)	7 (63.6)
Reduction	15 (48.4)	11 (55.0)	10 (55.6)	2 (25.0)	5 (38.5)	4 (36.4)
Discontinuation	8 (25.8)	4 (20.0)	4 (22.2)	2 (25.0)	4 (30.8)	4 (36.4)
Disease Progression	1 (3.2)	1 (5.0)	1 (5.6)	0	0	0
Other AEs except Disease Progression	7 (22.6)	3 (15.0)	3 (16.7)	2 (25.0)	4 (30.8)	4 (36.4)
Patients with Study Drug Adjustments Due to Treatment-related AE	16 (51.6)	13 (65.0)	11 (61.1)	3 (37.5)	5 (38.5)	3 (27.3)
Interruption [1]	16 (51.6)	13 (65.0)	11 (61.1)	3 (37.5)	5 (38.5)	3 (27.3)
Reduction	13 (41.9)	10 (50.0)	9 (50.0)	2 (25.0)	4 (30.8)	3 (27.3)
Discontinuation	3 (9.7)	2 (10.0)	2 (11.1)	1 (12.5)	1 (7.7)	1 (9.1)
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	3 (9.7)	2 (10.0)	2 (11.1)	1 (12.5)	1 (7.7)	1 (9.1)

Source: 16.4.1.101.1 - 16.4.1.101.8.
Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Cabo., Cabozantinib; Vand., Vandetanib.
Adjacent AEs for the same preferred term are linked per patient.
[1] Dose interruptions include doses interrupted due to an adverse event and missed due to an adverse event.

Table 1 Most common related treatment emergent adverse events

Preferred Term	Pralsetinib start dose at 400 mg QD			
	Treatment Related AEs <65 years old (N=371) n (%)	Treatment Related SAEs <65 years old (N=371) n (%)	Treatment Related AEs ≥65 years old (N=166) n (%)	Treatment Related SAEs ≥65 years old (N=166) n (%)
Aspartate aminotransferase increased	160 (43.1)	1 (≤1)	64 (38.6)	1 (≤1)
Anaemia	142 (38.3)	14 (3.8)	63 (38.0)	4 (2.4)
Alanine aminotransferase increased	124 (33.4)	1 (≤1)	45 (27.1)	1 (≤1)
White blood cell count decreased	103 (27.8)	0	38 (22.9)	0
Constipation	101 (27.2)	1 (≤1)	46 (27.7)	1 (≤1)
Neutrophil count decreased	100 (27.0)	0	31 (18.7)	0
Hypertension	89 (24.0)	1 (≤1)	53 (31.9)	3 (1.8)
Neutropenia	85 (22.9)	6 (1.6)	29 (17.5)	2 (1.2)
Hyperphosphataemia	70 (18.9)	0	16 (9.6)	0
Blood creatine phosphokinase increased	67 (18.1)	4 (1.1)	17 (10.2)	0
Diarrhoea	65 (17.5)	2 (≤1)	29 (17.5)	1 (≤1)
Blood creatinine increased	63 (17.0)	0	26 (15.7)	0
Fatigue	54 (14.6)	1 (≤1)	32 (19.3)	0
Dysgeusia	45 (12.1)	0	27 (16.3)	0
Leukopenia	44 (11.9)	0	11 (6.6)	0
Hypocalcaemia	44 (11.9)	1 (≤1)	15 (9.0)	0
Asthenia	42 (11.3)	0	16 (9.6)	2 (1.2)
Dry mouth	41 (11.1)	0	26 (15.7)	0
Lymphocyte count decreased	39 (10.5)	0	18 (10.8)	0
Lymphopenia	37 (10.0)	1 (≤1)	14 (8.4)	0
Pneumonitis	34 (9.2)	13 (3.5)	20 (12.0)	10 (6.0)

Notes: CCOD: 18 October 2021. AEs are coded using MedDRA version 19.1. AEs refer to treatment emergent AEs.

If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count.
Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_111_01_06a, T14_03_02_116_01_06a

Assessor's comments:

Fewer patients were included in the ≥65 years age category (N=31) compared to those in the <65 years age category (N=114). Grade 4 AEs and AEs leading to discontinuation increases with age

which is as expected, since patients are more frail and have more comorbidities with increasing age. However, numbers are small. Deaths due to AEs were significantly higher in the older age group compared to the younger group where it was 25.8% and 7%, respectively. The MAH has elaborated on and discussed this fact. Compared to the new update as of 18 Oct 2021 the frequency of deaths is the same. The PT disease progression was the most common death due to AE in the ≥65 age group, all of the patients were male with metastatic disease at baseline, half of the patients were White, and median age was 69 years of age. It is reported that the risk of death with distant metastasis is greater in older compared to younger patients (96% versus 63%) (Lechner and Hershman 2000). As the MAH explains, there were no significant differences in terms of demographic background (i.e. gender and race/ethnicity) between the age categories that would further explain the differences in frequency of deaths due to AEs apart from the physiological changes related to aging, multimorbidity and multi-pharmacy that is very common in the elderly population.

Upon request the MAH has discussed dose reduction among the elderly and has provided a list for all patients treated in Study BO42863 with the most common (≥10%) AEs which were considered related to study treatment (by the investigator) for all patients, including seriousness information (Table 1). AEs that occurred more often (>5%) in patients ≥65 years old as compared to <65 years old patients were hypertension. In the general population, hypertension occurs in more than two thirds of elderly (≥65 years) and the severity of hypertension increases markedly with aging. The vast majority (42/53 patients) of the elderly patients with hypertension were managed with anti-hypertensive medication and no patient had to discontinue due to the event.

SAEs (considered related to study drug by the investigator) that occurred more often (>2%) in patients ≥65 years old as compared to <65 years old patients were pneumonitis. Of the 10 patients who experienced serious pneumonitis, all but one recovered from the event. As suggested within the protocol of BO42863, pralsetinib related pneumonitis was mainly managed by dose modifications.

Sex

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.3.1.101.1.4b Summary of Adverse Events by Sex (adjacent events linked)
Safety Population - RET-mutation MTC Patients Treated at 400 mg QD

Sex: Female

	Overall (N=52) n (%)	Prior Systemic Treatment (N=28) n (%)	Prior Cabo./Vand. Treatment (N=23) n (%)	Prior Cabo. And Vand. Treatment (N=9) n (%)	No Prior Cabo./Vand. Treatment (N=29) n (%)	No Prior Systemic Treatment (N=24) n (%)
Patients with AE	52 (100)	28 (100)	23 (100)	9 (100)	29 (100)	24 (100)
Patients with Grade 3/4/5 AE	39 (75.0)	21 (75.0)	17 (73.9)	7 (77.8)	22 (75.9)	18 (75.0)
Patients with AE Related to Study Drug	52 (100)	28 (100)	23 (100)	9 (100)	29 (100)	24 (100)
Patients with Grade 3/4/5 AE Related to Study Drug	29 (55.8)	17 (60.7)	13 (56.5)	6 (66.7)	16 (55.2)	12 (50.0)
Patients with SAE	30 (57.7)	18 (64.3)	14 (60.9)	6 (66.7)	16 (55.2)	12 (50.0)
Patients with Grade 3/4/5 SAE	26 (50.0)	16 (57.1)	13 (56.5)	5 (55.6)	13 (44.8)	10 (41.7)
Patients with SAE Related to Study Drug	16 (30.8)	9 (32.1)	7 (30.4)	2 (22.2)	9 (31.0)	7 (29.2)
Deaths Due to AE	3 (5.8)	2 (7.1)	1 (4.3)	0	2 (6.9)	1 (4.2)
Deaths Due to AEs Related to Study Drug	0	0	0	0	0	0
Patients with AE by Highest NCI CTCAE Grade						
Grade 1	1 (1.9)	0	0	0	1 (3.4)	1 (4.2)
Grade 2	12 (23.1)	7 (25.0)	6 (26.1)	2 (22.2)	6 (20.7)	5 (20.8)
Grade 3	22 (42.3)	12 (42.9)	9 (39.1)	4 (44.4)	13 (44.8)	10 (41.7)
Grade 4	14 (26.9)	7 (25.0)	7 (30.4)	3 (33.3)	7 (24.1)	7 (29.2)
Grade 5	3 (5.8)	2 (7.1)	1 (4.3)	0	2 (6.9)	1 (4.2)

Sex: Female

	Overall (N=52) n (%)	Prior Systemic Treatment (N=28) n (%)	Prior Cabo./Vand. Treatment (N=23) n (%)	Prior Cabo. And Vand. Treatment (N=9) n (%)	No Prior Cabo./Vand. Treatment (N=29) n (%)	No Prior Systemic Treatment (N=24) n (%)
Patients with SAE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	4 (7.7)	2 (7.1)	1 (4.3)	1 (11.1)	3 (10.3)	2 (8.3)
Grade 3	14 (26.9)	9 (32.1)	7 (30.4)	2 (22.2)	7 (24.1)	5 (20.8)
Grade 4	9 (17.3)	5 (17.9)	5 (21.7)	3 (33.3)	4 (13.8)	4 (16.7)
Grade 5	3 (5.8)	2 (7.1)	1 (4.3)	0	2 (6.9)	1 (4.2)
Patients with Study Drug Adjustments Due to AE	42 (80.8)	24 (85.7)	19 (82.6)	7 (77.8)	23 (79.3)	18 (75.0)
Interruption [1]	40 (76.9)	23 (82.1)	18 (78.3)	6 (66.7)	22 (75.9)	17 (70.8)
Reduction	26 (50.0)	13 (46.4)	12 (52.2)	5 (55.6)	14 (48.3)	13 (54.2)
Discontinuation	10 (19.2)	7 (25.0)	5 (21.7)	3 (33.3)	5 (17.2)	3 (12.5)
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	10 (19.2)	7 (25.0)	5 (21.7)	3 (33.3)	5 (17.2)	3 (12.5)
Patients with Study Drug Adjustments Due to Treatment-related AE	34 (65.4)	20 (71.4)	15 (65.2)	6 (66.7)	19 (65.5)	14 (58.3)
Interruption [1]	33 (63.5)	19 (67.9)	14 (60.9)	5 (55.6)	19 (65.5)	14 (58.3)
Reduction	25 (48.1)	13 (46.4)	12 (52.2)	5 (55.6)	13 (44.8)	12 (50.0)
Discontinuation	5 (9.6)	3 (10.7)	1 (4.3)	1 (11.1)	4 (13.8)	2 (8.3)
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	5 (9.6)	3 (10.7)	1 (4.3)	1 (11.1)	4 (13.8)	2 (8.3)

Source: 16.4.1.101.1 - 16.4.1.101.8.
Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Cabo., Cabozantinib; Vand., Vandetanib.
Adjacent AEs for the same preferred term are linked per patient.
[1] Dose interruptions include doses interrupted due to an adverse event and missed due to an adverse event.

Protocol: BO42863
Data cutoff date: 12 Apr 2021

Table 14.3.1.101.1.4b Summary of Adverse Events by Sex (adjacent events linked)
Safety Population - RET-mutation MTC Patients Treated at 400 mg QD

Sex: Male

	Overall (N=93) n (%)	Prior Systemic Treatment (N=50) n (%)	Prior Cabo./Vand. Treatment (N=44) n (%)	Prior Cabo. And Vand. Treatment (N=15) n (%)	No Prior Cabo./Vand. Treatment (N=49) n (%)	No Prior Systemic Treatment (N=43) n (%)
Patients with AE	93 (100)	50 (100)	44 (100)	15 (100)	49 (100)	43 (100)
Patients with Grade 3/4/5 AE	83 (89.2)	47 (94.0)	42 (95.5)	14 (93.3)	41 (83.7)	36 (83.7)
Patients with AE Related to Study Drug	90 (96.8)	47 (94.0)	41 (93.2)	13 (86.7)	49 (100)	43 (100)
Patients with Grade 3/4/5 AE Related to Study Drug	59 (63.4)	33 (66.0)	31 (70.5)	8 (53.3)	28 (57.1)	26 (60.5)
Patients with SAE	47 (50.5)	30 (60.0)	28 (63.6)	12 (80.0)	19 (38.8)	17 (39.5)
Patients with Grade 3/4/5 SAE	45 (48.4)	28 (56.0)	26 (59.1)	12 (80.0)	19 (38.8)	17 (39.5)
Patients with SAE Related to Study Drug	8 (8.6)	5 (10.0)	5 (11.4)	1 (6.7)	3 (6.1)	3 (7.0)
Deaths Due to AE	13 (14.0)	9 (18.0)	9 (20.5)	5 (33.3)	4 (8.2)	4 (9.3)
Deaths Due to AEs Related to Study Drug	1 (1.1)	1 (2.0)	1 (2.3)	0	0	0
Patients with AE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	10 (10.8)	3 (6.0)	2 (4.5)	1 (6.7)	8 (16.3)	7 (16.3)
Grade 3	56 (60.2)	31 (62.0)	27 (61.4)	7 (46.7)	29 (59.2)	25 (58.1)
Grade 4	14 (15.1)	7 (14.0)	6 (13.6)	2 (13.3)	8 (16.3)	7 (16.3)
Grade 5	13 (14.0)	9 (18.0)	9 (20.5)	5 (33.3)	4 (8.2)	4 (9.3)

Sex: Male

	Overall (N=93) n (%)	Prior Systemic Treatment (N=50) n (%)	Prior Cabo./Vand. Treatment (N=44) n (%)	Prior Cabo. And Vand. Treatment (N=15) n (%)	No Prior Cabo./Vand. Treatment (N=49) n (%)	No Prior Systemic Treatment (N=43) n (%)
Patients with SAE by Highest NCI CTCAE Grade						
Grade 1	0	0	0	0	0	0
Grade 2	2 (2.2)	2 (4.0)	2 (4.5)	0	0	0
Grade 3	24 (25.8)	14 (28.0)	13 (29.5)	6 (40.0)	11 (22.4)	10 (23.3)
Grade 4	8 (8.6)	5 (10.0)	4 (9.1)	1 (6.7)	4 (8.2)	3 (7.0)
Grade 5	13 (14.0)	9 (18.0)	9 (20.5)	5 (33.3)	4 (8.2)	4 (9.3)
Patients with Study Drug Adjustments Due to AE	75 (80.6)	44 (88.0)	40 (90.9)	11 (73.3)	35 (71.4)	31 (72.1)
Interruption [1]	70 (75.3)	43 (86.0)	39 (88.6)	11 (73.3)	31 (63.3)	27 (62.8)
Reduction	53 (57.0)	34 (68.0)	31 (70.5)	4 (26.7)	22 (44.9)	19 (44.2)
Discontinuation	13 (14.0)	8 (16.0)	7 (15.9)	2 (13.3)	6 (12.2)	5 (11.6)
Disease Progression	1 (1.1)	1 (2.0)	1 (2.3)	0	0	0
Other AEs except Disease Progression	12 (12.9)	7 (14.0)	6 (13.6)	2 (13.3)	6 (12.2)	5 (11.6)
Patients with Study Drug Adjustments Due to Treatment-related AE	58 (62.4)	35 (70.0)	32 (72.7)	7 (46.7)	26 (53.1)	23 (53.5)
Interruption [1]	53 (57.0)	33 (66.0)	30 (68.2)	7 (46.7)	23 (46.9)	20 (46.5)
Reduction	48 (51.6)	30 (60.0)	27 (61.4)	4 (26.7)	21 (42.9)	18 (41.9)
Discontinuation	2 (2.2)	2 (4.0)	2 (4.5)	0	0	0
Disease Progression	0	0	0	0	0	0
Other AEs except Disease Progression	2 (2.2)	2 (4.0)	2 (4.5)	0	0	0

Source: 16.4.1.101.1 - 16.4.1.101.8.
Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Cabo., Cabozantinib; Vand., Vandetanib.
Adjacent AEs for the same preferred term are linked per patient.
[1] Dose interruptions include doses interrupted due to an adverse event and missed due to an adverse event.

Assessor's comments:

Numbers of F/M included in the study were N=52/N=93. There were more Grade 4 AEs in females, 26.9% compared to 15.1% in males. The reporting rates of the Grade 4 AEs based on the newer CCOD of 18 Oct 2021 has not significantly changed and remained higher in females (T14_03_01_101_01_04b_aeall_mtc_400mg_sex_new). Otherwise, there are no major or relevant differences between males and females.

Upon request, The MAH has elaborated on and discussed the fact that there were more Grade 4 AEs seen in females compared to males. The most common PTs (reported in ≥2 patients) of Grade 4 AEs in female patients were blood creatine phosphokinase increased (2 patients), hypocalcaemia (2 patients), platelet count decreased (2 patients) and hypophosphataemia (2 patients). The most common PTs of Grade 4 AEs in male patients were blood creatine phosphokinase increased (2 patients) and lymphocyte count decreased. There were no specific AE driving the difference between the 2 groups and there were no trends that could further explain the differences in Grade 4 AEs between the 2 groups, apart from the older median age range of the female group compared to the male group, 61 vs 52.5 years, respectively.

Race

Of note, a smaller proportion of patients were included in the 'Other' category (N=14) compared to White (N=107) and Asian (N=54) patients.

Table 1 Summary of Adverse Events by Race Group (adjacent events linked), Safety Population - All Patients treated at 400 mg QD

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Category	**White (N=107) n (%)**	**Asian (N=54) n (%)**	**Other (N=14) n (%)**	**White (N=291) n (%)**	**Asian (N=205) n (%)**	**Other (N=41) n (%)**
All Grade AEs	107 (100)	54 (100)	14 (100)	290 (99.7)	205 (100)	41 (100)
Most common PTs (>10%)						
Anaemia	65 (60.7)	22 (40.7)	6 (42.9)	142 (48.8)	115 (56.1)	18 (43.9)
Hypertension	53 (49.5)	15 (27.8)	4 (28.6)	104 (35.7)	73 (35.6)	8 (19.5)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Category	**White (N=107) n (%)**	**Asian (N=54) n (%)**	**Other (N=14) n (%)**	**White (N=291) n (%)**	**Asian (N=205) n (%)**	**Other (N=41) n (%)**
Aspartate aminotransferase increased	52 (48.6)	28 (51.9)	6 (42.9)	131 (45.0)	119 (58.0)	13 (31.7)
Diarrhoea	44 (41.1)	15 (27.8)	6 (42.9)	109 (37.5)	54 (26.3)	13 (31.7)
Constipation	43 (40.2)	29 (53.7)	5 (35.7)	119 (40.9)	95 (46.3)	19 (46.3)
Fatigue	40 (37.4)	10 (18.5)	3 (21.4)	101 (34.7)	34 (16.6)	11 (26.8)
Hypocalcaemia	40 (37.4)	25 (46.3)	4 (28.6)	61 (21.0)	59 (28.8)	5 (12.2)
Alanine aminotransferase increased	36 (33.6)	22 (40.7)	4 (28.6)	99 (34.0)	87 (42.4)	11 (26.8)
White blood cell count decreased	36 (33.6)	23 (42.6)	3 (21.4)	66 (22.7)	78 (38.0)	7 (17.1)
Pyrexia	35 (32.7)	10 (18.5)	3 (21.4)	84 (28.9)	56 (27.3)	8 (19.5)
Blood creatinine increased	34 (31.8)	12 (22.2)	3 (21.4)	77 (26.5)	48 (23.4)	9 (22.0)
Cough	33 (30.8)	6 (11.1)	5 (35.7)	71 (24.4)	50 (24.4)	14 (34.1)
Hyperphosphataemia	33 (30.8)	19 (35.2)	2 (14.3)	54 (18.6)	39 (19.0)	2 (4.9)
Lymphocyte count decreased	32 (29.9)	8 (14.8)	3 (21.4)	47 (16.2)	27 (13.2)	7 (17.1)
Dyspnoea	29 (27.1)	4 (7.4)	2 (14.3)	64 (22.0)	33 (16.1)	12 (29.3)
Headache	29 (27.1)	9 (16.7)	5 (35.7)	60 (20.6)	23 (11.2)	12 (29.3)
Neutropenia	29 (27.1)	5 (9.3)	6 (42.9)	77 (26.5)	32 (15.6)	14 (34.1)
Arthralgia	28 (26.2)	4 (7.4)	2 (14.3)	46 (15.8)	8 (3.9)	3 (7.3)
Lymphopenia	27 (25.2)	1 (1.9)	2 (14.3)	59 (20.3)	2 (<1)	4 (9.8)
Myalgia	27 (25.2)	3 (5.6)	4 (28.6)	44 (15.1)	10 (4.9)	8 (19.5)
Oedema peripheral	27 (25.2)	9 (16.7)	3 (21.4)	56 (19.2)	28 (13.7)	7 (17.1)
Dysgeusia	24 (22.4)	5 (9.3)	3 (21.4)	60 (20.6)	15 (7.3)	10 (24.4)
Nausea	24 (22.4)	6 (11.1)	3 (21.4)	64 (22.0)	29 (14.1)	8 (19.5)

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Category	**White (N=107) n (%)**	**Asian (N=54) n (%)**	**Other (N=14) n (%)**	**White (N=291) n (%)**	**Asian (N=205) n (%)**	**Other (N=41) n (%)**
Dizziness	23 (21.5)	5 (9.3)	1 (7.1)	51 (17.5)	26 (12.7)	3 (7.3)
Asthenia	22 (20.6)	1 (1.9)	5 (35.7)	57 (19.6)	17 (8.3)	13 (31.7)
Decreased appetite	22 (20.6)	10 (18.5)	5 (35.7)	42 (14.4)	50 (24.4)	8 (19.5)
Neutrophil count decreased	22 (20.6)	17 (31.5)	2 (14.3)	43 (14.8)	92 (44.9)	3 (7.3)
Urinary tract infection	22 (20.6)	5 (9.3)	0	56 (19.2)	19 (9.3)	4 (9.8)
Dysphonia	20 (18.7)	3 (5.6)	2 (14.3)	33 (11.3)	9 (4.4)	3 (7.3)
Dry mouth	19 (17.8)	5 (9.3)	4 (28.6)	59 (20.3)	17 (8.3)	11 (26.8)
Hypokalaemia	19 (17.8)	6 (11.1)	2 (14.3)	39 (13.4)	44 (21.5)	3 (7.3)
Abdominal pain	17 (15.9)	5 (9.3)	1 (7.1)	42 (14.4)	12 (5.9)	3 (7.3)
Hyponatraemia	17 (15.9)	2 (3.7)	0	33 (11.3)	32 (15.6)	1 (2.4)
Pneumonia	16 (15.0)	15 (27.8)	0	40 (13.7)	49 (23.9)	2 (4.9)
Pneumonitis	16 (15.0)	2 (3.7)	2 (14.3)	34 (11.7)	20 (9.8)	5 (12.2)
Back pain	15 (14.0)	3 (5.6)	0	50 (17.2)	23 (11.2)	4 (9.8)
Rash	15 (14.0)	4 (7.4)	2 (14.3)	26 (8.9)	19 (9.3)	5 (12.2)
Vomiting	15 (14.0)	7 (13.0)	2 (14.3)	46 (15.8)	25 (12.2)	5 (12.2)
Blood bilirubin increased	14 (13.1)	4 (7.4)	2 (14.3)	24 (8.2)	30 (14.6)	4 (9.8)
Gastrooesophageal reflux disease	13 (12.1)	2 (3.7)	3 (21.4)	26 (8.9)	3 (1.5)	5 (12.2)
Hypoalbuminaemia	13 (12.1)	15 (27.8)	1 (7.1)	19 (6.5)	58 (28.3)	1 (2.4)
Pain in extremity	12 (11.2)	7 (13.0)	1 (7.1)	37 (12.7)	16 (7.8)	3 (7.3)
Stomatitis	12 (11.2)	5 (9.3)	2 (14.3)	21 (7.2)	12 (5.9)	2 (4.9)
Upper respiratory tract infection	12 (11.2)	8 (14.8)	1 (7.1)	23 (7.9)	20 (9.8)	2 (4.9)
Platelet count decreased	11 (10.3)	6 (11.1)	1 (7.1)	21 (7.2)	39 (19.0)	2 (4.9)
Blood creatine phosphokinase increased	10 (9.3)	13 (24.1)	6 (42.9)	21 (7.2)	53 (25.9)	15 (36.6)
Grade 3+ AEs Most common PTs (>2%)	**93 (86.9)**	**38 (70.4)**	**14 (100)**	**232 (79.7)**	**167 (81.5)**	**36 (87.8)**

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Category	White (N=107) n (%)	Asian (N=54) n (%)	Other (N=14) n (%)	White (N=291) n (%)	Asian (N=205) n (%)	Other (N=41) n (%)
Hypertension	33 (30.8)	6 (11.1)	3 (21.4)	60 (20.6)	31 (15.1)	4 (9.8)
Anaemia	26 (24.3)	9 (16.7)	4 (28.6)	56 (19.2)	54 (26.3)	8 (19.5)
Lymphopenia	20 (18.7)	0	1 (7.1)	42 (14.4)	0	3 (7.3)
Lymphocyte count decreased	18 (16.8)	5 (9.3)	1 (7.1)	26 (8.9)	16 (7.8)	4 (9.8)
Neutropenia	11 (10.3)	2 (3.7)	5 (35.7)	33 (11.3)	19 (9.3)	9 (22.0)
Pneumonia	10 (9.3)	11 (20.4)	0	25 (8.6)	31 (15.1)	2 (4.9)
Corona virus infection	9 (8.4)	0	1 (7.1)	14 (4.8)	0	2 (4.9)
White blood cell count decreased	8 (7.5)	5 (9.3)	3 (21.4)	11 (3.8)	19 (9.3)	4 (9.8)
Urinary tract infection	8 (7.5)	3 (5.6)	0	16 (5.5)	7 (3.4)	1 (2.4)
Hyponatraemia	7 (6.5)	2 (3.7)	0	13 (4.5)	11 (5.4)	0
Sepsis	6 (5.6)	1 (1.9)	0	13 (4.5)	5 (2.4)	2 (4.9)
Hypophosphataemia	6 (5.6)	0	0	16 (5.5)	18 (8.8)	1 (2.4)
Disease progression	6 (5.6)	1 (1.9)	2 (14.3)	32 (11.0)	14 (6.8)	4 (9.8)
Hypocalcaemia	5 (4.7)	7 (13.0)	1 (7.1)	7 (2.4)	12 (5.9)	1 (2.4)
Fatigue	5 (4.7)	1 (1.9)	0	10 (3.4)	2 (<1)	2 (4.9)
Pneumonitis	5 (4.7)	0	1 (7.1)	7 (2.4)	7 (3.4)	2 (4.9)
Blood creatine phosphokinase increased	4 (3.7)	6 (11.1)	4 (28.6)	11 (3.8)	21 (10.2)	9 (22.0)
Aspartate aminotransferase increased	4 (3.7)	3 (5.6)	1 (7.1)	21 (7.2)	14 (6.8)	1 (2.4)
Hypokalaemia	4 (3.7)	2 (3.7)	0	8 (2.7)	12 (5.9)	1 (2.4)
Hypercalcaemia	4 (3.7)	0	0	4 (1.4)	1 (<1)	0
Asthenia	4 (3.7)	0	1 (7.1)	8 (2.7)	1 (<1)	1 (2.4)
Dyspnoea	4 (3.7)	0	1 (7.1)	9 (3.1)	3 (1.5)	2 (4.9)
Acute respiratory failure	4 (3.7)	0	0	5 (1.7)	0	0
Diarrhoea	4 (3.7)	2 (3.7)	1 (7.1)	9 (3.1)	6 (2.9)	1 (2.4)
Syncope	4 (3.7)	0	0	8 (2.7)	1 (<1)	

	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
Category	**White (N=107) n (%)**	**Asian (N=54) n (%)**	**Other (N=14) n (%)**	**White (N=291) n (%)**	**Asian (N=205) n (%)**	**Other (N=41) n (%)**
Alanine aminotransferase increased	3 (2.8)	2 (3.7)	1 (7.1)	14 (4.8)	10 (4.9)	2 (4.9)
Leukopenia	3 (2.8)	0	0	9 (3.1)	4 (2.0)	0
Hypotension	3 (2.8)	0	0	5 (1.7)	2 (<1)	0
Neutrophil count decreased	2 (1.9)	9 (16.7)	1 (7.1)	9 (3.1)	46 (22.4)	1 (2.4)
Platelet count decreased	2 (1.9)	2 (3.7)	1 (7.1)	4 (1.4)	12 (5.9)	1 (2.4)
Pyrexia	2 (1.9)	1 (1.9)	1 (7.1)	4 (1.4)	1 (<1)	2 (4.9)
SAEs Most common PTs (>2%)	**65 (60.7)**	**22 (40.7)**	**10 (71.4)**	**183 (62.9)**	**120 (58.5)**	**26 (63.4)**
Pneumonia	10 (9.3)	10 (18.5)	0	28 (9.6)	31 (15.1)	2 (4.9)
Corona virus infection	9 (8.4)	0	1 (7.1)	15 (5.2)	0	2 (4.9)
Anaemia	8 (7.5)	0	1 (7.1)	17 (5.8)	11 (5.4)	1 (2.4)
Urinary tract infection	7 (6.5)	2 (3.7)	0	15 (5.2)	4 (2.0)	1 (2.4)
Disease progression	6 (5.6)	1 (1.9)	2 (14.3)	33 (11.3)	17 (8.3)	4 (9.8)
Pneumonitis	6 (5.6)	0	1 (7.1)	10 (3.4)	13 (6.3)	3 (7.3)
Sepsis	6 (5.6)	1 (1.9)	0	12 (4.1)	6 (2.9)	2 (4.9)
Acute respiratory failure	4 (3.7)	0	0	5 (1.7)	0	0
Hyponatraemia	4 (3.7)	0	0	5 (1.7)	3 (1.5)	0
Pyrexia	4 (3.7)	0	1 (7.1)	7 (2.4)	6 (2.9)	2 (4.9)
Dyspnoea	3 (2.8)	0	1 (7.1)	8 (2.7)	2 (<1)	1 (2.4)

Clinical cut-off date: 18 October 2021

Notes: Adverse Events are coded using MedDRA 19.1. All treatment emergent adverse events including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple events of the same severity, relationship or outcome, then they are counted only once in that severity, relationship or outcome. However, patients can be counted more than once overall. Related to study drug is as per investigator assessment. Adjacent AEs for the same preferred term are linked per patient.

Assessor's comments:

There was a higher proportion of White patients compared to Asian patients in the study, N=107 and N=54, respectively. More Asian patients died (11.6%) due to AEs compared to White patients (6.7%). Upon request the MAH has provided a table with data for all three subgroups according to race for the overall patient population (N=537) and for the RET-altered patients (N=175) with data for the most common AEs, grade 3 or higher AEs, and SAEs with a clinical cut-off date (CCOD) of 18 October 2021 (Table 1).

For RET-altered thyroid cancer patients, higher AE reporting rates in Asian as compared to White patients (>10% difference) were observed for pneumonia, constipation, neutrophil count decreased, and blood creatine phosphokinase increased. Other than pneumonia, there were no higher reporting rates of serious AEs occurred by Asian patients compared to non-Asian patients.

For RET-altered TC patients, higher reporting rates of Grade ≥3 AEs in Asian patients as compared to White (≥2% difference) were observed for pneumonia, neutrophil count decreased, blood creatine phosphokinase increased and hypocalcaemia.

The MAH has discussed the differences between Asian as compared to White patients. According to the MAH in summary, different reporting practices, small patient numbers (with the risk of chance findings), have contributed to the differences seen for Asian patients. Other factors were discussed, but remain speculative. However, there is no doubt that the Asian patients had more side effects than the White patients.

Region

Table 1 Overview of Most Common Adverse Events, Grade 3 or higher Adverse Events and Serious Adverse Events by Region (United States, Europe and Asia) in the Overall Safety and RET-altered Thyroid Cancer Patients treated at 400mg

Preferred Term	United States		Europe		Asia	
	Overall Safety (N=157)	RET-altered TC (N=68)	Overall Safety (N=187)	RET-altered TC (N=58)	Overall Safety (N=193)	RET-altered TC (N=49)
Most Common AEs (≥10%)						
Patient with AE	157 (100)	68 (100)	186 (99.5)	58 (100)	193 (100)	49 (100)
Anaemia	83 (52.9)	42 (61.8)	81 (43.3)	30 (51.7)	111 (57.5)	21 (42.9)
Hypertension	66 (42.0)	37 (54.4)	52 (27.8)	22 (37.9)	67 (34.7)	13 (26.5)
Aspartate aminotransferase increased	73 (46.5)	32 (47.1)	76 (40.6)	29 (50.0)	114 (59.1)	25 (51.0)
Fatigue	68 (43.3)	32 (47.1)	49 (26.2)	14 (24.1)	29 (15.0)	7 (14.3)
Diarrhoea	63 (40.1)	31 (45.6)	61 (32.6)	20 (34.5)	52 (26.9)	14 (28.6)
Constipation	62 (39.5)	30 (44.1)	82 (43.9)	21 (36.2)	89 (46.1)	26 (53.1)
White blood cell count decreased	54 (34.4)	30 (44.1)	25 (13.4)	11 (19.0)	72 (37.3)	21 (42.9)
Lymphocyte count decreased	42 (26.8)	29 (42.6)	14 (7.5)	6 (10.3)	25 (13.0)	8 (16.3)
Cough	44 (28.0)	26 (38.2)	45 (24.1)	13 (22.4)	46 (23.8)	5 (10.2)

Alanine aminotransferase increased	55 (35.0)	25 (36.8)	57 (30.5)	17 (29.3)	85 (44.0)	20 (40.8)
Hypocalcaemia	37 (23.6)	25 (36.8)	30 (16.0)	19 (32.8)	58 (30.1)	25 (51.0)
Dizziness	43 (27.4)	24 (35.3)	15 (8.0)	2 (3.4)	22 (11.4)	3 (6.1)
Asthenia	12 (7.6)	8 (11.8)	61 (32.6)	20 (34.5)	14 (7.3)	0
Pyrexia	41 (26.1)	22 (33.8)	56 (29.9)	17 (29.3)	51 (26.4)	8 (16.3)
Arthralgia	34 (21.7)	22 (32.4)	17 (9.1)	8 (13.8)	6 (3.1)	4 (8.2)
Blood creatinine increased	1 (<1)	21 (30.9)	6 (3.2)	18 (31.0)	3 (1.6)	10 (20.4)
Oedema peripheral	44 (28.0)	21 (30.9)	22 (11.8)	10 (17.2)	25 (13.0)	8 (16.3)
Headache	46 (29.3)	21 (30.9)	31 (16.6)	15 (25.9)	18 (9.3)	7 (14.3)
Nausea	36 (22.9)	21 (30.9)	40 (21.4)	8 (13.8)	25 (13.0)	4 (8.2)
Hyperphosphataemia	28 (17.8)	20 (29.4)	32 (17.1)	18 (31.0)	35 (18.1)	16 (32.7)
Neutrophil count decreased	34 (21.7)	20 (29.4)	14 (7.5)	4 (6.9)	90 (46.6)	17 (34.7)
Dyspnoea	31 (19.7)	18 (26.5)	46 (24.6)	13 (22.4)	32 (16.6)	4 (8.2)
Myalgia	28 (17.8)	18 (26.5)	26 (13.9)	15 (25.9)	8 (4.1)	1 (2.0)
Hyponatraemia	27 (17.2)	17 (25.0)	8 (4.3)	1 (1.7)	31 (16.1)	1 (2.0)
Urinary tract infection	34 (21.7)	16 (23.5)	26 (13.9)	6 (10.3)	19 (9.8)	5 (10.2)
Lymphopenia	31 (19.7)	16 (23.5)	32 (17.1)	13 (22.4)	2 (1.0)	1 (2.0)
Dysgeusia	35 (22.3)	15 (22.1)	38 (20.3)	13 (22.4)	12 (6.2)	4 (8.2)
Pneumonia	25 (15.9)	15 (22.1)	18 (9.6)	1 (1.7)	48 (24.9)	15 (30.6)
Dry mouth	42 (26.8)	15 (22.1)	31 (16.6)	10 (17.2)	14 (7.3)	3 (6.1)
Leukopenia	8 (5.1)	3 (4.4)	31 (16.6)	12 (20.7)	16 (8.3)	1 (2.0)

Decreased appetite	22 (14.0)	14 (20.6)	31 (16.6)	15 (25.9)	47 (24.4)	8 (16.3)
Hypokalaemia	19 (12.1)	13 (19.1)	24 (12.8)	8 (13.8)	43 (22.3)	6 (12.2)
Abdominal pain	29 (18.5)	13 (19.1)	18 (9.6)	6 (10.3)	10 (5.2)	4 (8.2)
Vomiting	29 (18.5)	13 (19.1)	26 (13.9)	4 (6.9)	21 (10.9)	7 (14.3)
Neutropenia	39 (24.8)	13 (19.1)	57 (30.5)	25 (43.1)	27 (14.0)	2 (4.1)
Thrombocytopenia	14 (8.9)	8 (11.8)	18 (9.6)	7 (12.1)	13 (6.7)	0
Blood creatinine phosphokinase increased	5 (3.2)	5 (7.4)	31 (16.6)	11 (19.0)	53 (27.5)	13 (26.5)
Dysphonia	17 (10.8)	12 (17.6)	20 (10.7)	10 (17.2)	8 (4.1)	3 (6.1)
Chills	19 (12.1)	12 (17.6)	5 (2.7)	4 (6.9)	1 (<1)	1 (2.0)
Nasal congestion	16 (10.2)	11 (16.2)	2 (1.1)	1 (1.7)	1 (<1)	1 (2.0)
Hypophosphataemia	18 (11.5)	11 (16.2)	18 (9.6)	2 (3.4)	32 (16.6)	0
Pneumonitis	18 (11.5)	9 (13.2)	21 (11.2)	9 (15.5)	20 (10.4)	2 (4.1)
Back pain	32 (20.4)	9 (13.2)	23 (2.3)	6 (10.3)	22 (11.4)	3 (6.1)
Pain in extremity	24 (15.3)	9 (13.2)	18 (9.6)	5 (8.6)	14 (7.3)	6 (12.2)
Rash	20 (12.7)	10 (14.7)	12 (6.4)	8 (13.8)	18 (9.3)	3 (6.1)
Mucosal inflammation	2 (1.3)	2 (2.9)	32 (17.1)	9 (15.5)	4 (2.1)	0
Weight increased	9 (5.7)	3 (4.4)	5 (2.7)	2 (3.4)	39 (20.2)	11 (22.4)
Platelet count decreased	14 (8.9)	10 (14.7)	12 (6.4)	2 (3.4)	38 (19.7)	6 (12.2)
Hypoalbuminaemia	13 (8.3)	10 (14.7)	7 (3.7)	4 (6.9)	58 (30.1)	15 (30.6)
Grade 3 or higher AEs						
Patients with Grade 3/4/5 AE	135 (86.0)	60 (88.2)	142 (75.9)	50 (86.2)	158 (81.9)	35 (71.4)
Hypertension	39 (24.8)	21 (30.9)	27 (14.4)	16 (27.6)	29 (15.0)	5 (10.2)
Lymphocyte count decreased	27 (17.2)	18 (26.5)	5 (2.7)	1 (1.7)	14 (7.3)	0

Anaemia	36 (22.9)	17 (25.0)	28 (15.0)	13 (22.4)	54 (28.0)	9 (18.4)
Lymphopenia	22 (14.0)	12 (17.6)	23 (12.3)	9 (15.5)	0	0
Neutropenia	18 (11.5)	8 (11.8)	26 (13.9)	9 (15.5)	17 (8.8)	1 (2.0)
Neutrophil count decreased	8 (5.1)	3 (4.4)	4 (2.1)	0	44 (22.8)	9 (18.4)
Pneumonia	18 (11.5)	9 (13.2)	10 (5.3)	1 (1.7)	30 (15.5)	11 (22.4)
Serious Adverse Events						
Patients with SAE	96 (61.1)	40 (58.8)	117 (62.6)	35 (60.3)	116 (60.1)	22 (44.9)
Pneumonia	18 (11.5)	9 (13.2)	13 (7.0)	1 (1.7)	30 (15.5)	10 (20.4)
Disease progression	11 (7.0)	1 (1.5)	27 (14.4)	7 (12.1)	16 (8.3)	1 (2.0)
Coronavirus infections	10 (6.4)	6 (8.8)	7 (3.7)	4 (6.9)	0	0
Sepsis	14 (8.9)	6 (8.8)	(1 <1)	0	5 (2.6)	1 (2.0)
Urinary tract infection	10 (6.4)	6 (8.8)	6 (3.2)	1 (1.7)	4 (2.1)	2 (4.1)
Anaemia	10 (6.4)	5 (7.4)	8 (4.3)	4 (6.9)	11 (5.7)	0
Acute Respiratory Failure	5 (3.2)	4 (5.9)	3 (1.6)	0	0	0
Pneumonitis	5 (3.2)	4 (5.9)	8 (4.3)	3 (5.2)	13 (6.7)	0
Pyrexia	4 (2.5)	4 (5.9)	5 (2.7)	1 (1.7)	6 (3.1)	0

Clinical cut-off date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_102_01_06c_ae_reg_new; T14_03_02_110_01_06c_aegrade_reg_new; T14_03_02_105_01_06c_saept_reg_new; T14_03_02_102_01_07c_ae_reg_ra_thyr_400mg_new; T14_03_02_105_01_07c_saept_thyr_400mg_reg_new; T14_03_02_110_01_07c_ae_grade_thyr_400mg_reg_new

Assessor's comments:

Based on the updated clinical cut-off date (CCOD) 18 October 2021, a higher number of patients were enrolled in the US (N=55) and Europe (N=50) compared to Asia (N=40) in the RET-mutant MTC population (Table 1). Grade 4 AEs were well balanced across the regions (U.S. 11, 20.0%; Europe 9, 18.0% and Asia 9, 22.5%). In reviewing the deaths due to AEs, there were 8 patients (16.0%) from Europe who died due to an AE which is higher compared to 5 patients (12.5%) from Asia and 3 patients (5.5%) from the U.S. In comparing the deaths due to AEs in Europe with the other 2 regions, the majority were PT of disease progression which was driving the higher numbers.

Patients from US regarding both the overall safety group and the RET-altered TC group experienced significantly more hypertension, fatigue, diarrhoea, dizziness, arthralgia, nausea and hyponatraemia compared to the other two regions. Oppositely, patients from Asia (RET-altered TC group) experienced significantly more hypocalcaemia, neutrophil count than patients from EU and US. However, it was not the case for neutropenia.

The same pattern was seen regarding Grade ≥3 AEs (Hypertension, neutrophil count decreased and neutropenia). Regarding SAEs significantly more patients with pneumonia was seen in the Asian population.

Overall, there were widely differences in experienced side effects between the three regions.

Weight

Table 1 Overview of Most Common Adverse Events, Grade 3 or higher Adverse Events and Serious Adverse Events by Weight Subgroup (<60kg, ≥60 and <=75kg and ≥75kg) in the Overall Safety and RET-altered Patient Population treated at 400mg.

Preferred Terms	<60kg		≥60 and <=75kg		>75kg	
	Overall Safety (N=173)	RET-altered TC (N=52)	Overall Safety (N=203)	RET-altered TC (N=63)	Overall Safety (N=159)	RET-altered TC (N=58)
Most Common AE (≥10%)						
Patient with AE	173 (100)	52 (100)	202 (99.5)	63 (100)	159 (100)	58 (100)
AST increased	87 (50.3)	24 (46.2)	109 (53.7)	34 (54.0)	66 (41.5)	27 (46.6)
Anaemia	87 (50.3)	14 (26.9)	119 (58.6)	40 (63.5)	68 (42.8)	28 (48.3)
Constipation	80 (46.2)	24 (46.2)	85 (41.9)	26 (41.3)	66 (41.5)	25 (43.1)
ALT increased	68 (39.3)	20 (38.5)	77 (37.9)	24 (38.1)	52 (32.7)	18 (31.0)
Diarrhoea	57 (32.9)	16 (30.8)	69 (34.0)	28 (44.4)	49 (30.8)	20 (34.5)
Neutrophil count decreased	53 (30.6)	11 (21.2)	55 (27.1)	19 (30.2)	30 (18.9)	11 (19.0)
Hypertension	50 (28.9)	13 (25.0)	70 (34.5)	25 (39.7)	63 (39.6)	32 (55.2)
Neutropenia	43 (24.9)	14 (26.9)	37 (18.2)	9 (14.3)	41 (25.8)	15 (25.9)
Pneumonia	29 (16.8)	8 (15.4)	42 (20.7)	17 (27.0)	20 (12.6)	6 (10.3)
Pyrexia	48 (27.7)	10 (19.2)	56 (27.6)	17 (27.0)	43 (27.0)	20 (34.5)
Hypocalcaemia	48 (27.7)	22 (42.3)	49 (24.1)	26 (41.3)	27 (17.0)	20 (34.5)
White blood cell count decreased	46 (26.6)	16 (30.8)	59 (29.1)	22 (34.9)	46 (28.9)	24 (41.4)
Cough	44 (25.4)	10 (19.2)	43 (21.2)	14 (22.2)	47 (29.6)	19 (32.8)
Fatigue	42 (24.3)	15 (28.8)	49 (24.1)	18 (28.6)	55 (34.6)	20 (34.5)
Nausea	36 (20.8)	8 (15.4)	35 (17.2)	8 (12.7)	30 (18.9)	17 (29.3)
Decreased appetite	36 (20.8)	13 (25.0)	38 (18.7)	12 (19.0)	26 (16.4)	12 (20.7)

Hyperphosphataemia	35 (20.2)	16 (30.8)	35 (17.2)	19 (30.2)	24 (15.1)	18 (31.0)
Dyspnoea	34 (19.7)	7 (13.5)	36 (17.7)	12 (19.0)	38 (23.9)	15 (25.9)
Blood creatinine phosphokinase increased	33 (19.1)	11 (21.2)	32 (15.8)	10 (15.9)	23 (14.5)	7 (12.1)
Headache	32 (18.5)	14 (26.9)	25 (12.3)	12 (19.0)	37 (23.3)	16 (27.6)
Blood creatinine increased	31 (17.9)	10 (19.2)	54 (26.6)	17 (27.0)	49 (30.8)	22 (37.9)
Vomiting	30 (17.3)	9 (17.3)	23 (11.3)	6 (9.5)	23 (14.5)	9 (15.5)
Hypokalaemia	29 (16.8)	7 (13.5)	39 (19.2)	14 (22.2)	18 (11.3)	6 (10.3)
Hypoalbuminaemia	29 (16.8)	8 (15.4)	41 (20.2)	14 (22.2)	8 (5.0)	7 (12.1)
Oedema peripheral	27 (15.6)	8 (15.4)	36 (17.7)	17 (27.0)	28 (17.6)	14 (24.1)
Asthenia	27 (15.6)	9 (17.3)	35 (17.2)	9 (14.3)	23 (14.5)	8 (13.8)
Dysgeusia	27 (15.6)	13 (25.0)	25 (12.3)	7 (11.1)	32 (20.1)	5 (8.6)
Hyponatraemia	26 (15.0)	6 (11.5)	29 (14.3)	8 (12.7)	11 (6.9)	5 (8.6)
Lymphocyte count decreased	25 (14.5)	11 (21.2)	29 (14.3)	13 (20.6)	27 (17.0)	19 (32.8)
Urinary Tract Infection	26 (15.0)	10 (19.2)	28 (13.8)	7 (11.1)	25 (15.7)	10 (17.2)
Dry mouth	17 (9.8)	5 (9.6)	30 (14.8)	10 (15.9)	37 (23.3)	13 (22.4)
Lymphopenia	18 (10.4)	9 (17.3)	22 (10.8)	10 (15.9)	25 (15.7)	11 (19.0)
Arthralgia	16 (9.2)	11 (21.2)	16 (7.9)	11 (17.5)	25 (15.7)	12 (20.7)
Myalgia	15 (8.7)	8 (15.4)	25 (12.3)	13 (20.6)	21 (13.2)	12 (20.7)
Thrombocytopenia	14 (8.1)	2 (3.8)	15 (7.4)	3 (4.8)	12 (7.5)	10 (17.2)
Grade 3 or higher AE						
Patients with Grade 3/4/5 AE	142 (82.1)	41 (78.8)	160 (78.8)	51 (81.0)	131 (82.4)	51 (87.9)
Anaemia	40 (23.1)	12 (23.1)	51 (25.1)	16 (25.4)	26 (16.4)	10 (17.2)
Neutrophil count decreased	27 (15.6)	7 (13.5)	22 (10.8)	3 (4.8)	7 (4.4)	2 (3.4)
Hypertension	23 (13.3)	8 (15.4)	35 (17.2)	14 (22.2)	35 (22.0)	18 (31.0)
White blood cell count decreased	18 (10.4)	6 (11.5)	7 (3.4)	2 (3.2)	9 (5.7)	8 (13.8)
Neutropenia	20 (11.6)	6 (11.5)	19 (9.4)	3 (4.8)	21 (13.2)	8 (13.8)
Lymphocyte count decreased	18 (10.4)	5 (9.6)	17 (8.4)	7 (11.1)	16 (10.1)	12 (20.7)
Pneumonia	22 (12.7)	8 (15.4)	27 (13.3)	11 (17.5)	9 (5.7)	2 (3.4)
Serious Adverse Events						
Patients with SAE	106 (61.3)	31 (59.6)	133 (65.5)	39 (61.9)	89 (56.0)	26 (44.8)
Pneumonia	26 (15.0)	8 (15.4)	24 (11.8)	10 (15.9)	11 (6.9)	2 (3.4)

Disease Progression	18 (10.4)	4 (7.7)	21 (10.3)	5 (7.9)	15 (9.4)	0
Pneumonitis	13 (7.5)	3 (5.8)	11 (5.4)	3 (4.8)	2 (1.3)	1 (1.7)
Anaemia	11 (6.4)	3 (5.8)	9 (4.4)	1 (1.6)	9 (5.7)	5 (8.6)
Sepsis	10 (5.8)	3 (5.8)	5 (2.5)	2 (3.2)	5 (3.1)	2 (3.4)
Coronavirus infection	2 (1.2)	0	6 (3.0)	5 (7.9)	9 (5.7)	4 (6.9)

Clinical cutoff date: 18 October 2021.

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.

Source: T14_03_02_102_01_07e_ae_wt_ra_thyr_400mg_new; T14_03_02_105_01_07e_saept_thyr_400mg_wght_new; T14_03_02_110_01_07e_ae_grade_thyr_400mg_wght_new; T14_03_02_102_01_06e_ae_wgt_new; T14_03_02_105_01_06e_saept_wght_new; T14_03_02_110_01_06e_ae_grade_wght_new.

Assessor's comments:

Patients experienced grade ≥3 AEs were balanced between weight groups. More deaths due to AEs were seen in the groups ≥60 kg and ≤75 kg, 12.5% and 17.0%, respectively compared to 4.0% in the ›75 kg group. The MAH has elaborated on and discussed the more deaths due to AEs in the groups ≥60 kg and ≤75 kg. The reporting rates of deaths due to AEs in RET-mutant MTC with the newer CCOD of 18 October 2021 are unchanged. The deaths for the ≥60kg - ≤75 kg weight group was mostly due to progressive disease and infections which is comparable across weight groups. In the <60kg weight group, the PTs with outcome of death include disease progression (2 patients), respiratory failure (1 patient), general physical health deterioration (1 patient) and asphyxia (1 patient) and all events were assessed as not related to pralsetinib. In the >75kg weight group, the 2 PTs with outcome of death include Pneumocystis jirovecii pneumonia (1 patient, related) and pneumonia (1 patient, not related).

Overall, there were no trends or patterns identified that would explain the observed higher frequency of deaths in the 60kg - ≤75 kg weight group. Moreover, the numbers were small. The population PK model suggested that body weight is not a clinically relevant predictor of pralsetinib exposure in adults.

Safety related to drug-drug interactions and other interactions

In a clinical drug-drug interaction study, coadministration of itraconazole (strong CYP3A and P-gp inhibitor) and rifampin (strong CYP3A and P-gp inducer) significantly altered the PK of pralsetinib (Study BP42861 Clinical Study Report). Therefore, strong CYP3A inhibitors, strong CYP3A inducers, and combined P-gp and strong CYP3A inhibitors should be avoided.

If coadministration of pralsetinib with a strong CYP3A inhibitor cannot be avoided, the starting dose of pralsetinib should be reduced. If coadministration with a strong CYP3A inducer cannot be avoided, starting dose of pralsetinib should be increased.

In vitro, pralsetinib is a direct inhibitor of CYP2C8, CYP2C9, and CYP3A4/5 at clinically relevant concentrations, and is also a time-dependent inhibitor of CYP3A4/5. Pralsetinib is also an inducer of CYP2C8, CYP2C9, and CYP3A4/5 at clinically relevant concentrations.

In addition, pralsetinib is an inhibitor of transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K in vitro at clinically relevant concentrations.

Discontinuation due to adverse events

Discontinuations

Table 1 Disease progression and most common AEs (>1%) leading to permanent discontinuation of treatment (Safety Population Patients Treated at 400 mg QD)

Reason for Discontinuation	RET-altered Thyroid Cancer Patients N=175 n (%)	All Patients N=537 n (%)
Disease Progression	35 (20.0)	193 (35.9)
AE	30 (17.1)	92 (17.1)
Disease progression	2 (1.1)	18 (3.4)
Pneumonia	4 (2.3)	11 (2.0)
Anaemia	4 (2.3)	6 (1.1)
Sepsis	2 (1.1)	5 (<1)
Fatigue	2 (1.1)	4 (<1)
Corona virus infection	2 (1.1)	3 (<1)
Acute respiratory failure	2 (1.1)	2 (<1)
Pneumonia aspiration	2 (1.1)	2 (<1)

Clinical cutoff date: 18 October 2021
Note: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient.
Source: T14_01_02_01_01_07_ds_ra_thyr_400mg; T14_01_02_01_01_06_ds_all; T14_03_02_121_01_07_aeptdis_ra_thyr_400mg_new; T14_03_02_121_01_06_aeptdis_new

Table 3 Selected Adverse Event Leading to permanent discontinuation of treatment and time to analysis (Safety Population Patients Treated at 400 mg QD)

Grouped term Preferred term	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
	Patients who discontinued treatment n (%)	Median TTO (weeks)	Median TTR (weeks)	Patients who discontinued treatment n (%)	Median TTO (weeks)	Median TTR (weeks)
Grouped Pneumonia	5 (2.9)	67.86	NA	12 (2.2)	29.57	1.57[a]
Pneumonia	4 (2.3)			11 (2.0)		
Pneumocystis jirovecii pneumonia	1 (<1)			1 (<1)		
Grouped Pneumonitis	1 (<1)	11.71	3.14	13 (2.4)	9.43	10.00[b]
Pneumonitis	1 (<1)			11 (2.0)		
Interstitial lung disease	0			2 (<1)		
Grouped term Anemia	4 (2.3)	41.14	1.86[c1]	6 (1.1)	40.21	6.14[c2]
Anaemia	4 (2.3)			6 (1.1)		
Grouped term Neutropenia	0	NA	NA	5 (<1)	37.43	22.64[d]
Neutropenia	0			3 (<1)		
Neutrophil count decreased	0			2 (<1)		
Grouped term Thrombocytopenia	0	NA	NA	3 (<1)	10.00	<1[e]
Thrombocytopenia	0			2 (<1)		
Platelet count decreased	0			1 (<1)		
Grouped Hypertension	0	NA	NA	1 (<1)	5.00	1.00[f]
Hypertension	0			1 (<1)		
Diarrhoea (not grouped)	0	NA	NA	0	NA	NA

Alanine aminotransferase increased (not grouped)	0	NA	NA	0	NA	NA
Aspartate aminotransferase increased (not grouped)	0	NA	NA	0	NA	NA

Data cutoff date: 18 October 2021. NA = Not applicable

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs).

All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has

multiple occurrences of an AE, the patient is presented only once in the respective patient count.

Adjacent AEs for the same preferred term are linked per patient.

[a] 3 patients who discontinued due to the event recovered from the event

[b] 7 patients who discontinued due to the event recovered from the event

[c1] 1 patient who discontinued due to the event recovered from the event

[c2] 2 patients who discontinued due to the event recovered from the event

[d] 2 patients who discontinued due to the event recovered from the event

[e] 1 patient who discontinued due to the event recovered from the event

[f] 1 patient who discontinued due to the event recovered from the event

Source: T14_03_02_137_01_15_aesi_pt_doswth_retalt_400mg ; T14_05_01_102_01_15_ttoae_rt400mg_dscnt; T14_05_03_102_01_15_ttrae_rt400mg_dscnt.

Assessors comment:

In Table 1 it is seen that more patients progressed, which lead to more treatment discontinuation, in the overall safety group than in the RET-altered group, 35.9% vs 20%, respectively. Regarding the most common AEs that lead to permanent discontinuation of treatment, the numbers are too small to interpret.

Median time to onset (TTO) and resolution (TTR) of pneumonia, pneumonitis, anaemia, neutropenia, thrombocytopenia, hypertension, diarrhoea, increased AST and ALT for patients who discontinued treatment due to the respective event and the number of patients who resolved from the AEs are presented in Table 3. Pneumonia (grouped) treatment discontinuation rate was comparable between the two populations. Within the overall safety population 13 (2.4%) patients discontinued treatment due to a pneumonitis event (grouped). Patients' median time on treatment prior to the first occurrence of the event was 9.4 weeks. In general, the number of events is very low. Neutropenia, thrombocytopenia, hypertension, diarrhoea, increased AST and ALT did not lead to treatment discontinuation in any RET-altered thyroid cancer patients.

Dose modifications

Table 2 Most common AEs leading to Dose Modification (≥2%) (Safety Population Patients Treated at 400 mg QD)

Reason for Dose modification	RET-altered Thyroid Cancer Patients N=175 n (%)	All Patients N=537 n (%)
Patients with AE Leading to Dose Modification	139 (79.4)	397 (73.9)
Anaemia	29 (16.6)	83 (15.5)
Neutropenia	13 (7.4)	52 (9.7)
Neutrophil count decreased	11 (6.3)	47 (8.8)
Hypertension	18 (10.3)	45 (8.4)
Pneumonia	16 (9.1)	45 (8.4)
Pneumonitis	12 (6.9)	44 (8.2)
Blood creatine phosphokinase increased	13 (7.4)	39 (7.3)
Pyrexia	11 (6.3)	28 (5.2)
Aspartate aminotransferase increased	7 (4.0)	26 (4.8)
White blood cell count decreased	9 (5.1)	25 (4.7)
Fatigue	8 (4.6)	24 (4.5)
Lymphopenia	10 (5.7)	21 (3.9)
Alanine aminotransferase increased	5 (2.9)	20 (3.7)
Diarrhoea	9 (5.1)	20 (3.7)
Lymphocyte count decreased	10 (5.7)	20 (3.7)
Corona virus infection	9 (5.1)	17 (3.2)
Asthenia	9 (5.1)	14 (2.6)
Sepsis	6 (3.4)	14 (2.6)
Urinary tract infection	8 (4.6)	14 (2.6)
Vomiting	7 (4.0)	14 (2.6)
Thrombocytopenia	4 (2.3)	13 (2.4)
Dyspnoea	5 (2.9)	12 (2.2)
Platelet count decreased	2 (1.1)	11 (2.0)
Abdominal pain	5 (2.9)	10 (1.9)
Hyponatraemia	4 (2.3)	9 (1.7)
Hypocalcaemia	7 (4.0)	8 (1.5)
Blood creatinine increased	5 (2.9)	7 (1.3)
Myalgia	5 (2.9)	7 (1.3)
Headache	4 (2.3)	5 (<1)

Clinical cutoff date: 18 October 2021

Table 4 Selected Adverse Event Leading to Dose Modification and time to analysis (Safety Population Patients Treated at 400 mg QD)

Grouped term Preferred term	RET-altered Thyroid Cancer Patients N=175			All Patients N=537		
	Patients with dose modified n (%)	Median TTO (weeks)	Median TTR (weeks)	Patients with dose modified n (%)	Median TTO (weeks)	Median TTR (weeks)
Grouped Pneumonia	20 (11.4)	32.00	1.43 [a1]	55 (10.2)	16.14	1.43[a2]
Pneumonia	16 (9.1)			45 (8.4)		
Pneumocystis jirovecii pneumonia	0			3 (<1)		
Pneumonia bacterial	1 (<1)			2 (<1)		
Pneumonia staphylococcal	2 (1.1)			2 (<1)		
Pneumonia viral	1 (<1)			2 (<1)		
Atypical pneumonia	0			1 (<1)		
Lung infection	0			1 (<1)		
Pneumonia pseudomonal	0			1 (<1)		
Grouped Pneumonitis	12 (6.9)	17.86	4.14 [b1]	49 (9.1)	16.14	4.43[b2]
Pneumonitis	12 (6.9)			44 (8.2)		
Interstitial lung disease	0			5 (<1)		
Grouped term Anemia	29 (16.6)	17.43	12.14 [c1]	85 (15.8)	16.14	16.14[c2]
Anaemia	29 (16.6)			83 (15.5)		
Haemoglobin decreased	0			2 (<1)		
Grouped term Neutropenia	24 (13.7)	3.71	3.14 [d1]	96 (17.9)	4.14	2.71[d2]
Neutropenia	13 (7.4)			52 (9.7)		

Neutrophil count decreased	11 (6.3)			47 (8.8)		
Grouped term Thrombocytopenia	6 (3.4)	3.14	2.29 [e1]	24 (4.5)	3.57	2.71 [e2]
Thrombocytopenia	4 (2.3)			13 (2.4)		
Platelet count decreased	2 (1.1)			11 (2.0)		
Grouped Hypertension	18 (10.3)	2.07	1.14 [f1]	45 (8.4)	2.14	1.14 [f2]
Hypertension	18 (10.3)			45 (8.4)		
Aspartate aminotransferase increased	7 (4.0)	3.14	47.43 [g1]	26 (4.8)	8.57	4.71 [g2]
Alanine aminotransferase increased	5 (2.9)	16.57	7.00 [h1]	20 (3.7)	15.36	2.50 [h2]
Diarrhoea	9 (5.1)	13.57	2.43 [i1]	20 (3.7)	13.21	1.14 [i2]

Clinical cut-off date: 18 October 2021

[a1] 17 patients with a dose modification due to the event recovered from the event
[a2] 47 patients with a dose modification due to the event recovered from the event
[b1] 8 patients with a dose modification due to the event recovered from the event
[b2] 33 patients with a dose modification due to the event recovered from the event
[c1] 15 patients with a dose modification due to the event recovered from the event
[c2] 50 patients with a dose modification due to the event recovered from the event
[d1] 24 patients with a dose modification due to the event recovered from the event
[d2] 95 patients with a dose modification due to the event recovered from the event
[e1] 5 patients with a dose modification due to the event recovered from the event
[e2] 20 patients with a dose modification due to the event recovered from the event
[f1] 13 patients with a dose modification due to the event recovered from the event
[f2] 30 patients with a dose modification due to the event recovered from the event
[g1] 5 patients with a dose modification due to the event recovered from the event
[g2] 18 patients with a dose modification due to the event recovered from the event
[h1] 4 patients with a dose modification due to the event recovered from the event
[h2] 14 patients with a dose modification due to the event recovered from the event
[i1] 9 patients with a dose modification due to the event recovered from the event
[i2] 19 patients with a dose modification due to the event recovered from the event

Notes: Adverse Events (AEs) are coded using MedDRA 19.1. AEs refer to treatment emergent adverse events (TEAEs). All TEAEs including treatment emergent serious adverse events are included in summary statistics. If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count. Adjacent AEs for the same preferred term are linked per patient. Dose modifications include dose interruptions and dose reductions.
Source outputs: T14_03_02_141_01_15_aesi_pt_dosmod_retalt_400mg; T14_05_01_103_01_15_ttoae_rt400mg_dosmod; T14_05_03_103_01_15_ttrae_rt400mg_dosmod

Assessor's comments:

Most common AEs (≥2%) leading to dose modifications (include dose interruptions and dose reductions) are displayed for the RET-altered TC population and the overall safety population in Table 2. AEs reported with a higher reporting rate (≥2%) in RET-altered TC patient group included

the PTs lymphocyte count decreased, asthenia, urinary tract infection, and hypocalcaemia. The AEs were manageable with dose modification and led to treatment discontinuation only in a small fraction of patients (as seen in Table 1).

Median time to onset and resolution of pneumonia, pneumonitis, anaemia, neutropenia, thrombocytopenia, hypertension, diarrhoea, increased AST and ALT for patients who had dose interruptions/reductions for the respective event and the number of patients who resolved from the AEs are provided in Table 4. Dose modification rates for the selected AEs were comparable between the two populations. Two% difference (higher rate for all patient population as compared to RET-altered TC population) occurred for pneumonitis and neutropenia. Time to onset for the respective events were comparable between RET-altered TC population and overall safety population. Exceptions were pneumonia (median TTO RET-altered thyroid cancer patients: 32.0 weeks, all patients: 16.1 weeks) and aspartate aminotransferase increased (median TTO RET-altered thyroid cancer patients: 3.1 weeks, overall safety population: 8.6 weeks).

Post marketing experience

Cumulatively since the International Birth Date (4 September 2020), there were no findings related to the post-marketing experience of pralsetinib.

3.5.1. Discussion on clinical safety

From the indication of non-small cell lung cancer, it is already known that the most common adverse reactions were anaemia (47.2%), aspartate aminotransferase increased (46.0%), neutropenia (43.9%), constipation (41.9%), musculoskeletal pain (39.8%), fatigue (37.3%), leukopenia (35.4%), alanine aminotransferase increased (33.9%), and hypertension (33.0%). The most common serious adverse reactions were pneumonia (11.7%), pneumonitis (5.3%) and anaemia (3.8%).

For the evaluation of safety, updated data from 537 patients who received pralsetinib at a starting dose of 400 mg QD in either phase 1 or 2 from study ARROW have been submitted. Incidence and severity of adverse events (AEs) in the subgroup of 175 RET-altered thyroid cancer patients have been compared to the overall patient population. The thyroid cancer group included RET mutation-positive medullary thyroid cancer (MTC) patients (n=145) and RET fusion-positive thyroid cancer patients (n=27) (CCOD: 18 October 2021).

The subgroup of patients with MTC was constituted of patients previously treated with cabozantinib and/or vandetinib (half of them) and treatment-naïve patients. Nearly all patients in the thyroid cancer subgroup had been pretreated.

Assessment of the available results regarding the incidence and type of AEs show a median duration of treatment for the MTC and TC patients of 18.47 and 14.26 months, respectively, which allows for an appropriate assessment of the safety of pralsetinib.

All patients in the ARROW study had at least one **AE**. Grade 3 or higher AEs constituted around 80% of AEs in the overall patient population (n=537) and the subgroup of patients with TC (n=175).

In the TC group (n=175), the most common AEs (PT occurring in ≥10%) were anaemia (53.1%), AST increased (49.1%), constipation (44.0%), hypertension (41.1%), hypocalcaemia (39.4%), diarrhoea (37.1%), white blood cell count decreased (35.4%), ALT increased (35.4%), hyperphosphataemia (30.9%) and fatigue 30.3%). This was overall consistent with the overall safety pool (n=537).

The majority of the patients in the TC group experienced high-grade (grade ≥3 AEs): 83.1%. The most common (occurring in ≥2%) were hypertension (24.0%), anaemia (22.3%), lymphocyte count

decreased (13.7%), lymphopenia (12.0%), pneumonia (10.3%), neutropenia (10.3%) and hypocalcaemia (7.4%). This was consistent with the safety pool, except for hypertension which was lower in the overall safety pool (17.7%). The MAH explains that hypertension was managed with anti-hypertensive treatment in the majority of patients and no patient withdrew treatment permanently due to hypertension in the RET-altered TC patient group. This is comparable to overall safety population, which were in general managed by standard clinical practice (dose interruptions/dose reductions and/or treatment for the event). The nature of the underlying disease and history of hypertension in about 30% of the RET-altered TC patients would help explain the lower rates in the overall safety population compared to RET-altered TC patient group.

The MAH defined 5 AEs as **AESIs**: Pneumonia, pneumonitis, tumour lysis syndrome (TLS), hypertension, and hepatotoxicity. Hepatotoxicity is the most common AESI (63.4%) with the most common Serious AESI being pneumonia (14.3%). However, it is considered that pralsetinib is causally involved in other AEs, which should be considered AESIs: Hypertension, haemorrhagic events, QT prolongation, diarrhoea, hypocalcaemia and hyperphosphataemia. Upon request, the MAH reevaluated the criteria that have been used to define the AESIs. The MAH argues, that although diarrhoea is regarded a risk of pralsetinib and is therefore, together with hypocalcaemia and hyperphosphatemia, included within the SmPC, it needs to be considered that these AEs are attributed to the underlying disease of thyroid cancer and its condition after surgery. Therefore, the MAH considers that these events are not AESIs. On request the MAH has reflected the higher incidence of hypertension, hypocalcaemia, hyperphosphataemia and diarrhoea in the RET-altered TC group in Section 4.8 of the SmPC.

SAEs were observed in 59.4% in the overall patient population (n=537) (29.9% of these being of grade 3 or higher) and in 54.1% in the RET-altered group with infections and infestations (pneumonia, corona virus infection, pneumonitis and hyponatraemia) as the most common. This was consistent with the overall safety group except pneumonitis (4.0% vs 3.2%) and hyponatraemia (2.3% vs 1.5%).

AEs leading to **deaths** (CCOD of 18 Oct 2021) were seen in 13.1 % in the RET-altered group (n=175) and 17.1% in the overall group (n=537). The reporting rate of AEs as primary cause of death in the RET-altered TC population was comparable to the overall patient population. The most common cause of a fatal AEs (›1%) were pneumonia, corona virus infection, pneumonia aspiration and sepsis, apparently in both groups.

Regarding **laboratory tests and vital signs** there were not seen significantly differences between the RET-altered and the overall safety groups except for the worsening to G3-4 for decreased albumin, decreased calcium and increased calcium which was more than doubled in the RET-altered group compared to the overall safety pool, which again is at least partly due to the underlying disease. QT prolongation was seen in 6.9% in the RET-altered group (n=175) and 5.2% in the overall safety group (n=537). Torsades des Pointes had not been reported nor true Hy's law cases.

Regarding the most common **AEs that lead to permanent discontinuation of treatment**, the numbers are too small to interpret**.** The most frequent causes were anaemia and pneumonia. Most common **AEs (≥2%) leading to dose modifications** (include dose interruptions and dose reductions) in RET-altered TC patient group included the PTs lymphocyte count decreased, asthenia, urinary tract infection, and hypocalcaemia. Overall any AE that lead to modifications was seen in 79.4%. The AEs were manageable with dose modifications and led to treatment discontinuation only in a small fraction of patients.

Assessment of paediatric data on clinical safety

Data unavailable, no paediatric patients were recruited in the pivotal trial.

3.5.2. Conclusions on clinical safety

Overall, the safety database in the two claimed indications is considered of limited extent (n=175), but nevertheless appropriate to assess safety in the ongoing procedure. The median duration of treatment for the MTC and TC patients was beyond one year in both cases. However, the higher incidence of hypertension, hypocalcaemia, hyperphosphataemia and diarrhoea in the RET-altered TC group compared to the overall safety pool has been reflected in Section 4.8 of the SmPC**.** There are currently no new safety findings nor any major concerns. The two ongoing phase III studies, AcceleRET-MTC and the TAPISTRY, will provide more comprehensive safety data.

3.5.3. PSUR cycle

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

4. Risk management plan

The MAH submitted an updated RMP version with this application. The rationale for submitting an updated RMP is addition of two new indications:

- Gavreto is indicated for the treatment of adult and paediatric patients 12 years of age and older with **locally advanced or metastatic RET-mutant medullary thyroid cancer (MTC)** who require systemic therapy following prior treatment with tyrosine kinase inhibitors and not previously treated with a RET inhibitor.
- Gavreto is indicated for the treatment of adults and paediatric patients 12 years of age and older with **locally advanced or metastatic RET fusion-positive thyroid cancer (TC)** who require systemic therapy following prior treatment with tyrosine kinase inhibitors and not previously treated with a RET inhibitor.

Summary of Significant Changes in his RMP

Part I	
Product Overview	Update to the product indications, dosage, and pharmaceutical form and strength
Part II	
SI.1.2	Information on indications RET mutation-positive medullary thyroid cancer (MTC) and RET fusion-positive thyroid cancer (TC) added.
SII	Clinical Trial Exposure: Exposure data for RET mutation-positive MTC and RET fusion-positive TC indication added, and the respective data cut-off dates added.
SIV	Populations not studied in clinical trials: Reasons for exclusion criteria in pivotal clinical studies within the development program updated.
SVII.1.1	Identified and potential risks: Impaired tooth development was added to the list of risks not considered important for inclusion in the list of safety concerns in the RMP.
SVII.1.2	Risks considered important for inclusion in the list of safety concerns in the RMP: Section updated to include new important potential risks of physeal dysplasia and tumor lysis syndrome, and missing information of use in pediatric patients 12-18

	years of age. Missing information of 'Use in patients with severe hepatic impairment' amended to 'Use in patients with hepatic impairment (moderate or severe)'.
SVII.3	Details of important identified risks, important potential risks, and missing information: Section updated to include new important potential risks of physeal dysplasia and tumor lysis syndrome, and missing information of use in pediatric patients 12-<18 years of age. Data for overall safety population also updated based on N= 532.
SVIII	Summary of the Safety Concerns: Updated to include new important potential risks of physeal dysplasia and tumor lysis syndrome, and missing information of use in pediatric patients 12-<18 years of age. Missing information of 'Use in patients with severe hepatic impairment' amended to 'Use in patients with hepatic impairment (moderate or severe)'.
Part III	
III.3	Summary Table of Additional Pharmacovigilance Activities: Final protocol submission and trial completion milestones removed as they are not imposed measures and protocols do not need submitting. Integrated safety analysis based on studies BO41932 (TAPISTRY) and CO42865 (AcceleRET MTC), added as Category 3.
Part IV	Plans for post-authorization efficacy studies: Study CO42865 (AcceleRET MTC) and integrated analysis of studies BO41932 (TAPISTRY) and BO42863 (ARROW) added.
Part V	
V.1	Description of Routine Risk Minimization Measures by Safety Concern: Table updated to include details on physeal dysplasia and tumor lysis syndrome and use in pediatric patients 12-<18 years of age.
V.3	Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern: Table updated to include details on physeal dysplasia and tumor lysis syndrome and use in pediatric patients 12-<18 years of age. Additional pharmacovigilance activities for transaminase elevations updated to 'none'.
Part VI	
II.A	List of Important Risks and Missing Information: Table updated to include details on physeal dysplasia and tumor lysis syndrome and use in pediatric patients 12-<18 years of age.
II.B	Summary of Important Risks: Table updated to include details on physeal dysplasia and tumor lysis syndrome and use in pediatric patients 12-<18 years of age. Additional pharmacovigilance activities for transaminase elevations updated to 'none'.
II.C.1	Studies that are conditions of the marketing authorization: Table updated to include SOBs Study CO42865 and Integrated analysis of studies BO41932 and BO42863.
II.C.2	Other studies in post-authorization development plan: Table updated to include Integrated analysis of studies BO41932 and CO42865.

Annexes	
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program: Final protocol submission and trial completion milestones removed. Status of Study GP43162 added as 'planned'. Integrated analysis of studies BO41932 and CO42865 added.
Annex 5	Protocols for Proposed and Ongoing Studies in RMP Part IV: Status of Study BO42864 added as 'ongoing'. Study BO42863 final CSR due date amended to 12/2022 to align with the EU-RMP core report. Study CO42865 and Integrated analysis of studies BO41932 and BO42863 added.
Annex 7	Added source outputs for RET mutation positive MTC and RET fusion positive TC indications and updated the literature references.
Annex 8	Summary of changes to the RMP over time added.

The most relevant sections of the updated RMP related to the new indication are summarised and assessed below.

4.1. Safety Specification

Epidemiology of the indications and target population

New indication: RET Mutation-Positive Medullary and RET Fusion-Positive Thyroid Cancer

Assessor's comment

Description of new indications: RET mutation-positive medullary and RET fusion-positive thyroid cancer, their incidence, prevalence, demographics and currently available treatment options are adequately described. Risk factors and natural history of diseases are summarized. The update to this section is acceptable.

Clinical trial exposure

Assessor's comment

This section has been updated with the exposure data for the proposed new indications from clinical studies RO7499790, CDT3037, BO42863 (data cut-off date 12 April 2021). The proposed indication includes also patients from 12 years of age; however, these pediatric patients were not studied.

In addition, information on clinical trial exposure in patients with RET fusion-positive advanced NSCLC was updated.

Identified and potential risks

Impaired tooth development was added to the list of risks not considered important for inclusion in the list of safety concerns in the RMP.

New risks considered important for inclusion in the list of safety concerns in the RMP:

Important potential risks:

- Physeal dysplasia

Physeal dysplasia in both rodents and non-human primates were observed at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Due to the non-clinical evidence, physeal dysplasia is an important potential risk of pralsetinib in pediatrics and adolescent patients with open growth plates.

Missing information

New safety concern was included to Missing information

- Use in pediatric patients 12-18 years of age.

  Although population pharmacokinetic data demonstrated that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib, and that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older treated with pralsetinib 400 mg QD, safety, effectiveness and recommended dose of pralsetinib have not been established in pediatric patients. Thus, use in pediatric patients aged 12-<18 years is considered missing information.

Missing information of 'Use in patients with severe hepatic impairment' amended to 'Use in patients with hepatic impairment (moderate or severe)'.

4.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Pneumonitis Hypertension Haemorrhage Transaminase Elevations
Important potential risks	Embryo-foetal toxicity ~~Severe Infections~~ QT prolongation **Physeal Dysplasia**
Missing information	Use in patients with hepatic impairment **(moderate or severe)** Drug-drug Interactions **Use in pediatric patients 12-<18 years of age**

The following issues should be addressed:

- Potential risk: Severe infections

Pneumonia and urinary tract infections are listed as very common. Severe infections are also described in section 4.8. of the SmPC:

"Infections were commonly experienced by 61.7% of 532 patients with the median treatment time of 11.8 months. Most frequently (>10%), the preferred terms of pneumonia and urinary tract infection were reported (15.6% and 13.5%, respectively). The majority of infections were mild (Grade 1 or 2) and resolved; severe infection (Grade ≥3) occurred in 27.3% patients (with fatal events reported for 3.4%).

Infections reported as serious adverse events occurred for 27.4 % of patients. The most common (>2%) serious infection preferred term was pneumonia (10.9%), followed by urinary tract infection (3.46%) and sepsis (3.4%)."

Having considered these, severe infections cannot be considered as potential risk. Since neither additional pharmacovigilance activities nor additional risk minimisation measures are ongoing or proposed, it is agreed to remove safety concern 'severe infections' from the RMP.

4.3. Pharmacovigilance plan

Table Part III.3.1: 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 authorizationunder 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 safetyconcern or evaluate the effectiveness or risk minimization activities				
Study GP43162(DDI Study) A Study to evaluate the effectof repeat doses of a P-gp inhibitor on the pharmacokinetics of pralsetinib and to inform appropriate dosing strategiesfor safe coadministration of pralsetinib with P-gp inhibitors.	• To assess the impact of coadministration of a P-gp inhibitor on the single-dose pharmacokineticsof pralsetinib. • To assess the safety and tolerability of a single-dose of pralsetinib alone and co administered with a P-gp inhibitor.	Drug-drug interaction	Final report submission	04/2022
Study GP43163 A Study to Evaluate the Pharmacokinetics of BLU-667 in Healthy and Hepatically Impaired Subjects.	• To characterize the pharmacokinetics of pralsetinib in patients with hepatic impairment.	Use in patients with hepatic impairment (moderate or severe)	Final report submission	09/2024
Integrated safety analysis to assess potential risks in pediatrics aged 12 years andolder based on studies BO41932 (TAPISTRY[a]) and CO42865 (AcceleRET MTC[b] [PAES]) Planned	• To characterize the potential risk of long-termadverse effects of pralsetinib on growth and development, including an assessment of growth plate abnormalities in paediatric patients	Use in pediatric patients 12-<18 years of age Physeal dysplasia	Enrolment of around 1 paediatric patient per year across both studies Estimated enrolment Completion (best case scenario* Final integrated analysis report	Study start date is based on First patient-in Q3 2032 Q2 2033

[a]TAPISTRY (BO41932):): A Phase 2, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations.

[b]AcceleRET MTC (BO42864): 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

DDI = drug-drug interaction; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PAES = Post-authorization efficacy study; P-gp = P- glycoprotein; RET = rearranged during transfection

In addition to two ongoing studies that investigate drug-drug interaction and Pharmacokinetics of pralsetinib in healthy and hepatically impaired subjects, an integrated safety analysis to assess

potential risks in pediatrics aged 12 years and older based on studies BO41932 (TAPISTRYa) and CO42865 (AcceleRET MTCb [PAES]) is included as category 3 study. The studies which are going to be included to the integrated safety analysis are listed as PAES. Ten paediatric patients are expected to be recruited to this integrated safety analysis. The due date for integrated safety analysis based on studies BO41932 (TAPISTRY) and CO42865 (AcceleRET MTC [PAES]) is 04/2033. The proposal is acceptable**.**

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan to identify and characterise the risks of the product is sufficient. The PhV plan is acceptable pending CHMP decision on the proposed new indications.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorization				
"A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU 667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC), and Other Advanced Solid Tumours (ARROW/BO42863)" 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 efficacy evaluable patients (approximately 116 treatment-naïve NSCLC patients and more follow-up of the 136 NSCLC previously treated with platinum therapy) of study BLU-667-1101, a Phase 1/2 Study of pralsetinib in patients with thyroid cancer, NSCLC and other advanced solid tumours.	Confirm the efficacy and safety of pralsetinib in the treatment of adult patients with RET fusion-positive advanced NSCLC	Final CSR (NSCLC indication)	12/2022
"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
A Phase 3, randomized, open-label study of pralsetinib versus standard of care for treatment of RET-mutated medullary thyroid cancer (AcceleRET-MTC/CO42865). Planned	In order to further confirm the efficacy and safety of pralsetinib in the treatment of patients 12 years of age and older with RET-mutant MTC, the MAH should submit the results of study CO42865 (AcceleRET-MTC), a multi-centre, randomized, open-label trial comparing pralsetinib to investigator's choice of either cabozantinib or vandetanib in multi-kinase inhibitor naïve patients with advanced or metastatic RET-mutant medullary thyroid cancer.	Confirm the efficacy and safety of pralsetinib in the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic RET-mutant medullary thyroid cancer.	Final CSR	01/2028
Integrated analysis of studies BO41932 (TAPISTRY*) and BO42863 (ARROW).	In order to confirm the efficacy and safety of pralsetinib in the treatment of adult and pediatric patients 12 years of age and older with RET fusion-positive TC, the MAH should submit the final report of integrated studies BO41932 (TAPISTRY) and BO42863 (ARROW) to provide a more precise estimation of the BICR-assessed overall response rate and duration of response in at least 50 patients.	Confirm the efficacy and safety of pralsetinib in the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer.	Final integrated analysis report	06/2025

*TAPISTRY (BO41932): A Phase 2, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations. Ongoing.

CSR: clinical study report; MAH = Marketing authorization holder; MTC = medullary thyroid cancer; NSCLC non-small cell lung cancer; RET: rearranged during transfection; TC = Thyroid cancer.

4.4. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures for new safety concerns

Important potential risks	
Physeal Dysplasia	**Routine risk communication:** SmPC Sections 4.4 and 5.3 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Physicians are advised to monitor growth plates in adolescent patients with open growth plates and to consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine
Missing information	
Use in pediatric patients 12-<18 years of age	**Routine risk communication:** SmPC section 4.4 and 5.2 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 and 5.2 includes information about safety and efficacy of pralsetinib in paediatric patients 12 years of age and older to be supported by extrapolation of evidence from clinical trials in adults to paediatric population, based on population pharmacokinetic data. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status** Pralsetinib is a prescription only medicine

Additional risk minimisation measures

No additional risk minimisation measures are proposed by the MAH.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

4.5. Elements for a public summary of the RMP

The elements for a public summary of the RMP are acceptable.

4.6. Overall conclusion on the RMP

The changes to the RMP are acceptable pending the decision of the CHMP on the new indications.

5. Changes to the Product Information

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

● No significant changes impacting the readability of the package leaflet are made. In particular, key safety messages are not affected by this extension. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.

● The posology proposed in this application is the same as for the currently approved indications.

In 2021, a user consultation was conducted in the context of the pralsetinib initial Marketing Authorisation Application (MAA) for treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.

The successful full User Test, confirmed that the package leaflet for pralsetinib complies with the current EU requirements for User Testing.

With this application, the Marketing Authorisation Holder (MAH) seeks to extend the use of pralsetinib in the following indications:

Adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib and not previously treated with a RET inhibitor.

Adult and paediatric patients 12 years of age and older with locally advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib and not previously treated with a RET inhibitor.

5.1.2. Additional monitoring

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

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

6. Benefit-Risk Balance

Gavreto (pralsetinib) is a rearranged during transfection (RET) inhibitor that is being studied in patients with unresectable advanced or metastatic solid tumours with RET alterations (RET fusions, activating mutations, and some resistance mutations).

The MAH is seeking a type II extension of indication for Gavreto in the following indications:

- *Adult and paediatric patients 12 years of age and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib and not previously treated with a RET inhibitor.*
- *Adults and paediatric patients 12 years of age and older with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib not previously treated with a RET inhibitor.*

The proposed dose of pralsetinib is 400 mg once daily (QD).

6.1. Therapeutic Context

6.1.1. Disease or condition

Thyroid cancer primarily consists of differentiated thyroid cancer (DTC) (~90% of cases, of which ~85% are papillary thyroid carcinoma (PTC) and ~5% are follicular thyroid cancer [FTC]), followed by medullary thyroid cancer (MTC) (~5% of cases) and anaplastic thyroid cancer (ATC) (~5% of cases).

MTC arises from parafollicular C cells and occurs in both hereditary and sporadic forms, while most cases of DTC and ATC arise sporadically from thyroid follicular cells. In adults, sporadic MTC accounts for 65–75% of MTC. The incidence of thyroid cancer has increased in different populations worldwide in the past 30 years.

Most (approximately 90%) cases of thyroid cancer in childhood are PTC; FTC is uncommon and MTC, ATC, and other types are rare. In paediatric patients, MTC is primarily an inherited disease occurring as a part of a multiple endocrine neoplasia type 2A or 2B (MEN2A or 2B).

RET is a receptor tyrosine kinase expressed in several neural, neuroendocrine and genitourinary tissue types that normally requires ligand and co-receptor binding for activation. Aberrant activation of RET is a critical driver of tumour growth and proliferation across a broad number of solid tumours. Oncogenic activation of RET can occur by two primary mechanisms, chromosomal rearrangements or point mutations. Both mechanisms of oncogenic activation result in constitutively active, ligand-independent RET kinase activity and activation of downstream signalling pathways. The predominance of RET mutations or fusions varies according to tumour histology (mutations more common in MTC, fusions more common in NSCLC and PTC), implying that the clinical behaviour of those tumours will also differ. Nevertheless, it is expected that inhibiting RET should exert an antiproliferative effect in either case, ultimately conducting to an efficacy benefit. Activating mutations of RET are present in 98% of the familial MTC and approximately 40% of the sporadic MTC.

Clinically, RET mutations are associated with poor outcomes, including larger tumour size, metastasis, and poorer survival, when compared with RET wildtype cases among patients with MTC.

6.1.2. Available therapies and unmet medical need

According to ESMO and NCCN guidelines, there are currently two available alternatives, cabozantinib and vandetanib for the treatment of RET-mutant medullary thyroid cancer (MTC). These two products are TKIs and have been investigated in placebo controlled randomised controlled trials.

Standard options for patients in first-line with advanced differentiated TC refractory to iodine include sorafenib and lenvatinib according to ESMO guidelines.

Currently, there are no treatment guidelines for RET mutation-positive MTC patients or RET fusion-positive thyroid cancer patients who have failed treatment with non-selective TKIs. However, selpercatinib, another RET inhibitor, is approved in Europe for RET-fusion positive NSCLC (line-

agnostic), RET-fusion positive thyroid cancer after sorafenib and/or lenvatinib and RET-mutant MTC after cabozantinib and/or vandetanib.

6.1.3. Main clinical studies

Data of efficacy and safety of pralsetinib for the sought indications come from study BO42863 (ARROW), a multi-centre, open-label, phase 1/2 study in patients with advanced solid tumours, including RET fusion-positive solid tumours (e.g., NSCLC, thyroid, pancreas, colorectal), RET-mutant MTC, and other tumours with RET activation (e.g., mutations in other tumour types or other evidence of RET activation). This study is ongoing and includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion); the study is currently in Phase 2.

6.2. Favourable effects

RET-mutated MTC

At data cut-off, with an estimated median follow-up time of 22.1 months, 90 out of the 145 patients from the efficacy dataset had achieved confirmed response by BICR, attaining ORR of 62.1% (95% CI 53.6, 70.0). Responses were durable, with a median duration of 29.5 months. Median PFS was 31.2 months, but median OS has not been reached.

Prior cabozantinib/vandetanib treatment

Results for this pre-treated patient group (n=67) showed slightly lower ORR of 52.2% (95% CI 39.7, 64.6); CR was seen in 3.0% of the patients and PR in 49.3% of them. Importantly, median duration of response in this subgroup was 25.8 months, whereas median PFS was 25.8 months and median OS has not been reached.

Cabozantinib/vandetanib naïve

In this group (n=67) the ORR was 71.6% (95% CI 59.3, 82.0); CR was seen in 6.0% of the patients and PR in 65.7%. Median DOR, PFS and OS were not reached.

RET-fusion positive TC

Of the 25/27 pre-treated patients, 21/25 patients from the efficacy dataset had achieved confirmed response by BICR, attaining an ORR of 84.0% (95% CI 63.9, 95.5); CR was obtained in 16.0% of the patients and PR was obtained in 68.0% of them. Patients reached SD were 16.0%. Median DOR was 23.6 months and OS has not been reached.

6.3. Uncertainties and limitations about favourable effects

The main limitations are related to the single-arm and open-label design of the study. This hampers the assessment, particularly of the time-to-event endpoints. ARROW was initially designed as a Phase I study (dose escalation and expansion). In view of the promising results seen in these patients, the design of the study was modified into the current basket (multi-histology) design. This change is considered to be potentially driven by results and might have impacted the overall quality of the data and the robustness of the evidence generated.

The MAH sought the indications including adolescents (12-18 years of age). However, there were no data on adolescents. The MAH has updated the Pop PK for RET-altered TC by excluding NSCLC data as requested and has submitted simulations for extrapolation to adolescents performed with the Final Pop-PK model as an addendum to the final model report. As there is no data available for adolescent patients, this exercise is considered as a full extrapolation.

To support this extension of indication variation, the MAH has grouped the enrolled patients with the same cancer and RET alteration from both the Phase I and Phase II cohorts into primary analysis sets for the RET-mutation MTC and RET-fusion positive TC populations. Hypothesis and statistical considerations seem not to be pre-planned and determined post hoc. Therefore, the associated statistics have a strong exploratory dimension and caution should be taken in interpreting the results of the analyses of these cohorts.

6.4. Unfavourable effects

- All patients from the RET-mutant MTC and RET-fusion positive thyroid cancer cohorts (n=175) in the ARROW study had at least one **AE**. Grade 3 or higher AEs constituted around 80% of AEs. The most common AE (PT occurring in 10%) was anaemia (53.1%), AST increased (49.1%), constipation (44.0%), hypertension (41.1%), hypocalcaemia (39.4%), diarrhoea (37.1%), white blood cell count decreased (35.4%), ALT increased (35.4%), hyperphosphataemia (30.9%) and fatigue 30.3%).
- The majority of the patients experienced **grade ≥3 AEs** (83.1%). The most common (PT occurring in ≥2%) were hypertension (24.0%), anaemia (22.3%), lymphocyte count decreased (13.7%), lymphopenia (12.0%), pneumonia (10.3%), neutropenia (10.3%) and hypocalcaemia (7.4%). However, more hypertension was seen in ARROW than in the overall population (17.7%).
- Five AEs were defined as **AESIs**: Pneumonia, pneumonitis, tumour lysis syndrome (TLS), hypertension, and hepatotoxicity. Hepatotoxicity is the most common AESI (63.4%) with the most common Serious AESI being pneumonia (14.3%). However, in the RET-altered patient group compared to the overall safety group there were seen higher incidences of hypertension (41.1% vs 34.5%), hypocalcaemia (39.4% vs 23.3%), hyperphosphataemia (30.9% vs 17.7%) and diarrhoea (37.1% vs 32.8%).
- **SAEs** (any grade) were observed in 54.1% with infections and infestations (pneumonia, corona virus infection, urinary tract infection and sepsis) as the most common followed by gastrointestinal disorders, blood and lymphatic system disorders (anaemia, thrombocytopenia), metabolism and nutrition disorders (hyponatraemia, hypokalaemia), nervous system disorders and vascular disorders (hypertension).
- AEs leading to deaths (CCOD of 18 Oct 2021) were seen in 13.1% in the RET-altered group (n=175) and 17.1% in the overall group (n=537). The most common cause of a fatal AEs (›1%) were pneumonia, corona virus infection, pneumonia aspiration and sepsis, apparently in both groups.
- Regarding **laboratory tests and vital signs** there was seen a worsening to G3-4 for decreased albumin, decreased calcium and increased calcium which was more than doubled in the RET-altered group compared to the overall safety pool, which again is at least in part due to the underlying disease.
- In the RET-fusion group 79.4 % experienced **dose reductions** and here the most frequent causes were anaemia, hypertension and neutropenia. The permanent **discontinuation** rates due to AEs and Treatment Related AEs were in the RET-altered group 18.0% and 5.2%, respectively. The most frequent cause was progression, anaemia and pneumonia.

6.5. Uncertainties and limitations about unfavourable effects

Overall, the safety database in the claimed indications in adults (RET-mutated MTC and RET-fusion positive TC patients) is considered of limited extent (n=175), missing long-term safety results.

Further, the uncontrolled design of the ARROW study and the limited median exposure (18.4 months) do not allow to clearly disentangle signs/symptoms of the underlying malignancy and pralsetinib-related adverse events (AEs), limiting precise evaluation of the safety profile of pralsetinib. However, there was a higher incidence of hypertension, hypocalcaemia, hyperphosphataemia and diarrhoea in the RET-altered TC group compared to the overall safety pool. This is considered to be at least in part due to the underlying disease. The overall safety population is also characterised by a significant heterogeneity in terms of age and type of underlying malignancy, that further complicates safety evaluations.

Based on the available data, it appears that the toxicity profile of pralsetinib worsens the symptoms of MTC patients such as hypertension, diarrhoea, hypocalcaemia and hyperphosphataemia.

Lack of data on adolescents and model predicted exposure metrics by weight group for simulated adolescent TC patients.

Finally, the long-term safety profile of pralsetinib should be further discussed.

6.6. Effects Table

Table 1. Effects Table for pralsetinib (data cut-off: 18 October 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
RET-mutant MTC						
ORR	rate	n (%) (95% CI)	90 (62.1) (53.6, 70.0)	NA		CCOD: 18 Oct 2021
DOR	median	Months (95% CI)	29.5 (24.0, NR)	NA		CCOD: 18 Oct 2021
PFS	median	Months (95% CI)	31.2 (25.8, NR)	NA		CCOD: 18 Oct 2021
RET-fusion positive TC						
ORR	rate	n (%) (95% CI)	21 (77.8) (57.7, 91.4)	NA		CCOD: 18 Oct 2021
DOR	median	Months (95% CI)	23.6 (15.1, NR)	NA		CCOD: 18 Oct 2021
PFS	median	Months (95% CI)	25.4 (13.0, -)	NA		CCOD: 18 Oct 2021
Unfavourable Effects						
AE that led to treatment discontinuation		n (%)	31 (18%)			CCOD: 12 April 2021
Hypertension		n (%)	72 (41.1%)			CCOD: 18 Oct 2021
Hypocalcaemia		n (%)	69 (39.4%)			CCOD: 18 Oct 2021
Hyperphosphataemia		n (%)	54 (30.9%)			CCOD: 18 Oct 2021
Diarrhoea		n (%)	65 (37.1%)			CCOD: 18 Octob 2021

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Death due to AE		n (%)	23 (13.1%)			CCOD: 18 Oct 2021
SAEs		n (%)	93 (54.4%)			CCOD: 12 April 2021
Grade ≥3 TEAE		n (%)	143 (83.1%)			CCOD: 12 April 2021

Abbreviations: ORR=overall response rate DOR=Duration of response PFS=progression-free survival NA=not available NE=not estimable NR=not reached

Notes:

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Current treatment choices for the first line of advanced RET-mutant MTC include multikinase tyrosine kinase inhibitors such as cabozantinib or vandetanib, whereas for advanced RET-fusion TC sorafenib or lenvatinib are recommended in the first line setting. After progression to first line treatment, selpercatinib (a RET inhibitor) is approved as second line treatment in both diseases.

Results from the relevant cohorts of study ARROW are considered compelling and of clinical relevance in the applied indications, with important response rates in the range of 62-78% across the sought indications and their subgroups. Such responses were durable with mDOR between 23.6 and 29.5 months.

From a safety point of view, the most common AEs reported with pralsetinib were anaemia, AST increased, constipation, hypertension, hypocalcaemia, diarrhoea, white blood cell count decreased, ALT increased, hyperphosphataemia and fatigue. There was a higher incidence of hypertension, hypocalcaemia, hyperphosphataemia and diarrhoea in the RET-altered TC group compared to the overall safety pool. This is considered to be at least in part due to the underlying disease. However, it appears that the toxicity profile of pralsetinib worsens the symptoms of MTC patients.

However, as a result of the uncontrolled efficacy and safety data, uncertainties remain due to the lack of direct controls and population heterogeneity.

The MAH proposes the use of Gavreto in patients from 12 years old. However, there are no data in patients below 18 years. The MAH has updated the Pop PK for RET-altered TC by excluding NSCLC data as requested and has submitted simulations for extrapolation to adolescents performed with the Final Pop PK model as an addendum to the final model report. As there is no data available for adolescent patients, this exercise is considered as a full extrapolation. Currently, the major objection on PK is not considered solved.

6.7.2. Balance of benefits and risks

The effect observed with pralsetinib in the intended target populations is considered of clinical relevance.

Uncertainties are still present due to the lack of direct controls and population heterogeneity of the database, but these will be addressed with the studies imposed as specific obligations (annex II), which will provide comprehensive data on both efficacy and safety aspects.

6.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

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

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating, life-threatening disease. Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

• The benefit-risk balance is currently negative but could be positive if the raised MO's will be solved, as the results from study BO42863 (ARROW) are of clinical relevance in the applied indications, with response rates ranging from 52.2% to 84.0% and a minimum duration of response of 23.6 to 25.8 months depending on the indication and the patient population. From a safety point of view, the most common AEs reported with pralsetinib were anaemia, followed by liver enzymes increased, constipation and hypertension. In view of the assumed clinical benefit, the safety of pralsetinib is considered acceptable

• It is likely that the applicant will be able to provide comprehensive data.

The CO42865 (AcceleRET MTC) study is a multi-center, open-label, randomized phase 3 study to evaluate the efficacy and safety of pralsetinib compared with SOC treatment (cabozantinib or vandetanib) for adult patients and adolescents (n=20) with advanced and metastatic RET-mutant MTC who have not previously received an SOC TKI therapy (n=198). The applicant expects the enrolment to be completed with a final CSR by January 2028.

An integrated efficacy analysis of RET fusion-positive solid tumour patients (excluding NSCLC) from the BO42863 (ARROW) and BO41932 (TAPISTRY) studies to provide additional data to support conversion to full approval. It is anticipated this integrated analysis will include at least 90 RET fusion-positive solid tumour patients with at least 8 months follow up, with at least 40 patients coming from BO42863 (ARROW) and at least 50 patients coming from BO41932 (TAPISTRY). One of the cohorts in BO41932 is evaluating pralsetinib in RET fusion-positive solid tumours (excluding NSCLC). The final integrated analysis report will be available by June 2025.

• Unmet medical needs will be addressed, in view of the high overall response rates and the long duration of response of pralsetinib in the applied indications. It can be assumed that there will be a clinical benefit in these patients which will be confirmed post authorisation as described above.

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

• As Retsevmo is conditionally approved, Gavreto needs to address the unmet medical need to a similar or greater extent as Retsevmo.

6.8. Conclusions

The overall B/R of pralsetinib is negative due to a remaining PK MO regarding extrapolation to adolescents.

The following measures are considered necessary to address issues related to clinical efficacy: post-authorisation data from the planned and confirmatory Phase III study in patients with advanced RET mutation-positive MTC (CO42865-AcceleRET-MTC), the Integrated Analysis of ARROW and TAPISTRY, as the SOB for the fusion-positive thyroid cancer indication should be reflected in Annex II.