15 September 2022
EMA/CHMP/30610/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Caprelsa

International non-proprietary name: vandetanib

Procedure No. EMEA/H/C/002315/II/0043

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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	30 Mar 2020	30 Mar 2020	☐
☐	CHMP Rapporteur Assessment Report	04 May 2020	20 May 2020	☐
☐	CHMP members comments	18 May 2020	25 May 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	20 May 2020	28 May 2020	☐
☐	Request for supplementary information	28 May 2020	28 May 2020	☐
☐	Re-start of procedure	26 Apr 2021	26 Apr 2021	☐
☐	CHMP Rapporteur Assessment Report	31 May 2021	4 Jun 2021	☐
☐	CHMP members comments	14 Jun 2021	14 Jun 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	17 Jun 2021	17 Jun 2021	☐
☐	2nd Request for supplementary information	24 Jun 2021	24 Jun 2021	☐
☐	CHMP Rapporteur Assessment Report	22 Nov 2021	25 Nov 2021	☐
☐	CHMP members comments	6 Dec 2021	6 Dec 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	9 Dec 2021	8 Dec 2021	☐
☐	3rd Request for supplementary information	16 Dec 2021	16 Dec 2021	☐
☐	CHMP Rapporteur Assessment Report	25 Apr 2022	25 Apr 2022	☐
☐	CHMP members comments	10 May 2022	10 May 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	12 May 2022	13 May 2022	☐
☐	4th Request for supplementary information	19 May 2022	19 May 2022	☐
☐	CHMP Rapporteur Assessment Report	22 Aug 2022	08 Aug 2022	☐
☐	CHMP members comments	5 Sep 2022	5 Sep 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	8 Sep 2022	8 Sep 2022	☐
☒	Opinion	15 Sep 2022	15 Sep 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional

pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Alexandre Moreau
Co-Rapporteur (lead for this procedure):	Paula van Hennik

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Genzyme Europe BV submitted to the European Medicines Agency on 10 March 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

C.I.4 Update of section 5.1 of the SmPC in order to update pharmacodynamic information based on interim results from study D4200C00104, listed as a specific obligation in the Annex II. This is an observational study (including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic thyroid cancer (MTC)), to confirm the efficacy and safety of Caprelsa in RET-negative patients with the aim to fulfil SOB001 and convert Caprelsa from conditional to normal Marketing Authorisation.
In addition the MAH takes to opportunity to rectify the Dutch translation of the Caprelsa Product Information.
The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

In the second round, the MAH also proposed to update section 4.4 of the SmPC.

2. Overall conclusion and impact on the benefit/risk balance

The MAH submitted a variation application under category C.1.4 of the variation classification Guideline with the scope to include "Update of section 5.1 of the SmPC in order to update pharmacodynamic information based on interim results from study D4200C00104, listed as a specific obligation in the Annex II. This is an observational study (including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic thyroid cancer (MTC)), to confirm the efficacy and safety of Caprelsa in RET-negative patients with the aim to fulfil SOB001 and convert the marketing authorization for Caprelsa from a conditional to normal marketing authorisation". No changes were proposed in section 4.1 'Therapeutic indications'.

In the current type II labelling variation, the MAH includes an update with the results of the data analysis from 23 MTC RET negative patients treated with vandetanib with the aim to fulfill SOB001 and convert the Marketing Authorisation from conditional to normal. Consequently, the MAH proposes to delete the provisions relative to the Specific Obligation from the Product Information. No changes are proposed in section 4.1 'Therapeutic indications'. In the second round, the MAH considered that the provisions relative to the RET mutation status embedded in section 4.4 'Special warnings and precautions for use' should also be modified.

In 2012, conditional marketing authorisation (CMA) was granted for vandetanib for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. The approval of vandetanib was based on the randomised, double-blind, placebo-controlled study D4200C00058. Superiority of vandetanib was demonstrated compared to placebo, with a 11.2 months increase (19.3 vs not reached [predicted 30.5 months]) of median PFS

(HR=0.46, 95% CI 0.31-0.69, p=0.0001). RET mutation status was positive in 187 (56.5%) patients, unknown in 138 (41.1%), and negative in 8 patients (2.4%), including 2 patients in the vandetanib group. A correlation between RET mutation status and clinical outcome could therefore not be evaluated. Following a post-hoc analysis, efficacy endpoints were studied for 79 patients (71 patients with sporadic MTC previously classified as RET mutation "unknown" and 8 patients with sporadic MTC previously classified as RET mutation "negative") that were identified as without M918T mutation and with no other RET mutation: 46 patients were randomised to vandetanib and 33 patients to placebo. In the RET mutation positive group (n=187) predicted median PFS was 29 months in the vandetanib group vs 18 months in the placebo group (HR=0.45, 95% CI 0.26-0.78). In the patients with no M918T mutation and no other identified mutation (n=79) predicted PFS was 28 vs 18 months in the vandetanib vs placebo group, respectively. In the vandetanib arm, ORR was 52% for RET mutation positive patients and 35% in patients with no M918T mutation and no other identified mutation. Therefore, a CMA was granted. A lack of knowledge allowing adequate B/R determination in RET negative patients was acted. The following information was added in the SmPC section 4.1: "For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision". In addition, in order to confirm the efficacy and safety of vandetanib, the MAH had to submit as a SOB the final clinical study report of study D4200C00104, an observational study to evaluate the B/R of vandetanib 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, and locally advanced/metastatic thyroid cancer. Forty RET mutation positive and forty RET mutation negative patients were planned to be enrolled in the study [EMEA/H/C/002315/0000, EPAR EMA/128076/2012].

In 2017, the MAH submitted a type II variation to request the switch of the CMA to a standard marketing authorisation not subject to specific obligations (EMEA/H/C/002315/II/0028). The MAH provided updated results of study D4200C00104. For efficacy, as of 02 August 2018, 34 patients have been enrolled, 26 of whom were RET mutation positive and 8 were RET mutation negative. The ORR was 19.2% (5 patients with CR or PR maintained for 2 or more consecutive assessments) in RET positive population and 0% for RET negative patients (3 patients with PR not maintained for 2 or more consecutive assessments). The DCR was similar in RET positive and negative patients (50% in each group) with at least SD observed post-baseline in 4 RET negative patients and in 13 RET positive patients. The data for PFS and OS were not mature. The CHMP was of the opinion that the data provided by the MAH to better define B/R in the RET negative population were immature and limited. The B/R remained positive in the overall population of the indication, but the data were still insufficient to define a clear B/R in the RET negative population. The information regarding RET mutation should not be deleted from the sections 4.1, 4.4 and 5.1 of the SmPC. As a result, the conditions were not fully met to convert CMA into full approval. The feasibility to obtain data from 40 patients was discussed and dismissed, with a sample size between 40 and 50 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC receiving vandetanib: 20 to 25 RET mutation negative and 20 to 25 RET mutation positive. The SOB with due date Q3 2020 was reworded as follows:

"In order to confirm the efficacy and safety of Caprelsa in RET-negative patients, the MAH should submit:

- *The clinical study report of Study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC).*
- *The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058."*

In the current type II variation, the MAH provides updated data from study D4200C00104 and re-analysis data from study D4200C00058. Data from the latter were already provided during the last renewal (EMEA/H/C/002315/R/0041).

In the final CSR and addendum to CSR for study D4200C00104 (OBS14778), data from the observational D4200C00104 study (prospectively and retrospectively enrolled patients) that started in Q1 2014 and the phase 3 D4200C00058 study (limited to reanalyzed samples that were previously categorized as RET mutation "unknown") were pooled. Regarding efficacy, tumour response was evaluated based on investigator assessment in 55 RET positive patients and 20 RET negative patients. The ORR was 41.8% (95% CI: 28.7-55.9) for RET positive patients (n=23 with 2 CR and 21 PR) and 5.0% (n=1 [PR]) for RET negative patients. More RET positive patients experienced a CR or PR compared to RET negative patients (CR: 3.6% versus 0%; PR: 38.2% versus 5.0%, respectively). The one patient achieving a PR in the RET negative cohort was from study D4200C00058 and had a RAS mutation. SD was reported in 43.6% of the RET positive patients and 85.0% of the RET negative patients. DCR (CR, PR, or SD) was 85.5% in the cohort with RET positive patients and 90% in the cohort with RET negative patients. Median DOR was 24.9 months in the RET positive patients and for the 1 RET negative patient this was 5.3 months. Median PFS (95% CI) was 24.6 months (95% CI: 15.6-31.8) in RET positive patients and 24.6 months (95% CI: 9.9-59.5) in RET negative patients. There were 4 deaths (11.1%) in RET positive patients and 2 (14.3%) in RET negative patients. Time dependent outcomes are difficult to interpret in this non-randomized, observational study. In the latest response, the MAH provided an addendum to the CSR with analyses based on blinded central review for the D500C00058 patients. The data from the patients included in the observational part did not change. Compared to the previous results, there were three additional evaluable patients in the RET positive population and one additional evaluable patient in the RET negative population from study D4200C0058 using the blinded central review data. ORR in the RET positive population was 39.7% (compared to 41.8% previously) and in the RET negative population ORR was 9.5% (compared to 5.0% previously) when using blinded central review for the patients in study D4200C0058. In total 2 out of 21 RET negative patients had a partial response based on central review, no complete responses were reported. Median DOR was not estimable for the RET negative population. The one responder per investigator assessment is different (E1201002) than the two responders per central review (E1001011 and E1701002). Per central review, patient E1201002 had stable disease. It should also be noted that for the patients in the observational part, only investigator assessment is available. It is, therefore, preferred to analyse all patients per investigator assessment.

ORR in the RET positive patients was comparable to that shown in study D4200C0058 (i.e. 45%). However, the response rate of 9.5% or 5%, depending on the used tumour assessment method, in RET negative patients was substantially lower than the response rate of 35% in the cohort of 46 patients who were classified as RET negative (i.e. "with no M918T mutation and no other identified mutation") and treated with vandetanib in the registration study. At time of CMA, RET mutation status was determined by sequencing the 6 most commonly mutated exons in MTC (exon 10, 11, 13, 14, 15, and 16) and by amplification refractory mutation system (ARMS) analysis. A RET negative mutation status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons plus the ARMS assay negative for a M918T mutation. According to the MAH, it was anticipated at that time that patients with no M918T mutation had a high probability to have no additional RET mutation. Using new technologies, part of the samples in study D4200C00058 were reanalysed, which confirmed RET negative status in only 11 of 46 patients previously classified as RET negative at time of CMA. The remaining 35 patients were reclassified as RET positive. The new technologies used were a custom Taqman assay to genotype the RET M918T mutation and, when adequate material was available, sequencing using Illumina technology to reveal any other RET mutations.

Regarding safety, 91 patients received at least 1 dose of vandetanib (64 RET positive and 27 RET negative) with a median exposure of around 2 years. Based on the provided results, a higher rate of AEs (98 vs 89%) and serious AEs (31 vs 22%) were reported in the RET positive compared to the RET negative patients. Most common AEs observed were diarrhea, rash, and hypertension. It is agreed with the MAH that the reported AEs are consistent with the known safety profile of vandetanib. It is noted that the toxicity profile is substantial and should be weighed against the benefit in RET negative patients.

The MAH concludes that based on the provided clinical and literature data, discrepancies in RET testing quality between institutions as well as the lack of standard of care for RET negative patients, vandetanib should remain a treatment option for patients with aggressive, symptomatic, unresectable, locally advanced or metastatic MTC. This is not agreed. The response rate of 35% in the group with "no M918T mutation and no other RET mutation identified" at time of the CMA now appears to be based on inaccurate data, as the majority of patients was actually RET positive. In a pooled set of 21 or 20 patients pending on the used tumour assessment, the response rate is at best 9.5% and DOR is not estimable. It is unlikely that the reported response rate of 9.5 or 5% in RET negative patients will translate into a clinical benefit. Combined with the known toxicity profile of vandetanib and that RET testing is expected to play a more and more important role in MTC, given the developments in treatments specifically targeting RET, the benefits do not outweigh the risks in the RET negative population and the indication is restricted to RET mutant patients, in which the B/R remains positive. In addition, the SOB can be considered fulfilled.

Based on the assessment of the data contained in the application, the CHMP is of the view that the following changes to the MA should be introduced "Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC to reflect the restriction of the indication for Caprelsa (vandetanib) for the treatment of aggressive and symptomatic RET mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease based on the results of the D4200C00104 study and the re-evaluation of efficacy in RET negative patients from study D4200C00058, both listed as a specific obligation in the Annex II; the Package Leaflet is updated accordingly. As a result of this variation, the CHMP also recommends the granting of a marketing authorisation no longer subject to specific obligations". These changes fall under category C.1.6 of the variation classification Guideline.

In reply to the request for supplementary information, the MAH updated the product information accordingly. In addition, the MAH was requested to provide a draft DHPC and communication plan regarding the restricted indication.

3. Recommendations

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

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC to reflect the restriction of the indication for Caprelsa (vandetanib) for the treatment of aggressive and symptomatic RET mutant medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease based on the results of the D4200C00104 study and the re-evaluation of efficacy in RET

negative patients from study D4200C00058, both previously listed as a specific obligation in the Annex II; the Package Leaflet is updated accordingly. As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligations and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligations. In addition, the Dutch translation of the Caprelsa (vandetanib) Product Information is rectified.

is recommended for approval.

The CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for Caprelsa (vandetanib).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB are recommended.

As a result of this variation, it is recommended that the following obligation is deleted from the Annex II to the Opinion:

Description	Due date
In order to confirm the efficacy and safety of Caprelsa in RET-negative patients, the MAH should submit: - the clinical study report of study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058.	Ongoing-due date March 2021

PSUR frequency

The current frequency of submission should be changed from 6 months to annually at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Caprelsa-H-C-002315-II-0043'

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Background on medullary thyroid cancer

Medullary thyroid cancer (MTC) is a neuroendocrine tumour of the parafollicular or C cells of the thyroid gland. Systemic symptoms may occur due to hormonal secretion by the tumour causing for example diarrhoea or flushing in patients with advanced disease [Tuttle et al., *UpToDate*, 2019].

RET and RAS proto-oncogene mutations are detected in about 90% of MTCs and are considered the predominant drivers of MTC. RET mutations occur sporadically or can be inherited as germline events associated with familial MTC or the multiple endocrine neoplasia syndromes type 2A and 2B (MEN2A and MEN2B). A quarter of MTCs occur as part of an inherited syndrome, and germline RET mutations are present in up to 10% of the patients presenting with apparently sporadic MTCs [Filetti et al., *Annals of Oncology*, 2019].

Distant metastases are present at diagnosis in approximately 10% of all MTC patients, but higher rates are observed during follow-up [Filetti et al., *Annals of Oncology*, 2019]. Patients with progressive or symptomatic metastatic disease who cannot be treated by surgery or radiotherapy should be considered candidates for systemic therapy [Sherman et al., *UptoDate*, 2020]. Cabozantinib and vandetanib are the first-line systemic treatments for progressive metastatic MTC according to the ESMO guideline for thyroid cancer [Filetti et al., *Annals of Oncology*, 2019].

Background on regulatory history

Vandetanib (Caprelsa) is a multi-target inhibitor targeting vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and RET tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase.

Vandetanib is indicated for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. The approval of vandetanib is based on the randomised, double-blind, placebo-controlled study D4200C00058. Superiority of vandetanib was demonstrated compared to placebo, with a 11.2 months increase (19.3 vs not reached [predicted 30.5 months]) of median PFS (HR=0.46, 95% CI 0.31-0.69, p=0.0001). RET mutation status was positive in 187 (56.5%) patients, unknown in 138 (41.1%), and negative in only 8 patients (2.4%), including 2 patients in the vandetanib group. A correlation between RET mutation status and clinical outcome could therefore not be evaluated. Following a post-hoc analysis, efficacy endpoints were studied for 79 patients (71 patients with sporadic MTC previously classified as RET mutation "unknown" and 8 patients with sporadic MTC previously classified as RET mutation "negative") that were identified as without M918T mutation and with no other RET mutation: 46 patients were randomised to vandetanib and 33 patients to placebo. Efficacy results in both groups are shown in Table 1.

Table 1. Efficacy endpoints in RET mutation positive patients and the 79 patients proven without M918T mutation and with no other RET mutation identified

Efficacy Endpoint	RET Mutation Positive (n=187)[a]	Patients with No M918T Mutation and No Other Identified Mutation (n=79)
PFS HR (95% confidence interval)	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)
Predicted median PFS (months) (vandetanib vs. placebo)	29 vs. 18	28 vs. 18
Objective response rate (vandetanib arm)	52%	35%
Duration of response (months)	22	18

a RET mutation positive hereditary and sporadic MTC patients

Therefore, conditional marketing authorisation was granted in 2012. A lack of knowledge allowing adequate B/R determination in RET negative patients was acted. The following information was added in the SmPC section 4.1: "For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision". In addition, in order to confirm the efficacy and safety of vandetanib, the MAH had to submit as a SOB the final clinical study report of study D4200C00104, an observational study to evaluate the B/R of vandetanib 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, and locally advanced/metastatic thyroid cancer. Forty RET mutation positive and forty RET mutation negative patients were planned to be enrolled in the study [EMEA/H/C/002315/0000, EPAR EMA/128076/2012].

In 2017, the MAH submitted a type II variation to request the switch of the conditional marketing authorisation to a standard marketing authorisation not subject to specific obligations (EMEA/H/C/002315/II/0028). The MAH provided updated results of study D4200C00104. For efficacy, as of 02 August 2018, 34 patients have been enrolled, 26 (76.5%) of whom are RET mutation positive and 8 (23.5%) are RET mutation negative. Median duration of follow-up was 1 year, and 14 patients (41.2%) including 4 RET negative are still receiving treatment with vandetanib in the study. Treatment was interrupted in 4 RET negative patients due to disease progression (n=2), due to lack of therapeutic response (n=1) and due to AE (n=1). Sixteen RET positive patients discontinued prior to completing the study, 5 due to "other" (reason not specified), 4 due to lack of therapeutic response, and 4 due to AEs. Two patients discontinued due to death (due to disease progression), and 1 discontinued due to patient decision. The ORR was 19.2% (5 patients with CR or PR maintained for 2 or more consecutive assessments) in RET positive population and 0% for RET negative patients (3 patients with PR not maintained for 2 or more consecutive assessments). The DCR was similar in RET positive and negative patients (50% in each group) with at least SD observed post-baseline in 4 RET negative patients and in 13 RET positive patients. The data for PFS and OS were not mature. The CHMP was of the opinion that the data provided by the MAH to better define B/R in the RET negative population were immature and limited. The data strongly suggested that inhibition of the RET pathway is not the single factor in MTC disease control and that other mechanisms are involved in tumour growth and inhibition, e.g. VEGFR and EGFR pathways. The B/R remained positive in the overall population of the indication, but the data were still insufficient to define a clear B/R in the RET negative population. The information regarding RET mutation should not be deleted from the sections 4.1, 4.4 and 5.1 of the SmPC. As a result, the conditions were not fully met to convert CMA into full approval. The feasibility to obtain data from 40 patients was discussed and dismissed, with a sample size between 40 and 50 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC receiving vandetanib: 20 to 25 RET mutation negative and 20 to 25 RET mutation positive. The SOB with due date Q3 2020 was reworded as follows:

"In order to confirm the efficacy and safety of Caprelsa in RET-negative patients, the MAH should submit:

- *The clinical study report of Study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC).*
- *The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058."*

In the current type II labelling variation, the MAH includes an update to the Caprelsa SmPC, section 5.1 'Pharmacodynamic properties', with the results of the data analysis from 23 MTC RET negative patients all treated with vandetanib with the aim to fulfill SOB001 and convert the Marketing Authorisation from conditional to normal. Consequently, the MAH proposes to delete the provisions relative to the Specific Obligation from the Product Information. No changes are proposed in section 4.1 'Therapeutic indications' and the provisions relative to the RET mutation status embedded in section 4.4 'Special warnings and precautions for use' are not modified.

Of note, the MAH states that as agreed with the EMA (in accordance with the communication dated 22 January 2020 and appended to the Cover Letter of this application), the MAH is not providing an updated RMP. That will be provided in another variation upon approval of the current type II labelling variation at a later stage. Moreover, the MAH is planning to provide the final clinical study report for study D4200C00104 final Clinical Study Report (CSR) at a later stage, and it is therefore not part of this submission package, which is according to the MAH in accordance to the CHMP and PRAC Rapporteurs' joint Final Assessment Report relative to procedure no. EMEA/H/C/002315/R/0041 dated 14 November 2019. The MAH stated during the renewal that a D4200C00104 CSR can only be produced once the Agency agrees that the SOB001 is lifted/considered fulfilled, since at that point the clinical study database can be locked, and this was supported by the CHMP.

6. Clinical Efficacy aspects

6.1. Study D4200C0104

Methods – analysis of data submitted

Study D4200C00104 is an international, multicenter, non-interventional (observational), prospective (for patients with RET mutation positive or negative status) and retrospective (for patients with RET mutation negative status) study of patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib 300 mg once daily and with a RET mutation positive or negative status. In addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC not prescribed vandetanib 300 mg but who are RET mutation negative will be allowed to enter the study.

The decision to prescribe vandetanib is taken independently of the enrollment into this study and is in line with the respective (local) prescribing information. The study is observational, meaning that vandetanib treatment initiation should never be delayed in order to meet any inclusion criteria of the study. Similarly, performing interventions on the patients that would specifically be for the study and would not be carried out in the "real life" setting is not permitted e.g., a biopsy. European countries where vandetanib is on the market (from February 2012) will participate in the study.

Twenty to 25 RET mutation positive and as many RET mutation negative patients as possible are planned to be enrolled in the study according to the MAH as described in the clinical overview.

The objectives of the study are:

- To determine the objective response rate (ORR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.
- To determine the disease control rate (DCR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.
- To assess the duration of response and time to response for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.
- To explore the clinical outcomes (including but not limited to progression-free survival [PFS] and ORR) amongst RET mutation negative patients not treated with vandetanib.
- Safety, including relevant adverse events (AEs) based on the safety profile outlined in the vandetanib summary of product characteristics (SmPC), and incidence of QTc prolongation and associated risks for QTc prolongation in patients receiving vandetanib who are RET mutation positive and RET mutation negative. In addition, the incidence of serious adverse events (SAEs) and AEs leading to discontinuation of vandetanib will be assessed.
- To compare PFS for patients treated with vandetanib who are RET mutation positive to patients treated with vandetanib who are RET mutation negative.

Study visits will include a screening visit and/or enrollment visit, where the eligibility of the prospective patient will be confirmed, plus additional follow up visits:

- Investigators are strongly recommended to perform a complete disease assessment (biomarkers, symptoms, and imaging) at least every 6 months according to both site normal clinical practice and International MTC guidelines. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be used as a base for calculation for disease assessment.

For retrospective patients (only advanced/metastatic MTC patients with RET mutation negative status):

- Data collection reporting time points will include a baseline time point before the start of their treatment for MTC (vandetanib or another treatment) where the eligibility of the patient will be confirmed, plus all subsequent time points that may be available in the patient file.

All AEs for patients treated with vandetanib will be collected actively throughout the study, and retrospectively for retrospective RET mutation negative patients.

Patients will be followed until objective progression, death, or until the end of study (whichever occurs first). End of study is defined as 14 months after the last patient has been enrolled in the study and when at least 10 PFS events (defined as disease progression based on RECIST 1.1 assessment, or death) in both treatment groups have been observed. If all patients have progressed prior to 14 months after the last patient is recruited, the study will stop.

Results

The present addendum to Clinical Overview (ACO) follows the Interim Report dated 24 July 2019, submitted as part of the Annual Renewal of the conditional marketing authorization application procedure no. EMEA/H/C/002315/R/0041 on 02 August 2020, and reflects updated data as of 10 February 2020.

The MAH notes that the D4200C00104 study data presented in the following section are a raw data extraction performed on 10 February 2020 in accordance with the Agency's agreement that the MAH would provide data in Q1 2020. Final conclusions from this study are pending the final statistical analysis (to be performed at the time of CSR preparation). Since these are raw data extractions, without

consistency checks and statistical analyses as they will be presented the final CSR, the MAH states that it is not possible to discuss the limitations of these data in the present Addendum to Clinical Overview, and these data should be interpreted with caution.

Recruitment over time

As of 10 February 2020 (the cut-off date for this extraction), 40 patients underwent formal screening, of whom 35 patients have been prospectively enrolled; there have also been 5 screen failures (3 patients had no RET mutation data available [1 of whom also had no measurable lesions], 1 patient was RET positive but did not meet the vandetanib requirements of inclusion criterion 06, and 1 RET positive patient had a contraindication to vandetanib). Of the 35 prospectively enrolled patients, 28 patients are RET mutation positive and 7 are RET mutation negative (please note that 2 of the 9 patients reported as RET negative in the Interim Report submitted in 2019 [dated 24 July 2019 and submitted in the Annual Renewal on 02 August 2019] were identified as RET negative due to data entry errors; their mutation status was corrected by the investigators as per source documentation, and these patients are reported as RET positive in this report).

In addition, 5 RET mutation negative patients have been retrospectively enrolled.

Figure 1 provides quarterly and cumulative enrollment data for prospective patients from study inception to 10 February 2020, and cumulative enrollment data for retrospective patients since the first country approval of the D4200C00104 amendment (Germany, 27 August 2019) up to 10 February 2020. The enrollment dates of individual prospective and retrospective patients are provided in Table 2 and Table 3, respectively.

A total of 30 sites in 8 countries are participating, including 3 sites involved in the retrospective data collection effort on RET negative patients specifically. Among the 30 sites, 7 sites responded that they did not have any RET patient to contribute to the retrospective data collection effort.

Figure 1. Study D4200C00104 enrolment by quarter and cumulative - Prospective and retrospective patients

Table 2. Study D4200C00104 enrolment by quarter and cumulative - Prospective patients

	2014				2015				2016[a]				2017				2018				2019				2020
	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q
Pts. Enrolled	1	1	5	3	3	4	3	5	1	2	1	0	2	2	1	0	0	1	0	0	0	0	0	0	0
Cumulative	1	2	7	10	13	17	20	25	26	28	29	29	31	33	34	34	34	35	35	35	35	35	35	35	35

a Sanofi Genzyme assumed Sponsor responsibility for the D4200C00104 study in 3Q 2016

Table 3. Study D4200C00104 enrolment by quarter and cumulative - Retrospective patients

	2019			2020
	2Q[a]	3Q	4Q[b]	1Q
Pts. Enrolled	0	0	4	1
Cumulative	0	0	4	5

a The retrospective arm was added to the D4200C00104 study protocol on 21 June 2019, and the first country approval of the amendment occurred in Germany on 27 August 2019.

b Retrospective enrollment began in fourth quarter 2019 in Italy.

Patient disposition (prospectively enrolled patients)

As of the date of data extraction, 12 patients remain in the study. Twenty-one patients discontinued study treatment early: 10 due to disease progression, 5 due to lack of therapeutic response, 5 due to AEs (2 patients due to cutaneous rash, 1 patient due to acute kidney injury, 1 patient due to empyema, and 1 patient due to an unspecified AE), and 1 due to patient decision. Two patients died (resulting from disease progression), see also Table 4.

Table 4. Study D4200C00104 prospective patient enrolment status

Patient	Date of Informed Consent	Status	Reason for Discontinuation	RET Mutation Status
3101001	9-Sep-14	Ongoing	N/A	negative
3101002	28-Oct-14	Ongoing	N/A	positive
3101004	20-Apr-16	Early discontinued	Disease Progressed	positive
3101005	11-Jan-17	Early discontinued	Disease Progressed	negative
3301001	4-Mar-15	Early discontinued	Disease Progressed	positive
3301002	8-Jun-15	Early discontinued	Disease Progressed	positive
3301003	23-Nov-15	Ongoing	N/A	positive
3304001	3-Sep-15	Early discontinued	Lack of Therapeutic Response	negative
3304002	1-Jun-17	Ongoing	N/A	negative
3402001	16-Jul-14	Ongoing	N/A	positive
3402002	3-Dec-14	Early discontinued	Disease Progressed	negative
3404001	29-Dec-15	Early discontinued	Lack of Therapeutic Response	positive
3404002	28-Sep-16	Early discontinued	Disease Progressed	positive
3404003	12-May-17	Ongoing	N/A	positive[a]
3406001	20-Aug-15	Early discontinued	Disease Progressed	positive
3406002	31-May-16	Ongoing	N/A	positive
3901002	2-Oct-14	Ongoing	N/A	positive
3901003	11-Feb-15	Ongoing	N/A	positive
3904001	17-Feb-14	Early discontinued	Lack of Therapeutic Response	positive
3904002	15-Apr-14	Early discontinued	Adverse Event (Cutaneous Rash)	positive
3904004	30-Sep-14	Early discontinued	Lack of Therapeutic Response	positive
3904005	2-Apr-15	Early discontinued	Adverse Event (Acute kidney injury)	positive
3904006	7-Apr-15	Early discontinued	Adverse Event (Empyema)	negative
3904007	18-Jun-15	Early discontinued	Disease Progressed	positive
3904008	9-Mar-16	Early discontinued	Disease Progressed	positive
3904009	28-Mar-17	Early discontinued	Adverse Event (Cutaneous Rash)	positive
3904010	11-Jul-17	Early discontinued	Early Discontinued - Adverse Event	positive
3905001	4-Oct-18	Early discontinued	Disease Progressed	positive[a]
3906001	18-Feb-15	Ongoing	N/A	positive
3907001	18-Nov-15	Ongoing	N/A	positive
3908001	4-Dec-15	Early discontinued	Death	positive
3908002	16-Dec-15	Ongoing	N/A	negative
4401001	29-Sep-15	Early discontinued	Lack of Therapeutic Response	positive
4405001	3-Jul-14	Early discontinued	Death	positive
4901002	29-Sep-14	Early discontinued	Subject Decision	positive

a Patients 3404003 and 3905001 were identified in the 2019 Interim Report (dated 24 July 2019 and submitted in the Annual Renewal on 02 August 2019) as RET negative due to data entry error. The entry was subsequently corrected by the investigators, and these patients are correctly reported as RET positive in this report.

Study conduct and compliance

Patient enrollment has been slower than was initially projected since study inception, with no additional patients recruited within the last six months and is now estimated to reach completion in Q3 2020.

Thirty-five (35) patients have been prospectively enrolled to date. No issues have been noted with regard to treatment compliance, compliance with efficacy and safety assessments or important protocol deviations. In addition, 5 patients have been retrospectively enrolled to date.

Baseline characteristics

A total of 35 patients have been prospectively enrolled as of the cut-off date for this report. The median age of patients enrolled to date is 54 years (range 20 to 85 years). Twenty (57.1%) patients are male; 15 (42.9%) are female. Most patients (88.6%) are white. Mutations of the RET gene were reported in 28 of the 35 (80.0%) prospectively enrolled patients to date; 7 (20.0%) prospectively enrolled patients are RET negative.

Additionally, there are a total of 5 patients enrolled retrospectively as of the cut-off date for this report. All were white, 80% were male, ranged in age from 33 to 67, and all were RET mutation negative. Demographics for all patients are summarized in Table 5.

All patients prospectively and retrospectively enrolled in study D4200C00104 were treated with vandetanib.

Table 5. Study D4200C00104 demographic characteristics - Enrolled subjects

	Statistic	Prospective RET +, vandetanib (N=28)	Prospective RET -, vandetanib (N=7)	Retrospective RET -, vandetanib (N=5)	All RET -, vandetanib (N=12)	Overall (N=40)
Sex	n	28	7	5	12	40
Female	n (%)	12 (42.9%)	3 (42.9%)	1 (20.0%)	4 (33.3%)	16 (40.0%)
Male	n (%)	16 (57.1%)	4 (57.1%)	4 (80.0%)	8 (66.7%)	24 (60.0%)
Race	n	28	6	5	11	39
Black	n (%)	1 (3.6%)	0	0	0	1 (2.6%)
Other	n (%)	0	2 (33.3%)	0	2 (18.2%)	2 (5.1%)
White	n (%)	27 (96.4%)	4 (66.7%)	5 (100.0%)	9 (81.8%)	36 (92.3%)
Age in Class(years)	n	28	7	5	12	40
18 to 22	n (%)	1 (3.6%)	0	0	0	1 (2.5%)
28 to 32	n (%)	5 (17.9%)	0	0	0	5 (12.5%)
33 to 37	n (%)	5 (17.9%)	0	1 (20.0%)	1 (8.3%)	6 (15.0%)
43 to 47	n (%)	3 (10.7%)	0	0	0	3 (7.5%)
48 to 52	n (%)	1 (3.6%)	2 (28.6%)	0	2 (16.7%)	3 (7.5%)
53 to 57	n (%)	3 (10.7%)	0	2 (40.0%)	2 (16.7%)	5 (12.5%)
58 to 62	n (%)	3 (10.7%)	1 (14.3%)	1 (20.0%)	2 (16.7%)	5 (12.5%)
63 to 67	n (%)	2 (7.1%)	2 (28.6%)	1 (20.0%)	3 (25.0%)	5 (12.5%)
68 to 72	n (%)	0	2 (28.6%)	0	2 (16.7%)	2 (5.0%)
73 to 77	n (%)	4 (14.3%)	0	0	0	4 (10.0%)
83 to 87	n (%)	1 (3.6%)	0	0	0	1 (2.5%)
Age (years)	n	28	7	0	7	35
	Mean (sd)	49.7(18.18)	61.1(8.05)	NA	61.1(8.05)	52.0(17.19)
	Median	47.0	63.0	NA	63.0	54.0
	Min:Max	20:85	50:71	NA	50:71	20:85
Height(cm)	n	28	7	3	10	38
	Mean (sd)	168.9(12.95)	170.6(9.25)	168.7(13.05)	170.0(9.79)	169.2(12.08)
	Median	171.2	170.0	170.0	170.0	170.2
	Min:Max	144:191	156:183	155:181	155:183	144:191
Weight(kg)	n	28	7	3	10	38
	Mean (sd)	73.4(21.16)	73.3(16.81)	61.3(7.77)	69.7(15.33)	72.4(19.67)
	Median	73.0	66.0	59.0	65.5	69.8
	Min:Max	47:133	56:100	55:70	55:100	47:133

Note: Actual age is not collected for retrospective subjects

Efficacy evaluation

As of the data cut-off date for this data extraction, results for the primary study objectives (ORR, DCR, time to response, and duration of response) are presented in Table 6. Of note, as of the time of this report these data are preliminary and monitoring and reconciliation activities are continuing. For instance, some patients are still alive, and for some patients the assessments are not yet reported. Therefore, the raw data presented below should be interpreted with caution.

The duration follow-up was based on the time between the date of last RECIST assessment and date of informed consent (prospective patients) or the first dose date (retrospective patients). The median duration of follow-up for RET positive (n=28) and all RET negative (n=12) patients was 635 days (range: 95-1829 days) and 1088 days (range: 85-2510 days), respectively. Of note, the duration of follow-up for 2 of the 5 RET negative retrospectively enrolled patients is not available; for one patient, there were no RECIST assessments entered into the database, and for the other, one RECIST assessment is available but it was made prior to the first dose of vandetanib.

The objective response rate (complete response [CR] or partial response [PR]) for RET positive patients was 21.4%, while none of the RET negative patients achieved a response; for RET positive patients, the median time to response was 231.0 days (range: 112-598 days), and the median duration of response was 519.5 days (range: 176-943 days).

The disease control rate (CR, PR, or stable disease [SD] lasting at least 24 weeks) was apparently not different for RET positive and RET negative patients (53.6% versus 50.0%, respectively).

Table 6. Study D4200C00104 Objective response rate, disease control rate, duration of response and time to response - Enrolled population

Parameter	Statistic	Prospective RET +, vandetanib (N=28)	Prospective RET -, vandetanib (N=7)	Retrospective RET -, vandetanib (N=5)	All RET -, vandetanib (N=12)	Overall (N=40)
Duration of follow-up[a] (days)	n	24	6	3	9	33
	Mean	756.5	921.0	1480.3	1107.4	852.2
	Median	635.0	926.5	1765.0	1088.0	709.0
	Std. Dev.	466.44	680.82	1197.65	852.35	602.65
	Min, Max	95, 1829	85, 1920	166, 2510	85, 2510	85, 2510
Objective Response Rate (ORR)	n (%)	6 (21.4)	0	0	0	6 (15.0)
Disease Control Rate	n (%)	15 (53.6)	5 (71.4)	1 (20.0)	6 (50.0)	21 (52.5)
Duration of Response[b] (days)	n	6	0	0	0	6
	Mean	535.2	NA	NA	NA	535.2
	Median	519.5	NA	NA	NA	519.5
	Std. Dev.	295.02	NA	NA	NA	295.02
	Min, Max	176, 943	NA	NA	NA	176, 943
Time to Response[c] (days)	n	6	0	0	0	6
	Mean	306.8	NA	NA	NA	306.8
	Median	231.0	NA	NA	NA	231.0
	Std. Dev.	200.15	NA	NA	NA	200.15
	Min, Max	112, 598	NA	NA	NA	112, 598

Enrolled population consists of all subjects that signed ICF and satisfy all eligibility criteria. A responder is a subject who has a Best Objective Response (BOR) of CR or PR.
If Scan date missing then RECIST assessment date was used for calculations

a Duration follow-up is based on last RECIST assessment date – [date of informed consent-prospective, first dose date-retrospective]+1.

b Only calculated for responders. Based on first date of disease progression (Scan date) or death (whichever is earlier) – Start date of response (scan date) +1. For those subjects who haven't progressed and are alive, scan date of last RECIST assessment is used.

c Only calculated for responders. Start date of response (scan date) - date of informed consent +1.

Discussion

At time of marketing authorisation, a CMA was granted because of the lack of knowledge allowing adequate B/R determination in RET negative patients. In order to confirm the efficacy and safety of vandetanib, study D4200C00104 was proposed to gain more information on RET negative patients.

In 2017 the MAH submitted a type II variation with data from study D4200C00104 with the goal to fulfil the SOB and switch to a full approval (EMEA/H/C/002315/II/0028). The CHMP however considered the data too limited to draw conclusions with the inclusion of 26 RET positive and 8 RET negative patients (of which 4 were still on treatment). ORR was 19.2% in the RET positive and 0% in the RET negative population, with DCR in both groups around 50%. Due to recruitment issues it was decided to adjust the SOB and the study protocol (sample size of 20-25 RET positive and 20-25 RET negative patients). In order to increase recruitment in the RET negative study population, a retrospective part was added in the study. The study protocol and RMP were adjusted accordingly.

During the renewal in 2019, the MAH reported that 9 RET negative patients were included in study D4200C00104 as of May 2019. The CHMP stated in the assessment report that at the time of submission of the type II variation to fulfill the SOB, data from 20 to 25 RET negative patients treated with vandetanib included in the D4200C00104 study, prospectively as well as retrospectively, should be available.

In the current procedure, 28 RET positive and 7 RET negative patients were included prospectively as of February 2020. It is noted that 2 patients were wrongly coded as RET negative during the data provided at the renewal and therefore the number of RET negative patients in the prospective study part is lower. Three of the 7 RET negative patients are still receiving treatment with vandetanib. In addition, 5 RET negative patients were included retrospectively. Data should be interpreted with caution since the data are raw and are not from a planned interim analysis. It is noted that for some patients the assessments are not yet reported. ORR was reported to be 21.4% in the RET positive population and 0% in the RET negative population. DCR was 53.6% versus 50.0%, respectively. PFS results were not provided.

In conclusion, in total 12 RET negative patients were included in study D4200C00104 and none of the patients showed an anti-tumour response. The number of patients is very limited and conclusions are therefore difficult to draw. The fact that the data are raw add to the difficulties interpreting the results. According to study protocol 20-25 RET negative patients were to be included, which was also reported by the CHMP in the assessment report of the renewal in 2019. The number is therefore lower than as agreed, but it is recognised that it is unlikely to complete the recruitment of 20-25 RET negative patients in this study given the recruitment rates and that the major referring sites in Europe are participating in the study according to the MAH. It can therefore be supported to close study D4200C00104, but the SOB is not considered fulfilled based on the raw data presented. The SOB currently states that the MAH should submit the clinical study report of study D4200C00104. In order to properly assess the data, this should include the final clinical study report and the MAH is requested to provide the final CSR within the current procedure. The final CSR was provided by the MAH in the first round of responses (see "Responses to the request for supplementary information 1").

Methods – analysis of data submitted

Study D4200C00058 was an international, randomised, double-blind, placebo-controlled, multicenter, phase 3 study designed to assess whether vandetanib (300 mg daily) improves PFS compared to placebo in patients with unresectable locally advanced or metastatic MTC. Patients were randomised in a 2:1 ratio to receive vandetanib 300 mg, once daily oral dose or matched placebo, continuing on blinded treatment until they had objective disease progression, provided they did not meet any other withdrawal criteria. Upon disease progression, patients were discontinued from blinded study treatment and then unblinded and given the option to begin open label treatment with vandetanib 300 mg (or receive a permanently reduced dose, if applicable), or entered follow-up for survival status.

Based on the assay technology available at the time the study was run, 56.5% of patients were found to be RET positive, 2.4% were RET negative, and 41.1% had an unknown RET mutation status due to the limitations of the assay.

As explained in the response document submitted on 20 December 2018, as part of variation procedure no. EMEA/H/C/002315/II/0028 (sequence 0114), to more reliably determine the true mutation status for the patients recruited in the original trial, an extensive molecular analyses of the MTC tumor samples would be performed and the results would be correlated with clinical data to determine whether there are significant relationships between molecular data and clinical outcomes. In particular, this tumor sample re-analysis is aimed to reclassify previously reported RET unknown patients and provide vandetanib efficacy and safety data according to their newly assessed RET status.

The overall objectives of this tumor sample re-analysis are:

- To perform a comprehensive molecular and genetic characterization of MTC tissue collected from patients participating in the D4200C00058 Study, to determine if there are previously undiscovered genetic mutations or chromosomal rearrangements present in the RET-negative and RET-unknown samples.
- To perform a genotype-phenotype correlation comparing the results of the molecular studies with the clinical course of individual patients participating in the D4200C00058 Study, and to determine if there are significant relationships between the molecular data and the clinical outcome data from patients participating in the D4200C00058 Study; so that the efficacy of vandetanib can be evaluated in the RET-negative groups.

Sample analysis

In study D4200C00058, of 331 patients, 287 (86.7%) had sporadic MTC, 33 (10.0%) patients had hereditary MTC, and 11 (3.3%) patients had unknown status. RET mutation status was determined to be positive in 187 (56.5%) patients, negative in 8 patients (2.4%), and unknown in 136 (41.1%) patients due to insufficient tumor DNA to fulfill stringent testing criteria.

The aim of this analysis is to reclassify the RET status of the available previously RET unknown and RET negative samples with new methodologies and to assess efficacy and safety in the RET negative patients.

For the reassessment of study D4200C00058, samples histology slides of residual tumor tissue from the clinical trial were reviewed and tumor containing regions were identified and marked by a pathologist. In a subset of samples with normal areas were identified for comparison with the tumor material. DNA

was extracted using standard methods. RET genotyping of the extracted DNA was carried out with one of the following platforms. Initially, some samples were genotyped for the RET M918T mutation using a custom Taqman assay. Samples with scant material were not analyzed further. Samples with adequate material were sequenced using Illumina technology to reveal any other RET mutations. Bar coded sequencing libraries were made from the tissue DNA. RET sequences were enriched using a custom Agilent SureSelect reagent and sequenced on an Illumina sequencer. Some samples went through the Illumina analysis more than once. Data processing and automated calling of RET variants was carried out using the Broad Genome Analysis ToolKit (GATK) pipeline with manual curation of any difficult cases using Broad Integrative Genomics Viewer (IGV).

Two different analyses were performed, the first analysis included all patients with RET status assessed with newer methodologies. For this first analysis, results were presented according to RET status (RET positive, RET negative/RAS negative/BRAF negative, RET negative/RAS positive, RET negative/BRAF positive, all RET negative). Demographic and safety data were provided. Safety data included the AEs; and for the patient incidence of AEs, the frequencies and percentages are presented. The safety summary tables show the patients' data while on randomized treatment, while on open label treatment, and while on randomized and open label treatment.

The second analysis included all RET positive patients and only RET negative patients assessed with the newer methodologies. For this last analysis efficacy data were provided and presented according to RET status and by treatment arm. The efficacy data included the primary endpoint, the PFS as well as the ORR and DCR. The median PFS were provided for each RET status and treatment arm where calculable, and in addition, the proportion of patients who had PFS at 6 months, 1 year and 2 years after randomisation was summarized by RET status and treatment arm. For the ORR, DCR, the frequencies and percentages are presented.

Results

Results of re-analysis (73 samples)

The available RET mutation status "unknown" samples (n=67), previously RET negative samples (n=2), and previously RET positive (n=4) were analyzed with the methodologies described. The remaining previously RET mutation status "unknown" samples (n= 69) and RET negative samples (n=6) could not be re-analyzed due to unavailability of the samples and therefore excluded from this analysis.

The reanalysis confirmed the four previously RET positive patients to be RET positive, and 1 of 2 previously RET negative patient was found to be RET positive. Out of the 67 RET unknown patients re-analyzed, 52 were reclassified as RET positive and 15 were found to be RET negative. In total, 17 patients were found to be RET negative. Two of the RET negative patients were also RAS and BRAF negative, while 1 was BRAF positive and 14 were RAS positive. Eleven of the RET negative patients received vandetanib during the double-blind treatment and 6 received placebo, while 11 received vandetanib during the open label phase.

The demographics of the reclassified patients according to RET, RAS and BRAF status are summarized in Table 7.

Table 7. Study D4200C00058 demographics - Randomized population

					RET -					
	RET + (N=239)		All RET - (N=17)		RAS - BRAF - (N=2)		RAS + (N=14)		BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Age (years) at screening										
Number	172	67	11	6	1	1	9	5	1	0
Mean (SD)	49.6 (14.5)	53.6 (12.1)	56.4 (14.9)	49.3 (15.0)	64.0 (NC)	59.0 (NC)	57.4 (15.2)	47.4 (15.9)	39.0 (NC)	
Median	49.0	52.0	49.0	52.0	64.0	59.0	49.0	45.0	39.0	
Min : Max	18 : 83	28 : 84	39 : 77	32 : 68	64 : 64	59 : 59	40 : 77	32 : 68	39 : 39	
Age group										
[18-40[	43 (25.0%)	6 (9.0%)	1 (9.1%)	2 (33.3%)	0	0	0	2 (40.0%)	1 (100%)	0
[40-65[	97 (56.4%)	48 (71.6%)	6 (54.5%)	3 (50.0%)	1 (100%)	1 (100%)	5 (55.6%)	2 (40.0%)	0	0
[65-75[	28 (16.3%)	10 (14.9%)	2 (18.2%)	1 (16.7%)	0	0	2 (22.2%)	1 (20.0%)	0	0
≥ 75 years	4 (2.3%)	3 (4.5%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Gender										
Male	103 (59.9%)	37 (55.2%)	7 (63.6%)	4 (66.7%)	1 (100%)	1 (100%)	6 (66.7%)	3 (60.0%)	0	0
Female	69 (40.1%)	30 (44.8%)	4 (36.4%)	2 (33.3%)	0	0	3 (33.3%)	2 (40.0%)	1 (100%)	0
Race										
White	163 (94.8%)	65 (97.0%)	11 (100%)	6 (100%)	1 (100%)	1 (100%)	9 (100%)	5 (100%)	1 (100%)	0
Black	1 (0.6%)	0	0	0	0	0	0	0	0	0
Asian	5 (2.9%)	1 (1.5%)	0	0	0	0	0	0	0	0
Other	3 (1.7%)	1 (1.5%)	0	0	0	0	0	0	0	0

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/ret_demo2.sas OUT=EXPLO/OUTPUT/ret_demo2_r_t_i.rtf (13FEB2020 - 17:12)

Results of efficacy analysis of 73 samples re-analyzed

The number (%) of patients with events (e.g., RECIST progression or death) were 44.6% for RET positive and 23.5% for RET negative. The median PFS in RET negative patients could not be calculated because an insufficient number of PFS events had occurred in the RET negative patients group at the time of data cut-off; the median PFS in the RET positive patients group was 21.1 months.

Results of efficacy analysis of study D4200C00058

In this efficacy analysis the RET positive patients (n=239) include the RET positive patients from Study D4200C00058 trial (n=187) and the newly found RET positive patients from this reanalysis (n=56) while the RET negative patients only include the RET negative patients found by this reanalysis (n=17). RET - includes patients who are RET - / RAS - / BRAF - (n=2), patients who are RET - / RAS + (n=14), and patients who are RET - / BRAF + (n=1).

In the vandetanib arm, the median PFS for the RET positive patients and RET negative was not calculable. The number of events seems to be lower in vandetanib arm (34.9% for RET positive patients and 9.1% for RET negative patients) than in placebo arm (56.7% for RET positive patients and 50.0% for RET negative patients) in both RET status subgroup patients. The percentage of patients progression-free or alive at 6 months, 1 year, and 2 years on vandetanib were respectively 90.9%, 83.3%, and 55.7% in the RET positive patients, and 90%, 90%, and 90% in the RET negative patients (see Table 8).

In the vandetanib arm, 51.7% (n=89) RET positive patients and 18.2% (n=2) RET negative patients had an ORR measured by RECIST. DCR was 86.6% (n=149) in the RET positive group and 72.7% (n=8) in the RET negative group (see Table 9).

Table 8. Study D4200C00058 summary of PFS - Full analysis set

	RET + (N= 239)		All RET - (N= 17)		RET-					
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	RAS-BRAF- Vandetanib (N=1)	RAS-BRAF- Placebo (N=1)	RAS+ Vandetanib (N=9)	RAS+ Placebo (N=5)	BRAF+ Vandetanib (N=1)	BRAF+ Placebo (N=0)
Number of events, n(%)	60 (34.9%)	38 (56.7%)	1 (9.1%)	3 (50.0%)	0	1 (100.0%)	1 (11.1%)	2 (40.0%)	0 (0.0%)	0
Median PFS (months)	NC	18.0	NC	NC		11.5	NC	NC	NC	
Percentage of patients at 6 months	90.9	71.2	90.0	100		100	88.9	100	100	
Percentage of patients at 1 year	83.3	61.9	90.0	66.7		0.0	88.9	80.0	100	
Percentage of patients at 2 years	55.7	40.1	90.0	50.0		0.0	88.9	60.0	100	

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
NC = not calculable due to an insufficient number of events.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/ret_pfs2.sas OUT=EXPLO/OUTPUT/ret_pfs2_r_t_i.rtf (13FEB2020 - 17:12)

Table 9. Study D4200C00058 objective response rate, disease control rate - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
Parameter	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Objective Response Rate (ORR)	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Disease Control Rate (DCR)	149 (86.6%)	45 (67.2%)	8 (72.7%)	6 (100%)	0	1 (100%)	7 (77.8%)	5 (100%)	1 (100%)	0

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/ret_resp2.sas OUT=EXPLO/OUTPUT/ret_resp2_r_t_i.rtf (13FEB2020 - 17:12)

Discussion

Of note, the results described above were reported previously to the CHMP (EMEA/H/C/002315/R/0041). In this part of the SOB, the MAH reanalysed samples of study D4200C00058 to provide a more accurate RET status based on current methodologies which were unavailable at the time of MAA. In total, 17 patients were found to be RET negative with the reanalysis. Two of the RET negative patients were also RAS and BRAF negative, while one was BRAF positive and 14 were RAS positive. Eleven of the RET negative patients received vandetanib during the double-blind treatment and 6 received placebo.

In 73 re-analysed samples median PFS could not be calculated, the number of patients with an event were 44.6% in the RET positive and 23.5% in the RET negative population.

Next, the MAH performed an analysis with the RET positive patients (n=239) including the RET positive patients from study D4200C00058 (n=187) and the newly found RET positive patients from this reanalysis (n=56) while the RET negative patients only include the RET negative patients found by this reanalysis (n=17). Again, median PFS could not be calculated. The number of events was 34.9% in the RET positive group and 9.1% for the RET negative group treated with vandetanib (numbers in placebo group were 56.7% vs 50.0%, respectively). ORR in patients treated with vandetanib was 51.7% in the RET positive group and 18.2% in the RET negative group. In patients who received placebo, in 14.9% a response was reported in the RET positive group, and no objective responses were observed in the 6 RET negative patients. DCR was 86.6% in the RET positive group and 72.7% in the RET negative group treated with vandetanib. In the placebo group these numbers were 67.2 vs 100%, respectively. The number of RET negative patients is very low and conclusions are difficult to draw, but there seems to be some anti-tumour activity in two RET negative, RAS positive tumours. However, results remain inconclusive given the limited data available. As the MAH provided the requested data, this part of the SOB is considered fulfilled.

7. Clinical Safety aspects

7.1. Study D4200C0104

Results

Cumulatively through 10 February 2020, 314 AEs at any grade have been reported in Study D4200C00104 in 35 patients (including both prospectively and retrospectively enrolled patients). A total of 201 AEs were considered to be related to the investigational product. The majority of events (94.6%) were reported as mild to moderate in severity grade.

Treatment-emergent AEs (TEAEs) were reported in 35 patients (87.5%); an overview of patients reporting TEAEs is provided in Table 10. The most commonly reported system organ classes ([SOCs] ≥10.0% of patients) were skin and subcutaneous tissue disorders (55.0%), gastrointestinal disorders (52.5%), investigations (42.5%), infections and infestations (40.0%), metabolism and nutrition disorders (37.5%), general disorders and administration site conditions (35.0%), musculoskeletal and connective tissue disorders (25.0%), vascular disorders (22.5%), renal and urinary disorders (20.0%), nervous system disorders (17.5%), psychiatric disorders (12.5%), blood and lymphatic system disorders (10.0%), eye disorders (10.0%), and respiratory, thoracic and mediastinal disorders (10.0%). Most patients (57.5%) reported mild or moderate severity as the worst TEAE severity they experienced.

A total of 9 patients (22.5%) reported 14 SAEs, of which 4 SAEs (reported in 3 patients [7.5%]) were considered related to Investigational Medicinal Product (IMP): 1 patient experienced moderate QTc prolongation, 1 patient experienced severe diarrhoea, and 1 patient experienced moderate nausea and severe *Clostridium difficile* infection. All SAEs related to IMP resolved following drug interruption. Other SAEs (not related to IMP) included pneumonia, gastroenteritis, cholecystitis, disease progression, bone pain, malignant tumor masses, pyelonephritis, vomiting, and multiple pulmonary aspergillomas. One RET positive patient (2.5%) experienced a SAE of disease progression (not related to IMP) that led to death.

A total of 8 patients (20.0%) had a TEAE leading to treatment discontinuation (whereas 5 patients stopped treatment due to AE as listed in Table 4; data cleaning is ongoing and the action taken for the AE will be corrected for the other 3 patients).

Overall, 96.4% of RET positive patients and 66.7% of RET negative patients experienced TEAEs, and 28.6% and 8.3% patients experienced SAEs in RET positive and negative patients, respectively.

A summary of TEAEs by SOC and preferred term (PT) and RET mutation status is provided in Section 7.1.3.1 of the Addendum to Clinical Overview.

Table 10. Study D4200C00104 overview of treatment-emergent adverse events - Enrolled patients

Parameter	Statistic	Prospective RET +, vandetanib (N=28)	Prospective RET -, vandetanib (N=7)	Retrospective RET -, vandetanib (N=5)	All RET -, vandetanib (N=12)	Overall (N=40)
Patients with any TEAE	n (%)	27 (96.4)	5 (71.4)	3 (60.0)	8 (66.7)	35 (87.5)
Patients with any treatment emergent SAE	n (%)	8 (28.6)	1 (14.3)	0	1 (8.3)	9 (22.5)
Patients with any TEAE leading to death	n (%)	1 (3.6)	0	0	0	1 (2.5)
Patients with any TEAE leading to permanent treatment discontinuation	n (%)	7 (25.0)	1 (14.3)	0	1 (8.3)	8 (20.0)
TEAEs by Grade						
Mild	n (%)	5 (17.9)	0	0	0	5 (12.5)
Moderate	n (%)	11 (39.3)	4 (57.1)	3 (60.0)	7 (58.3)	18 (45.0)
Severe	n (%)	10 (35.7)	1 (14.3)	0	1 (8.3)	11 (27.5)
Life-threatening or Disabling	n (%)	0	0	0	0	0
Death	n (%)	1 (3.6)	0	0	0	1 (2.5)

Note: Subjects with multiple events in the same category are counted only once in that category.
Note: Subjects may fall into more than one category.

Discussion

Numerically, TEAEs and SAEs occurred less often in RET negative versus RET positive patients, although the small sample size of patients with RET negative status hamper the assessment. The reported safety profile in study D4200C00104 does not raise new safety signals.

7.2. Study D4200C00058

Results

The summaries of AEs of the patients with RET status available are reported in Table 11 and Table 12.

Table 11. Study D4200C00058 overview of AEs whilst on randomized treatment - Safety population

					RET -					
	RET + (N=238)		All RET - (N=17)		RAS - BRAF - (N=2)		RAS + (N=14)		BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=66)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Any AEs	171 (99.4%)	60 (90.9%)	11 (100%)	6 (100%)	1 (100%)	1 (100%)	9 (100%)	5 (100%)	1 (100%)	0
Any causally [a] related AE	165 (95.9%)	36 (54.5%)	11 (100%)	4 (66.7%)	1 (100%)	1 (100%)	9 (100%)	3 (60.0%)	1 (100%)	0
Any AEs of CTCAE grade 3 and higher	107 (62.2%)	17 (25.8%)	5 (45.5%)	3 (50.0%)	1 (100%)	0	4 (44.4%)	3 (60.0%)	0	0
Any SAEs (including events with outcome = death)	65 (37.8%)	10 (15.2%)	3 (27.3%)	1 (16.7%)	0	0	3 (33.3%)	1 (20.0%)	0	0
Any SAEs with outcome = death	7 (4.1%)	2 (3.0%)	0	0	0	0	0	0	0	0
Treatment-Related Serious TEAEs	31 (18.0%)	2 (3.0%)	0	0	0	0	0	0	0	0
Any AEs leading to discontinuation	20 (11.6%)	3 (4.5%)	1 (9.1%)	0	1 (100%)	0	0	0	0	0
Any other significant AEs [b]	0	0	0	0	0	0	0	0	0	0

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
Note : Patients with multiple events in the same category are counted only once in that category.
[a] As assessed by the Investigator.
[b] Any AE deemed by the sponsor to be significant.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/ret_aeover2.sas OUT=EXPLO/OUTPUT/ret_aeover2_s_t_i.rtf (13FEB2020 - 17:13)

Table 12. Study D4200C00058 overview of AEs whilst on open label treatment - Open label analysis set

					RET -					
	RET + (N=115)		All RET - (N=11)		RAS - BRAF - (N=1)		RAS + (N=9)		BRAF + (N=1)	
	Vandetanib (N=65)	Placebo (N=50)	Vandetanib (N=7)	Placebo (N=4)	Vandetanib (N=0)	Placebo (N=1)	Vandetanib (N=6)	Placebo (N=3)	Vandetanib (N=1)	Placebo (N=0)
Any AEs	40 (61.5%)	50 (100%)	5 (71.4%)	4 (100%)	0	1 (100%)	4 (66.7%)	3 (100%)	1 (100%)	0
Any causally [a] related AE	20 (30.8%)	46 (92.0%)	1 (14.3%)	3 (75.0%)	0	1 (100%)	1 (16.7%)	2 (66.7%)	0	0
Any AEs of CTCAE grade 3 and higher	16 (24.6%)	28 (56.0%)	4 (57.1%)	1 (25.0%)	0	0	3 (50.0%)	1 (33.3%)	1 (100%)	0
Any SAEs (including events with outcome = death)	12 (18.5%)	14 (28.0%)	4 (57.1%)	0	0	0	3 (50.0%)	0	1 (100%)	0
Any SAEs with outcome = death	0	1 (2.0%)	1 (14.3%)	0	0	0	1 (16.7%)	0	0	0
Treatment-Related Serious TEAEs	5 (7.7%)	7 (14.0%)	0	0	0	0	0	0	0	0
Any AEs leading to discontinuation	1 (1.5%)	3 (6.0%)	0	2 (50.0%)	0	0	0	2 (66.7%)	0	0
Any other significant AEs [b]	0	0	0	0	0	0	0	0	0	0

Columns with Retmutation group (N) values: . are not shown
All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
Note : Patients with multiple events in the same category are counted only once in that category.
[a] As assessed by the Investigator.
[b] Any AE deemed by the sponsor to be significant.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/ret_aeover_ol2.sas OUT=EXPLO/OUTPUT/ret_aeover_ol2_s_t_i.rtf (13FEB2020 - 17:14)

Discussion

Again, the low number of patients in the RET negative group make it difficult to compare with the RET positive subgroup. It seems that vandetanib treatment is at least not more toxic in RET negative patients compared to RET positive patients.

7.3. Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on available data from data from the randomized study D4500C00058, and the observational study OBS14778, showing insufficient activity of vandetanib in patients with no identified RET mutations.

The (Co-)Rapporteur's comments on the DHPC and the draft communication plan are provided in Attachment 2.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent upon receipt of the Commission Decision with the revised SmPC with the changes highlighted to relevant healthcare professionals (healthcare professionals involved in prescribing and handling Of Caprelsa (vandetanib)).

7.4. PSUR cycle

Considering the marketing authorisation will no longer be subject to specific obligations, the CHMP is of the opinion that the already existing entry in the EURD list for vandetanib needs to be amended as follows: the PSUR cycle for the medicinal product should follow a yearly cycle.

8. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

In addition, black triangle and additional monitoring statements are being removed.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

8.1. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Caprelsa (vandetanib) is removed from the additional monitoring list once the conditions have been fulfilled.

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

9. RMP

The MAH did not provide an updated RMP but committed to provide the updated RMP in another variation upon approval of the current type II labelling variation at the next regulatory opportunity.

10. Request for supplementary information 1

10.1. Major objections

Clinical aspects

Not applicable

10.2. Other concerns

Clinical aspects

1. Given the recruitment rates, it seems that including 20-25 RET negative patients will not be feasible in a reasonable time frame. It can therefore be supported to close study D4200C00104, but the SOB cannot be considered fulfilled based on the raw data presented. In order to properly assess the data, this should include the **final** clinical study report and the MAH is requested to provide the final CSR within the current procedure.

11. Assessment of the responses to the request for supplementary information 1

11.1. Major objections

Clinical aspects

None.

11.2. Other concerns

Clinical aspects

Question 1

*Given the recruitment rates, it seems that including 20-25 RET negative patients will not be feasible in a reasonable time frame. It can therefore be supported to close study D4200C00104, but the SOB cannot be considered fulfilled based on the raw data presented. In order to properly assess the data, this should include the **final** clinical study report and the MAH is requested to provide the final CSR within the current procedure.*

Summary of the MAH's response

The MAH is providing the Agency with the final Clinical Study Report (CSR) of study OBS14778 (also named study D4200C00104) in accordance with the timelines agreed in June 2020 in the frame of this procedure. The main information for the CSR will be reported below the summary of the Applicant's response.

The CSR conclusion is that, although RET negative patients showed a lower objective tumor response than RET positive patients, DCR and PFS were comparable between both groups. There was a slightly higher rate of AEs and serious TEAEs among the RET positive patients compared to the RET negative. Overall, reported AEs are consistent with the known safety profile of vandetanib. Considering the results and limitations of this observational study, the positive benefit/risk profile of vandetanib already established in RET positive patients is confirmed and is considered acceptable in RET negative patients with unresectable locally advanced or metastatic MTC. Overall, the benefit-risk balance of vandetanib remains thus positive in the currently approved indication of use, regardless of the RET status.

In addition to the CSR, as proposed in December 2018 (in the frame of Response to RSI dated 18-Oct-2018 - procedure no. EMEA/H/C/002315/II/0028), the MAH also reviewed the benefit-risk ratio of vandetanib in the RET negative patient population, considering the evaluation of treatment efficacy and safety of vandetanib in RET negative patients based on compiled data compared to patients not treated with vandetanib. The MAH assesses that the benefit-risk balance of vandetanib is positive in the currently approved indications of use regardless of the RET status based on the B/R analysis below.

Medical need and important alternative

Epidemiology: MTC is a rare cancer

Thyroid cancer was responsible for 586,202 new cases and 44,000 deaths in 2020 (1). The global incidence rate is 3-fold higher in women than men and varies widely from country to country, with the highest figures (per 100,000 person-years) being reported in Micronesia/Polynesia (18.5), North America (18.4) Eastern Asia (17.8), Southern Europe (16.5) and Australia/New Zealand (15.3). Mortality rates are also higher in women (0.5) than men (0.3) with highest figures reported in North America (6.3), Australia/New Zealand (5.6), Eastern Asia (5.4) and Southern Europe (5.1) (1).

While the incidence of differentiated thyroid cancer has regularly increased during the last three decades, the incidence of medullary thyroid cancer (MTC) remains quite stable, accounting for only 2.1% of thyroid cancers (2, 3). MTC is a relatively indolent tumor with a 10-year overall survival (OS) rate of approximately 75% to 80% (4). However, patients with unresectable, locally advanced or metastatic MTC have limited therapeutic options, and their 10-year OS rate is not exceeding 40% (4).

Molecular alterations in MTC: RET mutation negative MTC is very rare

MTC is a rare form of neuroendocrine tumor which originates from calcitonin-producing parafollicular C cells (3). The majority (75%) of cases occur sporadically and in remaining 25% cases, it is inherited through germline mutation. Almost all patients with inherited MTC have germline mutations in proto-oncogene encoding the tyrosine kinase receptor rearranged during transfection (RET). This results in constitutive activation of the RET tyrosine kinase. In sporadic MTC, about half of the mutations occur in *RET* gene which is associated with more aggressive disease and a worse prognosis (3). *RET* mutation negative MTC patient population is very rare. Sporadic MTC usually occurs between the age of 40 and 60 years (5).

Management of MTC

Demonstration of calcitonin (CTN) expression is mandatory for the diagnostic of MTC (2). Determination of carcinoembryonic antigen (CEA) levels may also be useful. Monitoring of both CTN and CEA monitoring is recommended in patients with MTC.

Owing to limited responsiveness to non-surgical treatments (radioactive iodine therapy, external radiotherapy, and conventional chemotherapy), targeted therapy with tyrosine kinase inhibitors (vandetanib, cabozantinib) represent an important therapeutic option for first-line treatment of patients with advanced MTC (6).

International guidelines

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Thyroid Carcinoma version 3.2020 (7) recommends the following:

- Surgical resection of MTC is the primary treatment.
- For unresectable, recurrent or symptomatic and progressing disease consider systemic therapy:
  - Preferred regimens are vandetanib (Category 1), cabozantinib (Category 1), selpercatinib (if *RET*-mutation positive), pralsetinib (if *RET*-mutation positive); vandetanib or cabozantinib can be used as first-line or second-line therapy.
  - In certain circumstances pembrolizumab can be considered.

The European Society for Medical Oncology (ESMO) Clinical Practice Guideline for Thyroid Cancer (2) recommends the following:

- Surgical resection of MTC is the primary treatment.
- For symptomatic and advanced/metastatic MTC, first-line therapy includes vandetanib [I, A] and cabozantinib [I, A]. Choice of treatment depends on potential toxicity to each patient.
- In patients with RETM918T or RAS-mutant MTC, cabozantinib offers significant PFS and OS advantages over wild-type MTC [II, C].
- There is little evidence to support the use of either chemotherapy or radionuclide therapy in patients with MTC, although either might be considered when multikinase inhibitors are contra-indicated.
- There is currently no evidence supporting the value of routine screening of MTC patients for somatic *RET* mutations. However, if treatment of advanced MTC with selective *RET* inhibitors is planned, *RET* testing is needed to individualize therapy.

The American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (8) recommends the following:

- Surgical resection of MTC is the primary treatment.
- In patients with significant tumor burden and symptomatic or progressive metastatic disease according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria, vandetanib or cabozantinib can be used as single-agent first-line systemic therapy (Grade A recommendation).

Recent literature

In addition, recently published following studies (including real-world evidence) support therapeutic position of vandetanib in the treatment of MTC.

Study Title	Findings
Ramos et al. Long-term follow-up and safety of vandetanib for advanced medullary thyroid cancer (Endocrine. 2021;71(2):432-442. (9)	• Retrospective analysis of 76 patients (17.9% with *RET* mutation) with metastatic MTC treated with vandetanib followed for up to 11 years at Gustave Roussy Institute • Median treatment duration 17.6 months and median PFS 22.7 months • In 21 of 76 patients, the median duration of vandetanib treatment was 68.1 months which was considered as long-term use. • For long-term vandetanib users, ORR was 85.7%, median time to best response 27.8 months, median duration of response 70.4 months and median PFS 73.2 months. • 28 patients (36.8%) had dose reductions and 18 (23.7%) discontinued vandetanib due to toxicity. Main adverse events were folliculitis (73.7%), diarrhea (56.6%), asthenia (53.9%), hypertension (34.2%), and QTc prolongation (30.3%). • Among long-term users (21 patients received vandetanib for more than 48 months), main adverse events were QTc prolongation (n=5), diarrhea (n=2), renal failure (n=2), acute pancreatitis (n=2), heart failure (n=1), posterior encephalopathy (n=1), and basocellular carcinoma (n=1).
Koehler et al. Real-world efficacy and safety of cabozantinib and vandetanib in advanced medullary thyroid cancer (Thyroid. 2021;31(2):459-469. (10)	• Retrospective analysis of 48 patients with advanced MTC (13% with known *RET* mutation) treated with vandetanib (n=41) or -cabozantinib (n=7) in first-line setting (1L). • Median treatment duration 21 months with vandetanib versus 10 months with cabozantinib • Median PFS was 12 months with vandetanib versus 9 months with cabozantinib in 1L. • ORR and DCR in 1L were 24% and 63% with vandetanib versus 0% and 43% with cabozantinib • Median OS was 54 months with vandetanib but was not available for cabozantinib • Dose reductions were required in 32% of patients treated with vandetanib 1L versus 57% treated with cabozantinib 1L • 9 (19%) patients treated with vandetanib and 12 (52%) treated with cabozantinib discontinued treatment for TEAEs. Main TEAEs with vandetanib were diarrhea (40%), skin rash (38%), fatigue (28%), QTc prolongation (21%). Main TEAEs with cabozantinib were diarrhea (57%), loss of appetite/ loss of weight (56%), fatigue (39%), hand-foot syndrome (30%).
Kreissl et al. Efficacy and safety of vandetanib in progressive and symptomatic medullary thyroid cancer: Post-hoc analysis from the ZETA trial. J Clin Oncol. 2020;38:2773-2781.(11)	• This was a post-hoc analysis of ZETA phase III study. Of 331 patients with unresectable locally advanced or metastatic MTC, 184 had symptomatic and progressive disease at baseline. • Median PFS was 21.43 months with vandetanib versus 8.4 months with placebo (HR 0.43; 95% CI: 0.28 to 0.64; *P* <0.0001). • ORR was 37% with vandetanib versus 1.8% with placebo (P<0.001) • OS (HR=1.08; 95% CI: 0.72 to 1.61; *P* <0.71) and time to worsening of pain (HR=0.67; 95% CI 0.43 to 1.04; P=0.07) were similar in magnitude to the overall population. • The observed adverse events were consistent with the known safety profile of vandetanib.

Although findings of above studies corroborate with that of ZETA study, none of these studies have sub-group analysis available for efficacy and safety in RET negative MTC patients.

Newly identified information on efficacy and/or effectiveness

Two new studies evaluating the activity and safety of vandetanib in RET negative patients have become recently available and are summarized below:

The non-interventional post-authorization safety study (PASS) OBS14778: International Observational Study to Evaluate the Benefit/Risk of Vandetanib (Caprelsa™) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer (CSR provided)

Methods: OBS14778 was a multinational, multicenter, non-interventional study conducted to fulfill the post authorization specific obligation linked to the conditional marketing authorization of vandetanib. It was aimed at confirming the benefit/risk of vandetanib 300 mg in real-life conditions, both in rearranged during transfection (RET) mutation negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. Due to slow recruitment (owing to very rare availability of RET negative patients and lack of RET mutation status evaluation prior to treatment in routine clinical practice) and as agreed with the EMA, the protocol was amended to also allow retrospective enrollment of RET negative patients at study sites. The prospective and retrospective data collection was also enriched with patients from the randomized phase III study D4200C00058 who had an initially unknown RET status and were subsequently classified RET positive or RET negative following re-analysis of archived tumor samples.

The primary outcome was the objective response rate (ORR) based on RECIST criteria. Other outcomes included, disease control rate, progression-free survival (PFS), CTN and CEA serum levels and toxicities. There was no central review of imaging in the prospective and retrospective cohorts.

Results: Overall, 97 patients were enrolled (40 RET positive or RET negative patients recruited prospectively, 10 RET negative patients recruited retrospectively, 47 patients with RET status newly determined from Study D4200C00058). Of them, 91 patients were exposed to vandetanib and 75 patients were evaluable for effectiveness. Of these 75 patients, 55 were RET positive and 20 were RET negative, 47 (63%) were females, 63 (84%) had prior thyroidectomy and 62 (84%) had distant metastasis at enrollment.

- Median duration of vandetanib treatment was 23.4 months in RET positive patients versus 27.6 months in RET negative patients.
- All patients were evaluable for tumor response. Of the 55 RET positive patients, 2 (3.6%) had a confirmed complete response, 21 (38.2%) had a confirmed partial response and 24 (43.6%) had a confirmed stable disease, corresponding to an overall response rate (ORR) of 41.8% and a disease control rate (DCR) of 85.5%. Of the 20 RET negative patients, one patient (5%) had a confirmed partial response and 17 patients (85%) had a confirmed stable disease, corresponding to an ORR of 5% and a DCR of 90%.
- During a median follow-up of 27.8 months, 44 patients had disease progression (32 RET positive, 12 RET negative) and 6 patients died (4 RET positive, 2 RET negative). Median PFS was 24.6 months in both RET positive and RET negative patients. At 12 months, 27% of RET positive patients and 23% of RET negative patients were estimated to have progressed; at 24 months, 50% of RET positive patients and 41% of RET negative patients were estimated to have progressed. Overall survival was not mature.
- During the treatment with vandetanib, a decrease in calcitonin was achieved at faster rate in RET positive than RET negative patients. There was also a decrease in carcinogenic antigen (CEA) which was comparable in both RET positive and RET negative patients.
- Overall, 91 patients (64 RET positive, 27 RET negative) were exposed to at least one dose of vandetanib. Reported safety findings were in line with known safety profile of vandetanib. A slightly

higher percentage of RET positive patients compared to RET negative patients experienced treatment emergent adverse events (TEAEs, 98.4% versus 88.9%) and serious adverse events (SAEs, 31.3% versus 22.2%). The most commonly reported treatment emergent AEs included diarrhea (56%), rash (31.9%), and hypertension (23.1%). Grade 3-4 adverse events were reported by 36 patients (27 RET positive, 9 RET negative) and were mainly diarrhea (n=4), rash (n=4), disease progression (n=2), dysphagia (n=2) and QTc prolongation (n=2). Vandetanib was discontinued due to adverse events in 14 patients (15.4%), mainly due to skin toxicity (n=4), nausea (n=2) and chronic kidney disease (n=2). Four patients experienced an adverse event leading to death (disease progression, n=2; aspiration, n=1, acute cardiac failure with arrythmia, n=1).

Conclusions: Considering the limitations of this observational study, the positive benefit/risk profile of vandetanib already established in RET positive patients in a pivotal phase III study is confirmed and is considered acceptable in RET negative patients with unresectable locally advanced or metastatic MTC. Overall, the benefit-risk balance of vandetanib remains thus positive in the currently approved indication of use, regardless of the RET status.

Kim M, Yoon JH, Ahn J et al. Vandetanib for the Management of Advanced Medullary Thyroid Cancer: A Real-World Multicenter Experience. Endocrinol Metab 2020;35(3): 587-594 (12)

Background: Since only limited data regarding its use outside clinical trials are available, this study aimed to evaluate the efficacy and safety of vandetanib in patients with advanced MTC in routine clinical practice in Korea.

Methods: In this multicenter retrospective study, 12 patients with locally advanced or metastatic MTC treated with vandetanib at four tertiary hospitals in Korea were included and treated with vandetanib at a starting dose of 300 mg/day. The primary outcome was the objective response rate (ORR) based on RECIST criteria. The progression-free survival (PFS), overall survival (OS), and toxicities were also evaluated.

Results: All 12 patients had prior thyroidectomy. Of them, 8 patients were RET negative, one patient was RET positive and 3 patients were RET unknown. Eleven patients (92%) had distant metastasis and 10 (83%) had disease progression at enrollment.

- Median duration of vandetanib treatment was 25.3 months.
- All patients were evaluable for tumor response. Partial response (PR) was observed in five patients (42%) and seven patients (58%) had stable disease which lasted ≥24 weeks in five of them (83%). The ORR was thus 42% and the disease control rate (CR+PR+SD lasting ≥24 weeks) was 83%.
- During a median follow-up of 31.7 months, disease progression was seen in five patients (42%) and two patients died due to disease progression. The median PFS was 25.9 months, while the median OS was not reached.
- A decrease by ≥50% in serum CTN and CEA levels which was maintained for at least 4 weeks was observed in 8 patients (67%).
- Most common grade 3-4 adverse events were rash (n=4, 33%), diarrhea (n=3, 25%), mucositis (n=2, 17%) and QTc prolongation (n=2, 17%). Four patients had vandetanib dose reductions and 6 patients had dose interruptions. Vandetanib was discontinued in two patients due to skin toxicity.

Conclusion: Consistent with the phase III trial, this study which enrolled a majority of RET negative patients (67%) confirmed the efficacy of vandetanib for advanced MTC in terms of both ORR and PFS in the real-world setting. Vandetanib was well tolerated in the majority of patients, and there were no fatal AEs.

Characterisation of benefits

Based on the data presented, vandetanib is active in the treatment of unresectable, metastatic and advanced MTC. Findings from Study OBS14778 suggests that RET negative patients treated with vandetanib have a disease control rate and a PFS comparable to RET positive patients. The ORR was lower in RET negative patients but there was no central review of imaging in the prospective and retrospective cohorts.

Further, the study by Kim et al, 2021 which enrolled in majority *RET*-negative patients with advanced MTC showed an ORR of 42%, and a disease control rate of (83%) and a median PFS of 25.9 months (12).

The available new information suggests that vandetanib is effective regardless of *RET* status.

Integrated benefit-risk analysis for approved indications

Methodology

A structured systematic approach was applied to vandetanib in treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease with focus on RET negative patient population.

This assessment is based on labeling documents, sponsored clinical trials and post-marketing data especially the Study OBS14778 in order to evaluate the benefit-risk profile of vandetanib in RET negative population. Results presented were retrieved from the most up-to-date information from Study OBS14778 regarding the clinical efficacy/effectiveness and all sources of information regarding safety of vandetanib.

The data presentations are based on a descriptive framework developed for benefit-risk decision making in drug development and post-approval settings. The approach is meant to facilitate identification of critical issues regarding benefits and risks and improve transparency of the assumptions used by the MAH to evaluate the benefit-risk profile.

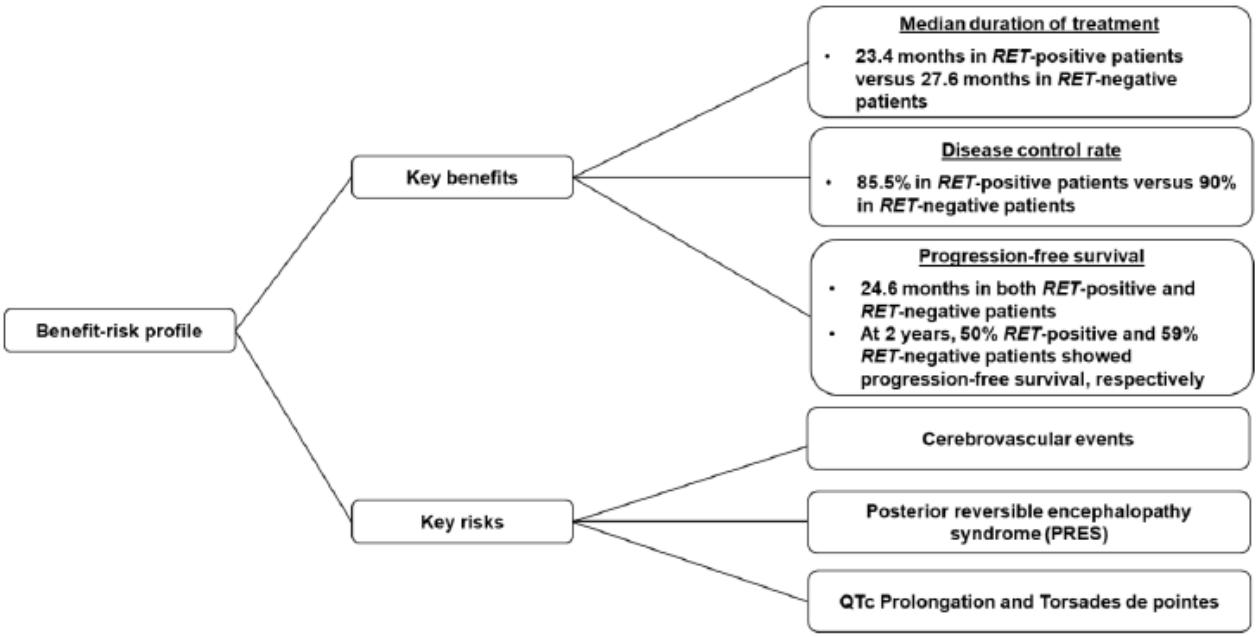
The steps from the framework were used to define the main problem to be addressed, i.e. the context in which a decision had to be made, to determine key benefits and key risk outcomes to construct a value tree, and to identify the data sources. The descriptive framework emphasizes relevant metrics to enable a comprehensive discussion of benefit-risk while providing complete transparency into the origin and format of the source data.

Key benefits are defined by favorable effects that contribute importantly to the overall benefit risk evaluation and that are important for the patient (clinically important, relevant, intense or durable). The key risks are defined by unfavorable effects that contribute importantly to the overall benefit-risk evaluation, and not necessarily include all important risks of the drug. The selection was based on medical judgment (clinically important risks because of their severity, frequency, duration, toxicity, irreversibility, or inability to be predicted or prevented). They may also include those that are considered for risk minimization activity beyond labeling.

Key benefits and risks of vandetanib were organized in a hierarchic manner to construct a "Value Tree". The data presentation consists on a descriptive benefit risk framework table and a "Value Tree".

Benefit-risk evaluation

A value tree providing a concise, visual representation of the key benefits and key risks considered in the overall benefit risk assessment is presented below.



The Benefit Risk Assessment table presented below provides an overall summary and assessment of the key decision factors that were considered for the benefit risk assessment of vandetanib in treatment of aggressive and symptomatic MTC in RET negative patients with unresectable locally advanced or metastatic disease.

	Evidence and uncertainties	Conclusion and reasons
Analysis of condition	MTC is a rare cancer (2.1% of all types of thyroid cancers). Of the the overall MTC cases, only 10% patients are *RET*-mutation negative, making it very rare population. In routine clinical practice, *RET* mutation status is rarely evaluated prior to the treatment.	There is paucity of information on efficacy of vandetanib in *RET*-negative patient population owing to rarity of this population.
Current treatment options	Surgery resection of MTC is the primary treatment. For unresectable, recurrent or symptomatic and progressing MTC, preferred options are vandetanib and cabozantinib as per international guidelines There is no head to head study comparing vandetanib versus cabozantinib	Vandetanib is an effective first-line treatment option for unserectable, advanced metastatic MTC.
Benefits	In *RET*-negative patients, vandetanib treatment showed comparable duration of treatment, disease control rate and PFS compared to *RET*-positive patients. Limitations: There was a low number of *RET*- patients enrolled and no central review of the response rate.	Based on the findings and study limitations, efficacy of vandetanib is acceptable in the *RET*-negative patients.
Risks and risk management	There was also a slightly higher rate of AEs and serious TEAEs among the *RET*-positive patients compared to the *RET*-negative patients but adverse events were in agreement with the known safety profile vandetanib. No new safety findings was identified in *RET*-negative patients.	Acceptable safety profile was observed in *RET*-negative patients with MTC. Current risk management strategy is appropriate to minimize the risks.

Benefit-risk conclusion

Considering the results and limitations of the observational study OBS14778 and all available information through literature, the positive benefit/risk profile of vandetanib already established in RET positive patients is confirmed and is considered acceptable in RET negative patients with unresectable locally advanced or metastatic MTC. Overall, the benefit-risk balance of vandetanib remains thus positive in the currently approved indication of use, regardless of the RET status according to the MAH.

As a consequence, and taking into account the lack of alternatives for RET negative patients, the MAH considers now that the provisions relative to the RET mutation status embedded in section 4.4 'Special warnings and precautions for use' should be modified as follows:

"*Rearranged during transfection (RET) status*

Patients without RET mutation may have a decreased benefit from vandetanib treatment and the benefit/risk balance for this group of patients may therefore differ from that of the group with RET mutations. For patients whose RET mutation status could be negative, a possible lower benefit should be taken into account before individual treatment decisions and the use of vandetanib should be carefully considered because of the treatment related risks. ~~Therefore, RET mutation testing is recommended. When establishing RET mutation status, tissue samples should be obtained if possible at the time of initiation of treatment rather than at the time of diagnosis~~ (see sections 4.1 and 5.1)."

In addition, the section 5.1 'Pharmacodynamic properties' of the SmPC is proposed to be modified to include the final results of the data analysis (instead of the interim results previously proposed).

To conclude, the MAH now considers that the SOB001 is fulfilled and can be lifted from the Marketing Authorisation in order to convert it from a conditional to a standard MA. The RMP of vandetanib will be updated in a second step.

References

1. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 0:1-41.
2. Filetti S, Durante C, Hartl D, Leboulleux S, Locati L, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2019;30:1856–1883.
3. Spielman D, Badhey A, Kadakia S, Inman J, Ducic Y. Rare Thyroid Malignancies: an Overview for the Oncologist. Clinical Oncology. 2017; 29(5):298-306.
4. Roman S, Lin R, Sosa J. Prognosis of medullary thyroid carcinoma. Cancer. 2006; 107(9):2134-2142.
5. Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: A 10-year follow-up study. Journal of Clinical Endocrinology and Metabolism. 2008; 93(3):682-687.
6. Valerio L, Pieruzzi L, Giani C, Agate L, Bottici V, Lorusso L, et al. Targeted therapy in thyroid cancer: state of the art. Clin Oncol (R Coll Radiol). 2017;29:316-24.
7. NCCN Clinical Practice Guideline for Thyroid Carcinoma version 3.2020.2021 Feb 02. [cited 2021 Mar 26]. Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
8. Wells S, Asa S, Dralle H, Elisei R, Evans D, Gagel R, et al.Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. Thyroid. 2015;25:567-610.
9. Ramos H, Hecht F, Berdelou A, Borget I, Leboulleux S, Baudin E, et al. Long-term follow-up and safety of vandetanib for advanced medullary thyroid cancer. Endocrine. 2021; 71(2):434-442.
10. Koehler V, Adam P, Frank-Raue K, Raue F, Berg E, Hoster E, et al. Real-World Efficacy and Safety of Cabozantinib and Vandetanib in Advanced Medullary Thyroid Cancer. Thyroid. 2021;31(2):459-469.
11. Kreissl M, Bastholt L, Elisei R, Haddad R, Hauch O, Jarzab B, et al. Efficacy and safety of vandetanib in progressive and symptomatic medullary thyroid cancer: Post-hoc analysis from the ZETA trial. Clin Oncol. 2020;38:2773-2781.

12. Kim M, Yoon J, Ahn J, Jeon M, Kim H, Lim D, et al. Vandetanib for the Management of Advanced Medullary Thyroid Cancer: A Real-World Multicenter Experience. Endocrinol Metab 2020;35:587-594.

The MAH also submitted final CSR for study OBS14778 (D4200C00104) in the response. For reference, the main findings will be presented below.

Methods – analysis of data submitted

Milestones

Milestone	Planned date[a]	Actual date	Comments
First IEC approval	Not Available[b,c]	12 August 2013	All milestones reflect delays due to recruitment challenges related to a relatively low prevalence of RET mutation negative patients in the locally advanced and metastatic MTC population (approximately 10% [1]), and due to medical practice standards (ie, RET mutation status not being evaluated prior to treatment). These considerations were the basis for the study revisions negotiated with EMA and incorporated in Amended Protocol 02 (see Section 8).
Start of data collection	Q1 2013	17 February 2014	
End of data collection	Q3 2015	10 July 2020	
Registration in the EU PAS register	Not Available[c]	11 May 2013	
Date of last patient last visit	Q3 2015	18 June 2020	
Database lock	Q3 2015	17 December 2020	
Interim report	N/A	16 July 2020	
Last IEC approval	Not Available[b,c]	02 November 2020	
Final report of study results	Q4 2015	09 April 2021	

a The planned dates listed below are the originally planned dates from the original protocol (dated 11 Mar 2013) initiated by AstraZeneca.
b See Table 13 in Annex 2 for a full list of Independent Ethics Committee (IEC) approvals.
c Not Available: Study D4200C00104 (OBS14778) was initiated under the Sponsorship of AstraZeneca; in 2015, territory rights for the clinical development and commercialization of vandetanib were granted from AstraZeneca to Genzyme Corporation. Hence, historical data on EU PAS registration cannot be provided.

OBS14778 was initiated as Study D4200C00104 (first patient in 17 February 2014) under the Sponsorship of AstraZeneca. Territory rights for the clinical development and commercialization of vandetanib were granted in 2015 from AstraZeneca to Genzyme Corporation. AstraZeneca had identified the participating sites based on their contemporary use of Caprelsa. All appropriate sites had a remote Pre-Study Site Visit and hence additional information on sites cannot be provided. Because the D4200C00104 study recruited very slowly (rarity of RET negative patients with MTC, and lack of RET mutation status evaluation prior to treatment in routine clinical practice), it was agreed with EMA (Amended Protocol 02, issued on 21 June 2019) that the study population would be enriched with 2 other population of patients:

- Firstly, retrospective RET negative patients (only) were allowed to be enrolled in the study.
- Secondly, both groups (RET positive and RET negative) would be pooled with patients issued from the randomized Phase 3 study (D4200C00058): the RET mutation unknown patients treated with vandetanib were re-analyzed based on archived tumor samples. Patients recognized as RET negative and RET positive would enrich the respective groups.

In addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC with a negative RET mutation status and treated or not with vandetanib were allowed to enrich both prospective and retrospective cohorts. The protocol was amended accordingly on 21 June 2019.

Objectives

- To determine the Objective Response Rate (ORR) for patients treated with vandetanib who were RET mutation positive and patients treated with vandetanib who were RET mutation negative.

- To determine the Disease Control Rate (DCR) for patients treated with vandetanib who were RET mutation positive and patients treated with vandetanib who were RET mutation negative.
- To assess the duration of response and time to response for patients treated with vandetanib who were RET mutation positive and patients treated with vandetanib who were RET mutation negative.
- To explore the clinical outcomes (including, but not limited to, PFS and ORR) among RET mutation negative patients not treated with vandetanib.
- To evaluate the incidence of QT (the interval between Q and T on electrocardiogram [ECG]) interval corrected for heart rate (QTc) prolongation and associated risks for QTc prolongation in patients receiving vandetanib who were RET mutation positive and RET mutation negative. In addition, the incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation of vandetanib was assessed.
- To compare PFS for patients treated with vandetanib who were RET mutation positive to patients treated with vandetanib who were RET mutation negative.

Protocol amendments

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 February 2016	Throughout the entire protocol. See Amended protocol 02 [14.2] for a full description	The protocol was updated to reflect Genzyme assumption of responsibility for the study from AstraZeneca.	Genzyme assumed responsibility for the study from AstraZeneca in 2015.
2	21 June 2019	Most sections of the protocol were affected. A full description is provided in Amended-protocol 02 [Protocol amendment summary of changes]	Retrospective data collection was added as a source of data for the study. The retrospective data collection includes the following: • Retrieval of more RET mutation negative patients by adapting the inclusion and exclusion criteria for retrospective data collection (eg, no ICF, no age restrictions, a determination of RET mutation negative status independent from vandetanib treatment initiation [administration start date]). • An extended recruitment period into the past (before study start). In addition, the sample size was revised and the provision for inclusion in the statistical analysis of patient data from Study D4200C00058.	Issued to allow the inclusion of retrospective RET mutation negative patients treated with vandetanib, within involved centers and potential new centers. These changes were motivated by the scarcity of RET mutation negative patients for recruitment and low use of RET status determination in clinical practice.

ICF: informed consent form; RET: rearranged during transfection.

Study design

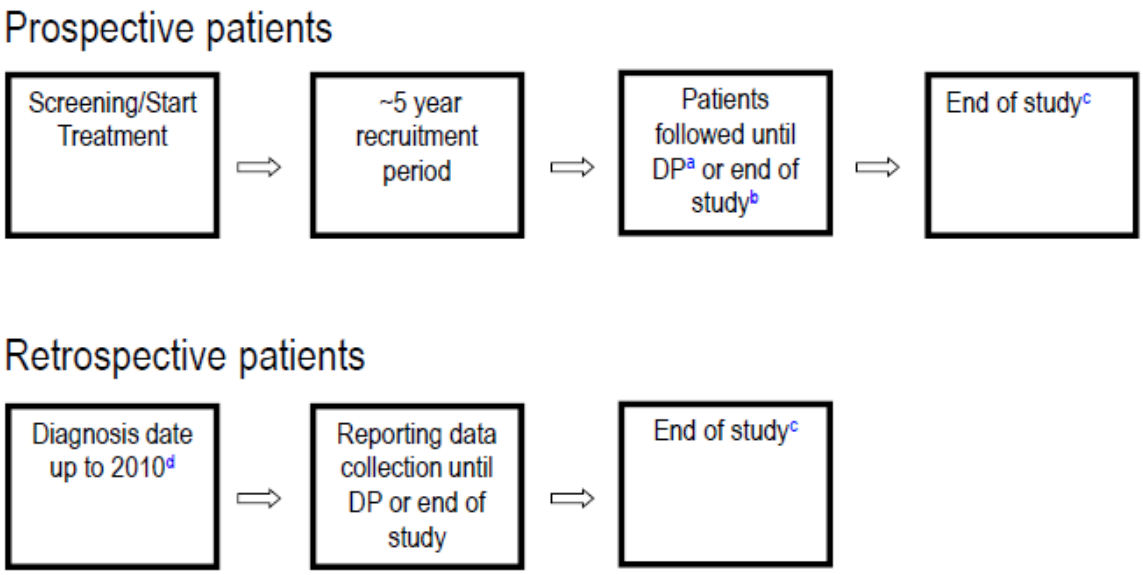
This was a prospective multinational, multicenter, noninterventional (observational) study of RET positive and RET negative patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC treated with Caprelsa (vandetanib). Because recruitment of RET negative patients was difficult, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC treated or not with vandetanib and who were RET mutation negative were also retrospectively recruited at study sites. In addition, a total of 47 patients from the pivotal study D4200C00058 with re-analyzed RET status (either positive or negative) were included, as described below.

The decision to prescribe vandetanib was made independently of the enrollment into this study and was in line with the respective (local) prescribing information.

The study was observational, meaning that vandetanib treatment initiation should have never been delayed to meet any inclusion criteria of the study. Similarly, performing interventions on the patients that were specific for the study and would not have been carried out in the "real-life" setting was not permitted (eg, a biopsy). European countries where vandetanib is on the market (from 2012) participated in the study.

Data collection and reporting were performed until objective progression, or until the end of study (whichever occurred first). For prospective patients included in OBS14778, the end of study was defined as 14 months after the last prospective patient was enrolled in the study and when at least 10 events in each treatment group had been observed. If all patients had progressed prior to 14 months after the last patient was recruited, the study was to stopped. The minimum follow-up time period of 14 months for the prospective arm was considered appropriate because approximately 80% of patients who had an objective response in a pivotal Phase 3 study achieved their response within 14 months of starting vandetanib. The study design is summarized in Figure 2.

Figure 2. Study flow chart



a DP = Disease progression

b Whichever occurs first

c End of study was defined as 14 months after the last prospective patient had been enrolled in the study and when at least 10 events in each treatment group had been observed. If all patients had progressed prior to 14 months after the last patient was recruited, the study was stopped.

d Diagnosis could be as early as 1995-2000, but the centers were requested to search for RET negative MTC patients in their databases and consider recruitment using 2010 as a cutoff, without any limitation for the date of diagnosis.

In addition to patients prospectively and retrospectively enrolled at study sites in OBS14778, patient data from study D4200C00058 were included in the final analysis of OBS14778. Study D4200C00058 was an international, randomized, double-blind, placebo-controlled, multicenter, Phase 3 study designed to assess whether vandetanib 300 mg daily improves PFS compared to placebo in patients with unresectable locally advanced or metastatic MTC. Data for patients who were categorized as RET mutation "unknown" and "negative" in the original analysis of D4200C00058 had their archived biopsy samples reanalyzed to categorize the patients as RET mutation positive or negative. Patients who remained with an "unknown" mutation status after reanalysis were not pooled with patients from OBS14778.

The study began with first patient in on 17 February 2014 and ended with last patient out on 18 June 2020. Prospective recruitment lasted from Q1 2014 through Q1 2020; retrospective recruitment started in Q4 2019 and lasted until Q2 2020. The study was terminated on 10 July 2020.

All prospective participants were followed when on treatment for at least 14 months provided it was considered appropriate for a patient to remain on treatment in the opinion of the Investigator. In any case, all included patients (prospective and retrospective) were followed for data collection until death, loss of follow-up, or end of the study.

Study participants

For prospective patients, once vandetanib was launched in the country and the participant site had the appropriate local approvals, the Investigator systematically identified and invited to participate in the study every consenting patient who fulfilled inclusion criteria and exclusion criteria. The recruitment of patients was centrally controlled by the study team through the Web-based Data Capture (WBDC) system.

For retrospective patients, the sites searched through their own database for MTC patients, reviewed the records using 2010 as a recruitment cutoff without any limitation for the date of diagnosis, identified all RET mutation negative patients and included them into the study (unless there was a contract with another company for a clinical trial that precludes this).

Inclusion criteria were:

1. Signed informed consent for prospective patients (a waiver was requested for retrospective patients).
2. Male or female aged 18 years or above for prospective patients. No age restriction for retrospective patients.
3. Histological diagnosis of MTC (for retrospective patients [prevalent MTC patients] diagnosis could be as early as possible, without any limitation for the date of diagnosis).
4. Patients with symptomatic and aggressive sporadic MTC, who had unresectable, locally advanced/metastatic disease
5. Measurable disease:
    - Assessment confirmed within the 12 weeks before start of treatment, and
    - Defined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1: at least 1 lesion, not irradiated, that could be accurately measured as ≥10 mm in the longest diameter (except lymph nodes which had short axis ≥15 mm) with computed tomography or magnetic resonance imaging and which was suitable for accurate repeated measurements. Measurable lesions with calcifications were not assessed as target lesions unless no other measurable lesion was available.
    - In patients with known definite RET mutation status (positive or negative).
        - For prospective patients prescribed vandetanib: positive or negative;
        - For prospective patients not prescribed vandetanib: negative;
        - For retrospective patients prescribed or not prescribed vandetanib: negative;
        - For prospective patients: RET mutation status was determined from a tumor sample obtained within 18 months prior to enrollment. It was strongly recommended that a tissue sample obtained within 6 months prior to enrollment was used. For retrospective patients: RET mutation negative mutation status could have been determined within 18 months before or after start of treatment (with vandetanib or another drug). In case of retrospective patient treated with another drug, the patient was supposed to be treated with vandetanib at any time
6. For prospective patients newly prescribed vandetanib 300 mg, the prescription was issued according to marketing authorization and following the vandetanib SmPC. The starting dose could have been

reduced to 200 mg in patients with moderate renal impairment. For retrospective patients, the prescription may or may not have been issued according to the SmPC.
7. The prescription of the medicinal product was clearly separated from the decision to include the patient in the non-interventional study.

Exclusion criteria were:

1. Current or planned inclusion/participation in a clinical trial, not applicable for retrospective patients.
2. Patients already receiving vandetanib or who had received vandetanib for their MTC before the study first visit; not applicable for retrospective patients.
3. Contraindications according to the vandetanib SmPC (not applicable for retrospective patients and for patients who did not receive vandetanib):
    - Patients with a QTc interval over 480 msec;
        - Congenital long QT syndrome
        - Concomitant use of vandetanib with the following medicinal products known to also prolong the QT interval and/or induce Torsades de pointes: arsenic, cisapride, erythromycin intravenous, toremifene, mizolastine, moxifloxacine, Class IA and III antiarrhythmics
    - Pregnant or breastfeeding;
    - Hypersensitivity to the active substance or to any of the excipients;
    - Severe renal impairment;
    - Serum bilirubin greater than 1.5 × the upper limit of reference range;
    - Potassium, magnesium, or calcium outside the normal laboratory range.

RET mutation status

For patients prospectively or retrospectively enrolled in OBS14778, the assay to determine mutation status will be done or may have been done (in case of retrospective patients) in certified laboratories and must be based on one of these 3 tests:

- Sequencing
- PCR including ARMS methodology
- Comparative genomic hybridization (CGH)

For this study, the criteria for definition of the RET status is as follows:

- If mutation is present in M918T (exon 16) or any other additional exon tested where RET mutations have been described (10, 11, 13 to16), then the patient is RET mutation positive.
- If mutation is absent in M918T (exon 16), and in any of the other additional exons where RET mutations have been described (10, 11, 13 to 16), then the patient is RET mutation negative.

For patients in study D4200C00058 in the original analysis, RET mutation status was determined by AstraZeneca's Tissue Bank Reception (Alderly Park, Macclesfield, Cheshire United Kingdom) by sequencing the 6 most commonly mutated exons in MTC (exons 10, 11, 13, 14, 15, and 16) and by evaluating for the M918T mutation using an amplification refractory mutation system (ARMS) analysis. Based on the assay technology available at the time the study was run, 56.5% of patients were found to be RET positive, 2.4% were RET negative, and 41.1% had an unknown RET mutation status due to the limitations of the assay.

To more reliably determine the true mutation status for the patients recruited in the original study, an extensive molecular analysis of the MTC tumor samples was performed for patients with adequate sample material available who had a RET mutation unknown or negative status in the original analysis. For this reassessment of study D4200C00058 samples, histology slides of residual tumor tissue from the clinical

study were reviewed and tumor-containing regions were identified and marked by a pathologist. In a subset of samples, normal areas were identified for comparison with the tumor material. The DNA was extracted using standard methods. The RET genotyping of the extracted DNA was carried out with 1 of the following platforms:

- Initially, some samples were genotyped for the RET M918T mutation using a custom Taqman assay. Samples with scant material were not analyzed further; samples with adequate material were sequenced using Illumina technology to reveal any other RET mutations.
- Barcoded sequencing libraries were made from the tissue DNA.
- The RET sequences were enriched using a custom Agilent SureSelect reagent and sequenced on an Illumina sequencer.
- Data processing and automated calling of RET variants were carried out using the Broad Genome Analysis ToolKit (GATK) pipeline with manual curation of any difficult cases using Broad Integrative Genomics Viewer (IGV).

The results of this reanalysis were correlated with clinical data to determine whether there are significant relationships between molecular data and clinical outcomes.

Study size

The study was originally designed to have a sample size of 80 patients (40 RET negative and 40 RET positive). However, due to recruitment challenges related to the rarity of RET mutation negative patients with locally advanced and metastatic MTC (approximately 10%) and due to medical practice standards (in current practice, RET mutation status is not evaluated prior to treatment), the sample size and sources of patients were revised in accordance with EMA agreement on 28 February 2019. In Amended Protocol 02 dated 21 June 2019, the sample size was reduced to 40 to 50 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC to yield 20 to 25 RET mutation negative and 20 to 25 RET mutation positive patients.

The Sponsor stopped the recruitment and terminated the study on 10 July 2020. The termination decision was supported by EMA per its conclusions and recommendations embedded in the Request of Supplementary Information relative to type II labelling variation procedure no. EMEA/H/C/002315/II/0043 dated on 28 May 2020.

Statistical methods

The enrolled population consisted of all patients enrolled in OBS14778 in the prospective cohort (after having signed an informed consent) and in the retrospective cohort (waiver); and patients from study D4200C00058 who were randomized to vandetanib and had a RET status evaluation based on a re-analysis of their archived tissue. The evaluable population consisted of all enrolled and eligible patients with a known RET mutation test status (positive or negative) treated with at least 1 dose of vandetanib and who had a RECIST assessment evaluable at baseline. The non-evaluable population consisted of all enrolled patients who did not meet the criteria to be in the evaluable population (eg, did not meet inclusion/exclusion criteria, did not take at least 1 dose of vandetanib, or did not have an evaluable baseline RECIST assessment). These patients were not included in any of the efficacy analyses. The safety population consisted of enrolled population who had received at least 1 dose of vandetanib.

Qualitative variables were described by number of observed values, percentage, and number of missing values, if pertinent 2-sided 95% confidence intervals (CIs) of proportion (patients with missing data were not to be included in the percentage calculation). Quantitative variables were described by the number of observed values, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. For time-to-event, the median time to event and number and percentage of each group

remaining at risk at the last point of observation were provided. The analyses were performed by RET mutation status, study, and overall unless otherwise specified for some variables.

Efficacy results

Participants

Three categories of patients were recruited in the study:

1. 40 patients prospectively (30 patients with RET positive mutation, 7 patients with RET negative mutation, 3 patients with unknown RET status)
2. 10 RET negative patients retrospectively recruited at study sites
3. 47 patients from the randomized study D4200C00058 who had their RET status reanalysed (36 patients with RET positive mutation, 11 patients with RET negative mutation).

As of 17 December 2020 (the database lock date), a total of 30 sites in 8 countries were participating (Belgium, France, Germany, Italy, Luxembourg, Netherlands, Spain, and the United Kingdom), including 4 sites specifically involved in the retrospective data collection effort on RET negative patients. Among the 30 sites, 18 sites responded that they did not have any RET negative patient to contribute to the retrospective data collection effort.

Overall, a total of 97 patients underwent formal screening for inclusion in this study. As summarized in Table 13, a total of 97 patients were screened and enrolled in this study, of whom 91 (93.8%) patients were exposed to at least 1 dose of vandetanib and included in the safety population; the other 6 patients were excluded from the safety population because they did not receive vandetanib.

Of the 97 patients screened, a total of 75 (77.3%) patients were evaluable for efficacy and 22 (22.7%) patients were non-evaluable (15 [15.5%] patients had no evaluable baseline RECIST assessment, 6 [6.2%] patients did not meet eligibility criteria, and 1 [1.0%] patient did not take at least 1 dose of vandetanib). Of the 75 evaluable patients, there were 55 RET positive patients and 20 RET negative patients included in this analysis. As summarized in Table 13, a higher proportion of RET negative patients were non-evaluable compared to RET positive patients (28.6% [RET negative] versus 16.7% [RET positive]).

Of the 75 patients evaluable for efficacy, 41 (54.7%) patients withdrew prematurely (see Table 14): 14 (18.7%) patients due to disease progression, 5 (6.7%) patients due to AEs (cutaneous rash, n=2; acute kidney injury, n=1; empyema, n=1; ALT increased, n=1), 1 (1.3%) patient due to disease progression (recorded also as safety reason), 1 (1.3%) due to severe non-compliance to protocol, 3 (4.0%) patients due to patient decision, and 8 (10.7%) patients due to other reasons. Nine (12.0%) patients died which led to premature withdrawal from the study.

There were 7 patients with major protocol deviations reported during the study, 5 patients in the RET positive group and 2 patients in the RET negative group. Of these 7 major protocol deviations, 4 were due to non-respect of inclusion/exclusion criteria.

Table 13. Analysis population - Enrolled population

	RET mutation positive			RET mutation negative				
Population	Prospective	D4200C00058	All	Prospective	D4200C00058	Retrospective	All	Overall[a]
Enrolled	30 (100.0%)	36 (100.0%)	66 (100.0%)	7 (100.0%)	11 (100.0%)	10 (100.0%)	28 (100.0%)	97 (100.0%)
Evaluable	22 (73.3%)	33 (91.7%)	55 (83.3%)	7 (100.0%)	10 (90.9%)	3 (30.0%)	20 (71.4%)	75 (77.3%)
Safety	28 (93.3%)	36 (100.0%)	64 (97.0%)	7 (100.0%)	11 (100.0%)	9 (90.0%)	27 (96.4%)	91 (93.8%)
Non-Evaluable	8 (26.7%)	3 (8.3%)	11 (16.7%)	0	1 (9.1%)	7 (70.0%)	8 (28.6%)	22 (22.7%)
Did not meet eligibility criteria	2 (6.7%)	0	2 (3.0%)	0	0	1 (10.0%)	1 (3.6%)	6 (6.2%)
Did not take at least 1 dose of vandetanib	0	0	0	0	0	1 (10.0%)	1 (3.6%)	1 (1.0%)
No evaluable baseline RECIST assessment	6 (20.0%)	3 (8.3%)	9 (13.6%)	0	1 (9.1%)	5 (50.0%)	6 (21.4%)	15 (15.5%)

Source: Table 14.1.1.1
RECIST = Response Evaluation Criteria in Solid Tumors; RET = Rearranged during transfection
Percentages are based on the number of patients in the enrolled population.
Evaluable population consisted of all enrolled and eligible patients with a known RET mutation test status (positive or negative) treated with at least 1 dose of vandetanib and who had an evaluable baseline RECIST assessment.
Safety population consisted of enrolled population who had received at least 1 dose of vandetanib.
Non-evaluable population consisted of enrolled patients who failed to meet criteria for the evaluable population.
a The following 3 enrolled patients, who did not meet eligibility criteria, do not have a RET mutation status and are counted in overall column only: 3101003, 4401002 and 4401003.

Table 14. Disposition of patients - Evaluable population

Parameter	RET mutation positive			RET mutation negative				Overall
	Prospective (N=22) n(%)	D4200C00058 (N=33) n(%)	All (N=55) n(%)	Prospective (N=7) n(%)	D4200C00058 (N=10) n(%)	Retrospective (N=3) n(%)	All (N=20) n(%)	(N=75) n(%)
Patient withdrew prematurely[a]	22 (100.0)	10 (30.3)	32 (58.2)	7 (100.0)	2 (20.0)	NA	9 (45.0)	41 (54.7)
Primary reason for premature withdrawal								
Subject Decision	1 (4.5)	1 (3.0)	2 (3.6)	0	1 (10.0)	NA	1 (5.0)	3 (4.0)
Eligibility Criteria Not Fulfilled	0	0	0	0	0	NA	0	0
Death	1 (4.5)	7 (21.2)	8 (14.5)	0	1 (10.0)	NA	1 (5.0)	9 (12.0)
Adverse Event	4 (18.2)	NA	4 (7.3)	1 (14.3)	NA	NA	1 (5.0)	5 (6.7)
Lack of Therapeutic Response	0	NA	0	0	NA	NA	0	0
Disease Progression	10 (45.5)	NA	10 (18.2)	4 (57.1)	NA	NA	4 (20.0)	14 (18.7)
Safety Reasons	NA	1 (3.0)	1 (1.8)	NA	0	NA	0	1 (1.3)
Severe Non-compliance to Protocol	NA	1 (3.0)	1 (1.8)	NA	0	NA	0	1 (1.3)
Patient Lost to Follow-up	0	0	0	0	0	NA	0	0
Other	6 (27.3)	0	6 (10.9)	2 (28.6)	0	NA	2 (10.0)	8 (10.7)
Patient discontinued study treatment	16 (72.7)	25 (75.8)	41 (74.5)	5 (71.4)	9 (90.0)	2 (66.7)	16 (80.0)	57 (76.0)
Main reason for discontinuing treatment[b]								
Adverse Event	5 (22.7)	3 (9.1)	8 (14.5)	1 (14.3)	1 (10.0)	2 (66.7)	4 (20.0)	12 (16.0)
Poor compliance to protocol	0	NA	0	0	NA	0	0	0
Disease Progression	9 (40.9)	18 (54.5)	27 (49.1)	4 (57.1)	5 (50.0)	0	9 (45.0)	36 (48.0)
Lost to Follow up	0	0	0	0	0	0	0	0
Investigator's Decision	0	NA	0	0	NA	0	0	0
Patient's Request	1 (4.5)	1 (3.0)	2 (3.6)	0	0	0	0	2 (2.7)
Other Reason	1 (4.5)	3 (9.1)	4 (7.3)	0	3 (30.0)	0	3 (15.0)	7 (9.3)

Source: Table 14.1.1.3
RET = Rearranged during transfection
Percentages are based on the number of patients in the evaluable population.

a Study 58 did not report if patients completed. The study 58 data only addressed if patient early withdrew.

b A study 58 patient that participates in both double-blind and open-label phase, may discontinue treatment in 1 or both phases. Hence, patients who discontinue from treatment in both phases and have different reasons, were counted in each reason.

Baseline characteristics

Demographic and patient characteristics

The median age of patients was 50 years (range: 20 to 77 years), higher for RET negative patients compared to RET positive (56.5 years versus 45.0 years). A total of 47 (62.7%) patients were males and 28 (37.3%) were females. Most patients (68 patients [91.9%]) were white. Median weight and height of patients was 74.0 kg and 172.0 cm, respectively (see Table 15).

Table 15. Demographics and patient characteristics - Evaluable population

	RET mutation positive			RET mutation negative				
Parameter	Prospective (N=22) n(%)	D4200C00058 (N=33) n(%)	All (N=55) n(%)	Prospective (N=7) n(%)	D4200C00058 (N=10) n(%)	Retrospective (N=3) n(%)	All (N=20) n(%)	Overall (N=75) n(%)
Age (years)[a]								
Number	22	33	55	7	10	3	20	75
Mean (StdD)	44.8 (16.33)	49.3 (13.01)	47.5 (14.45)	61.1 (8.05)	55.1 (15.02)	56.7 (2.89)	57.5 (11.67)	50.1 (14.39)
Median	40.0	50.0	45.0	63.0	48.5	55.0	56.5	50.0
Min, Max	20, 76	20, 74	20, 76	50, 71	39, 77	55, 60	39, 77	20, 77
Age Category (years), n(%)								
Number	22	33	55	7	10	3	20	75
18 to 27	1 (4.5)	3 (9.1)	4 (7.3)	0	0	0	0	4 (5.3)
28 to 37	10 (45.5)	1 (3.0)	11 (20.0)	0	0	0	0	11 (14.7)
38 to 47	3 (13.6)	12 (36.4)	15 (27.3)	0	4 (40.0)	0	4 (20.0)	19 (25.3)
48 to 57	2 (9.1)	9 (27.3)	11 (20.0)	2 (28.6)	2 (20.0)	2 (66.7)	6 (30.0)	17 (22.7)
58 to 67	4 (18.2)	5 (15.2)	9 (16.4)	3 (42.9)	1 (10.0)	1 (33.3)	5 (25.0)	14 (18.7)
68 to 77	2 (9.1)	3 (9.1)	5 (9.1)	2 (28.6)	3 (30.0)	0	5 (25.0)	10 (13.3)
78 to 87	0	0	0	0	0	0	0	0
>87	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Sex, n(%)								
Number	22	33	55	7	10	3	20	75
Male	13 (59.1)	23 (69.7)	36 (65.5)	4 (57.1)	6 (60.0)	1 (33.3)	11 (55.0)	47 (62.7)
Female	9 (40.9)	10 (30.3)	19 (34.5)	3 (42.9)	4 (40.0)	2 (66.7)	9 (45.0)	28 (37.3)
Missing	0	0	0	0	0	0	0	0
Ethnic Origin, n(%)								
Number	22	33	55	6	10	3	19	74
White	21 (95.5)	30 (90.9)	51 (92.7)	4 (66.7)	10 (100.0)	3 (100.0)	17 (89.5)	68 (91.9)
Black	1 (4.5)	0	1 (1.8)	0	0	0	0	1 (1.4)
Asian	0	3 (9.1)	3 (5.5)	0	0	0	0	3 (4.1)
Other	0	0	0	2 (33.3)	0	0	2 (10.5)	2 (2.7)
Missing	0	0	0	1	0	0	1	1
Height (cm)								
Number	22	32	54	7	10	2	19	73
Mean (StdD)	170.6 (13.01)	171.9 (11.24)	171.4 (11.89)	170.6 (9.25)	171.5 (9.30)	162.5 (10.61)	170.2 (9.25)	171.1 (11.21)
Median	172.5	172.5	172.5	170.0	173.0	162.5	171.0	172.0
Min, Max	145, 191	150, 192	145, 192	156, 183	155, 183	155, 170	155, 183	145, 192
Weight (kg)								
Number	22	33	55	7	10	2	19	74
Mean (StdD)	72.8 (19.00)	73.3 (17.40)	73.1 (17.88)	73.3 (16.81)	76.4 (20.52)	64.5 (7.78)	74.0 (17.93)	73.3 (17.78)
Median	74.0	76.0	75.0	66.0	73.5	64.5	69.0	74.0
Min, Max	50, 110	44, 106	44, 110	56, 100	53, 125	59, 70	53, 125	44, 125

Source: Table 14.1.2

RET = Rearranged during transfection; StdD = Standard Deviation

a For retrospective patients, age was collected as an age range. All retrospective patients fell into 1 of the ranges (5-year interval) covering 18 to 77 years of age. For purpose of analysis, Age (years) value for these patients was set to the median value of their respective collected age range.

Disease characteristics at baseline

Disease characteristics at baseline were somewhat variable between patients. The median time from MTC diagnosis to first dose of vandetanib was 71.4 months overall (65.9 months and 89.6 months for RET positive and RET negative patients, respectively). Median time from diagnosis of sporadic, unresectable, locally advanced/metastatic MTC to first dose of vandetanib was 10.3 months overall (5.5 months and 17.0 months for RET positive and RET negative patients, respectively). Most patients had

disease stage IVc at baseline (62 [83.8%] patients overall, 46 [83.6%] RET positive patients and 16 [84.2%] RET negative patients). The median time from last disease progression to first dose of vandetanib was 2.4 months overall (1.97 months and 5.6 months for RET positive and RET negative patients, respectively).

Prior medical and surgical history

Among 32 evaluable patients enrolled at study sites (prospectively or retrospectively), 13 (40.6%) patients reported a previous medical history and 25 (78.1%) patients reported current medical history (mainly hypothyroidism 68.8%, other relevant disease 34.4%, hypocalcemia 18.8%, and hypertension 18.8%). Among 43 evaluable patients from the Phase 3 study D4200C00058, 19 (44.2%) patients reported a previous medical history and 36 (83.7%) patients reported current medical history (mainly diarrhea 34.9%, hypothyroidism 18.6%, hypertension 18.6%, fatigue 14.0%, back pain 14.0%). A total of 66 (88.0%) patients had a prior surgical history among evaluable patients.

Prior anti-cancer therapy

Previous cancer therapies were as follows: 63 (84.0%) had prior thyroidectomy, 28 (37.3%) patients received prior radiotherapy, 8 (10.7%) patients received prior chemotherapy.

Prior and concomitant medications

In the evaluable population, a total of 74 (98.7%) patients had prior medications. The most frequent (>30%) anatomical classes (from ATC) were systemic hormonal preparations, excl. sex hormones and insulins (89.3% of patients), alimentary tract and metabolism (60.0%), and nervous system (30.7%).

All evaluable patients (n=75, 100.0%) had concomitant medications. The most frequent (>50%) anatomical classes (from ATC) were systemic hormonal preparations, excl. sex hormones and insulins (90.7% of patients), alimentary tract and metabolism (89.3%), nervous system (64.0%), cardiovascular system (54.7%), and anti-infectives for systemic use (50.7%).

A total of 24 (32.0%) patients used at least 1 opioid analgesic before enrollment, mainly for mild to moderate pain (17 patients) and severe pain (9 patients). The median number of opioids used per patient was 1.5 with a median cumulative duration of 5.0 months of use per patient. The most common opioids used were codeine with acetaminophen (9 patients), morphine sulphate (7 patients), oxycodone (4 patients), tramadol (4 patients), and other (5 patients).

Efficacy results

The median duration of follow-up was 27.6 months (range: 2.8 to 63.7 months) for RET positive patients (n=55) and 30.8 months (range: 2.8 to 82.5 months) for RET negative patients (n=20). Results for ORR, DCR, time to response, and DOR are presented in Table 16.

Tumor response was evaluated in 55 RET positive patients and 20 RET negative patients. Overall, 24 patients (32.0%) had an objective response which included 2 CR and 22 PR. The ORR for RET positive patients was 41.8% (95% CI: 28.7-55.9), and 5.0% (95% CI: 0.1-24.9) for RET negative patients. More RET positive patients experienced CR and PR compared to RET negative patients (CR: 3.6% versus 0%; PR: 38.2% versus 5.0% in RET positive and RET negative patients, respectively). More RET negative patients had SD compared to RET positive patients (85.0% versus 43.6%). Few patients experienced PD (5 [6.7%] patients overall, 4 [7.3%] in RET positive patients versus 1 [5.0%] in RET negative patients).

The DCR (CR, PR, or SD) was apparently not significantly different for RET positive and RET negative patients (85.5% [95% CI: 73.3-93.5] versus 90.0% [95% CI: 68.3-98.8], respectively).

The median time to response was 5.5 months (range: 2.7 to 30.7 months) in RET positive patients and 8.3 months for the RET negative patient (Table 17).

The median DOR was 24.9 months and 5.3 months in RET positive and RET negative patients, respectively. The Kaplan Meier curves for DOR are provided in Figure 3. The Waterfall plot for largest percentage change in sum of the longest diameters of the target lesions from baseline is provided in Figure 4.

Table 16. ORR, DCR, DoR and TTR - Evaluable population

	RET mutation positive			RET mutation negative				
Parameter	Prospective (N=22)	D4200C00058 (N=33)	All (N=55)	Prospective (N=7)	D4200C00058 (N=10)	Retrospective (N=3)	All (N=20)	Overall (N=75)
Duration of Follow-up[a] (months)								
Number	18	33	51	7	9	3	19	70
Mean (StdD)	26.30 (17.608)	23.42 (10.955)	24.43 (13.570)	28.40 (23.779)	28.75 (9.777)	31.38 (44.245)	29.03 (21.204)	25.68 (15.968)
Median	20.86	29.50	27.63	24.21	30.82	6.21	30.78	27.78
Min, Max	3.1, 63.7	2.8, 38.7	2.8, 63.7	2.8, 66.3	11.3, 38.6	5.5, 82.5	2.8, 82.5	2.8, 82.5
Objective Response Rate (ORR)								
n (%)	5 (22.7)	18 (54.5)	23 (41.8)	0	1 (10.0)	0	1 (5.0)	24 (32.0)
95% CI	(7.8, 45.4)	(36.4, 71.9)	(28.7, 55.9)	(NE, NE)	(0.3, 44.5)	(NE, NE)	(0.1, 24.9)	(21.7, 43.8)
Best Objective Response (BOR), n (%)								
CR	1 (4.5)	1 (3.0)	2 (3.6)	0	0	0	0	2 (2.7)
PR	4 (18.2)	17 (51.5)	21 (38.2)	0	1 (10.0)	0	1 (5.0)	22 (29.3)
SD	11 (50.0)	13 (39.4)	24 (43.6)	6 (85.7)	8 (80.0)	3 (100.0)	17 (85.0)	41 (54.7)
PD	2 (9.1)	2 (6.1)	4 (7.3)	1 (14.3)	0	0	1 (5.0)	5 (6.7)
NE	4 (18.2)	0	4 (7.3)	0	1 (10.0)	0	1 (5.0)	5 (6.7)
Missing	0	0	0	0	0	0	0	0
Disease Control Rate (DCR)								
n (%)	16 (72.7)	31 (93.9)	47 (85.5)	6 (85.7)	9 (90.0)	3 (100.0)	18 (90.0)	65 (86.7)
95% CI	(49.8, 89.3)	(79.8, 99.3)	(73.3, 93.5)	(42.1, 99.6)	(55.5, 99.7)	(29.2, 100.0)	(68.3, 98.8)	(76.8, 93.4)
Duration of Response[b] (months)								
Number	3	10	13	0	1	0	1	14
Mean (StdD)	27.75 (5.593)	15.12 (8.417)	18.03 (9.437)		5.32 (NA)		5.32 (NA)	17.12 (9.682)
Median	28.35	11.58	21.88		5.32		5.32	18.04
Min, Max	21.9, 33.0	5.6, 26.3	5.6, 33.0		5.3, 5.3		5.3, 5.3	5.3, 33.0
Time to Response[c] (months)								
Number	5	18	23	0	1	0	1	24
Mean (StdD)	5.60 (2.308)	8.52 (8.347)	7.88 (7.505)		8.34 (NA)		8.34 (NA)	7.90 (7.341)
Median	5.45	5.54	5.52		8.34		8.34	5.54
Min, Max	2.8, 9.2	2.7, 30.7	2.7, 30.7		8.3, 8.3		8.3, 8.3	2.7, 30.7

Source: Table 14.2.1.1

CI = Confidence interval; CR = Complete response; Max = Maximum; Min = Minimum; NA = Not applicable; NE= Not Estimable; PD = Progressive disease; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RET = Rearranged during transfection; SD = Stable disease; StdD = Standard Deviation

a Duration follow-up is based on last RECIST assessment date - first dose date of study medication + 1.

b Duration of Response (number of months from time of response until the first date of either of PD or death) for responders. Does not include responders who did not progress or die.

c Time to Response (number of months from start date of study medication to first documentation of response) is only calculated for responders.

Table 17. Time to response and duration of response, Kaplan Meier - Evaluable population

Parameter Statistics	RET mutation positive (N=55)	RET mutation negative (N=20)
Number of responders		
Responders, n (%)	23 (41.8)	1 (5.0)
Non-responders, n (%)	32 (58.2)	19 (95.0)
Time to response (months)		
Median (95% CI)	5.52 (2.858, 5.782)	8.34 (NE, NE)
1st quartile (95% CI)	2.83 (2.727, 5.454)	8.34 (NE, NE)
3rd quartile (95% CI)	8.28 (5.552, 19.417)	8.34 (NE, NE)
Min, Max[a]	2.7, 30.7	8.3, 8.3
Number of responders for duration[b]		
Experienced the event[c], n (%)	13 (56.5)	1 (100.0)
Censored, n (%)	10 (43.5)	0
Duration of response (months)		
Median (95% CI)	24.87 (14.193, 33.018)	5.32 (NE, NE)
1st quartile (95% CI)	14.19 (5.552, 24.805)	5.32 (NE, NE)
3rd quartile (95% CI)	33.02 (24.871, NE)	5.32 (NE, NE)
Min, Max[a]	5.6, 33.0	5.3, 5.3

Source: Table 14.2.2.1
CI = Confidence interval; Min = Minimum; Max = Maximum; NE = Not Estimable; RET = Rearranged during transfection
a Based on actual (that is, non-censored) values only
b Percentages are based on the number of responders.
c Responders who progressed or died.

Figure 3. Kaplan Meier Curves for Duration of Response - Evaluable population

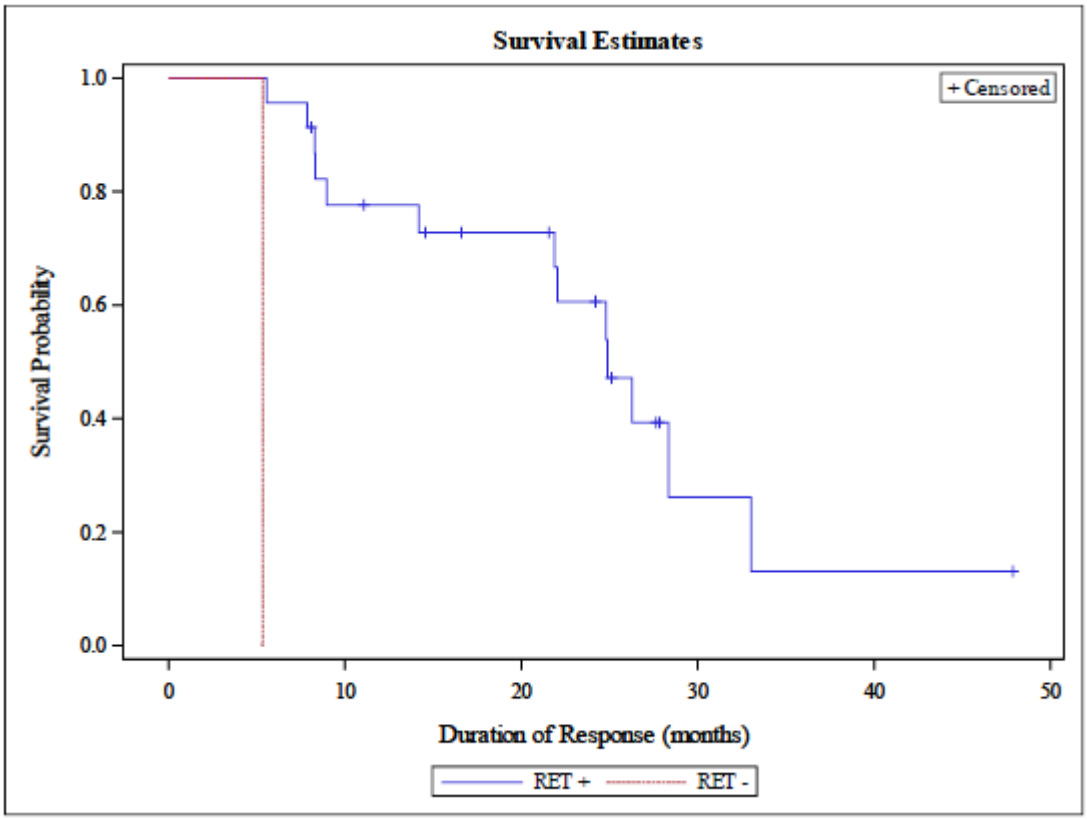
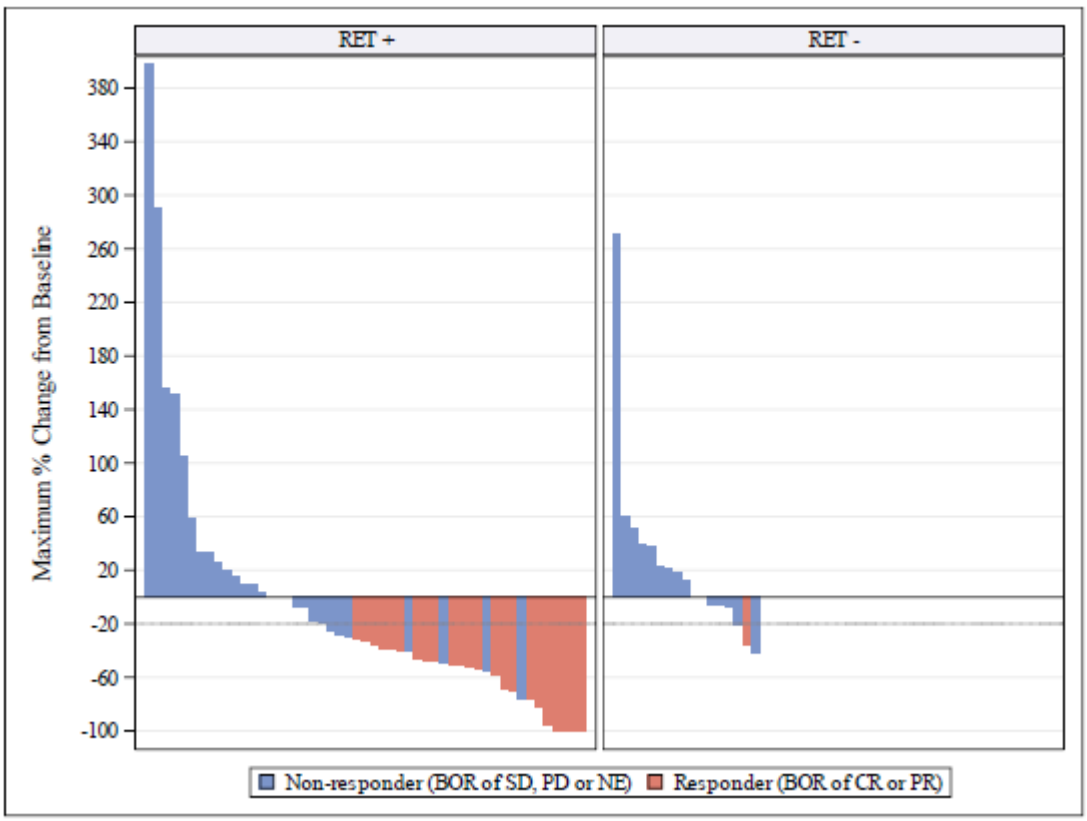


Figure 4. Waterfall Plot - Largest percentage change in sum of the longest diameters of the target lesions from baseline - Evaluable population



Overall, 50 progression events (disease progression or death from any cause) were noted at the time of the analysis, 36 (65.5%) in RET positive patients and 14 (70.0%) in RET negative patients. Of these progression events, there were 6 deaths (4 [11.1%] patients in RET positive patients and 2 [14.3%] in RET negative patients).

In the overall evaluable population, the median PFS (95% CI) was 24.6 months (95% CI: 15.6-31.8) in RET positive patients and 24.6 months (95% CI: 9.9-59.5) in RET negative patients. Details are provided in Table 18.

The Kaplan Meier estimate of PFS (95% CI) at 3, 6, 9, 12, 18, and 24 months for RET positive and RET negative patients is provided in Table 18. At 12 months, 27% of RET positive patients and 23% of RET negative patients were estimated to have progressed; at 24 months, 50% of RET positive patients and 41% of RET negative patients were estimated to have progressed. The Kaplan-Meier curves for PFS are provided in Figure 5.

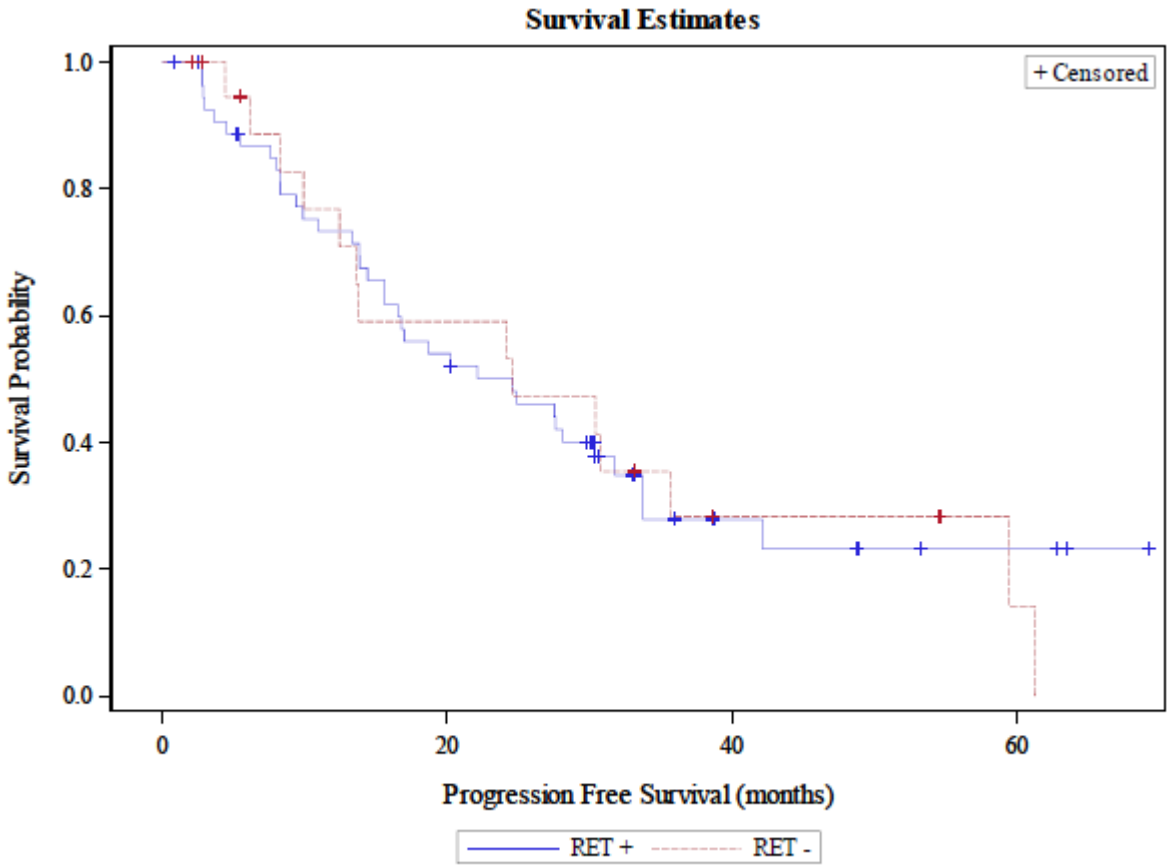
At the end of the study, no progression was observed in 25 (33.3%) patients overall (19 [34.5%] RET positive patients and 6 [30.0%] RET negative patients), 50 (66.7%) patients had progressed (36 [65.5%] RET positive patients and 14 [70.0%] RET negative patients), and 6 (8.0%) patients had died (4 [7.3%] patients were RET positive and 2 [10.0%] patients were RET negative).

Table 18. Progression Free Survival, Kaplan Meier - Evaluable population

Parameter Statistics	RET mutation positive (N=55)	RET mutation negative (N=20)
Experienced the event, n (%)	36 (65.5)	14 (70.0)
Death[b]	4 (11.1)	2 (14.3)
Progressive disease[b]	32 (88.9)	12 (85.7)
Censored, n (%)	19 (34.5)	6 (30.0)
Progression Free Survival (months)		
Median (95% CI)	24.64 (15.639, 31.803)	24.64 (9.922, 59.466)
Min, Max[a]	2.8, 42.2	4.4, 61.3
Kaplan Meier estimates of PFS, (95% CI)		
3 months PFS	0.92 (0.811, 0.971)	1.00 (NE, NE)
6 months PFS	0.87 (0.742, 0.935)	0.94 (0.666, 0.992)
9 months PFS	0.79 (0.653, 0.878)	0.83 (0.552, 0.941)
12 months PFS	0.73 (0.590, 0.832)	0.77 (0.492, 0.906)
18 months PFS	0.56 (0.415, 0.681)	0.59 (0.327, 0.780)
24 months PFS	0.50 (0.359, 0.627)	0.59 (0.327, 0.780)

Source: Table 14.2.3.1
NE = Not Estimable; PFS = Progression free survival; RET = Rearranged during transfection
a Based on actual (that is, non-censored) values only
b Percentages are based on the number of events.

Figure 5. Kaplan Meier curves for PFS - Evaluable population



Source: Figure 14.2.3.1
RET = Rearranged during transfection

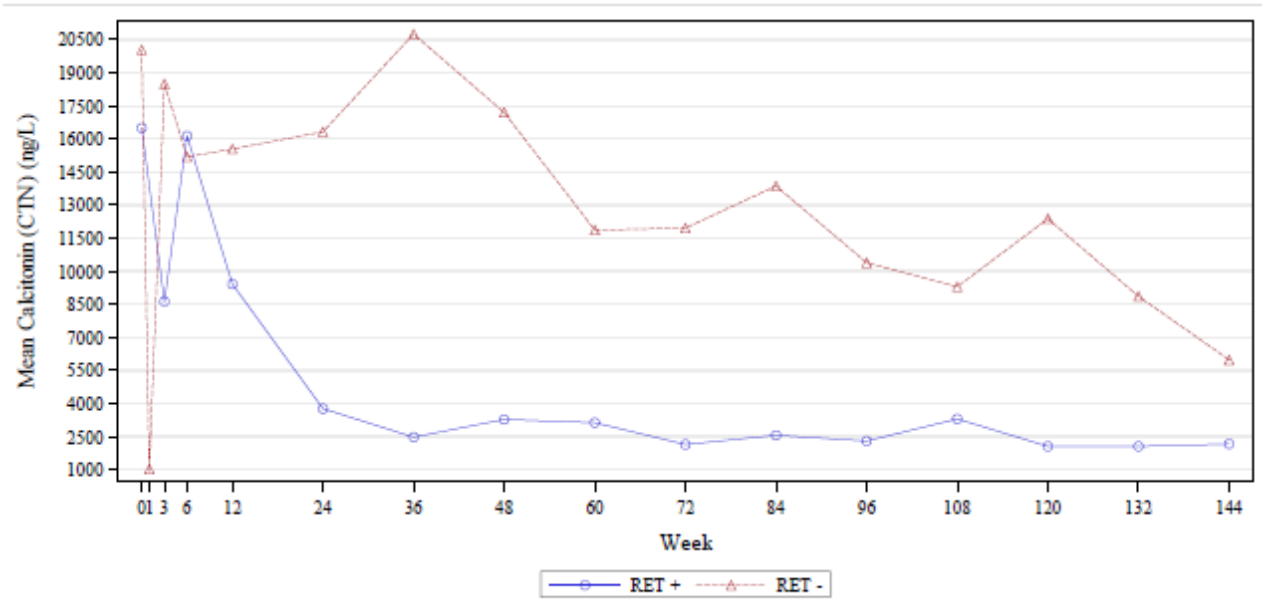
The calcitonin (CTN) values progressively decreased over time in the overall evaluable population and in both RET positive and RET negative patients, but the decrease appeared much more rapid in RET positive patients (see Figure 6).

In the overall evaluable population, the mean (SD) CTN value at baseline was 17457.5 (48035.8) ng/L, 11075.5 (31238.9) ng/L at Month 3, 7114.1 (13770.8) ng/L at Month 6, 7104.0 (13209.6) ng/L at Month 12, 5307.1 (6629.0) ng/L at Month 18, and 5113.5 (8279.8) ng/L at Month 30.

In RET positive patients, the mean (SD) CTN value at baseline was 16500.3 (51386.7) ng/L. The decrease in CTN value was quite rapid with mean (SD) values of 9415.9 (33081.5) ng/L at Month 3, 3764.8 (7237.4) ng/L at Month 6, 3275.3 (5187.2) ng/L at Month 12, 2140.8 (2620.1) ng/L at Month 18, and 2054.5 (3265.8) ng/L at Month 30.

In RET negative patients, the mean (SD) CTN value at baseline was 20041.8 (38599.5) ng/L. The decrease in CTN values was slower over time with mean (SD) values of 15543.5 (26300.5) ng/L at Month 3, 16324.4 (21908.3) ng/L at Month 6, 17197.8 (21227.4) ng/L at Month 12, 11956.5 (7661.9) ng/L at Month 18, and 12378.8 (11894.5) ng/L at Month 30.

Figure 6. Plot of calcitonin (CTN) through Week 144 - Evaluable population



n at weeks	0	1	3	6	12	24	36	48	60	72	84	96	108	120	132	144
RET +	54	0	31	33	35	33	29	29	25	21	18	20	19	19	8	3
RET -	20	2	13	14	13	12	12	11	10	10	9	8	8	8	4	4

Source: Figure 14.2.5.1
RET = Rearranged during transfection
Data graphed through Week 144.

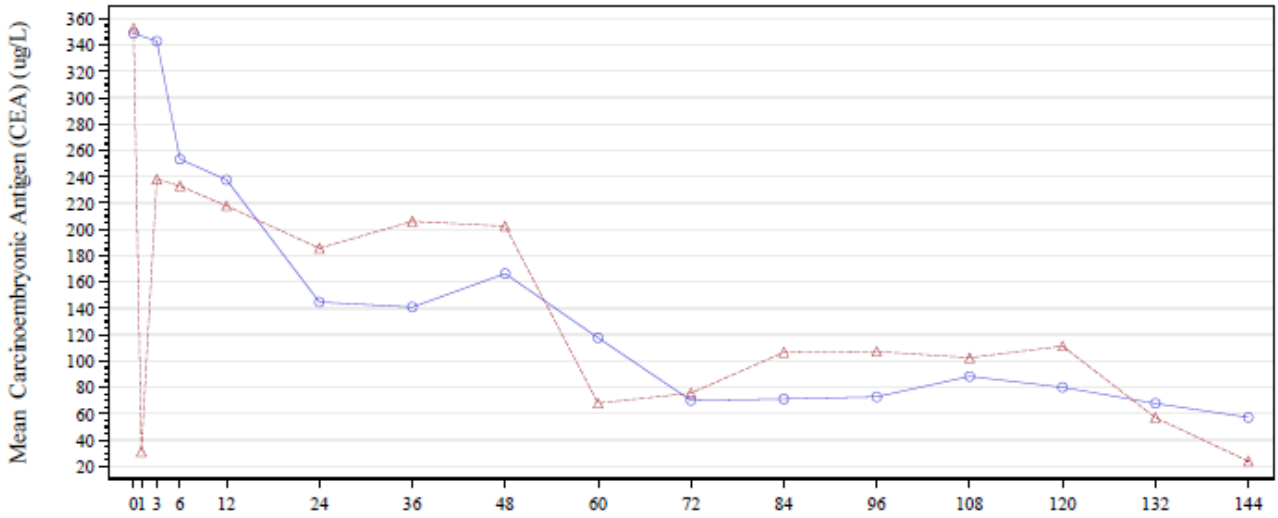
The carcinoembryonic antigen (CEA) values progressively decreased over time, overall, and in both RET positive and RET negative patients in a rather comparable manner (see Figure 7).

In the overall evaluable population, the mean (SD) CEA value at baseline was 349.9 (652.3) µg/L, 232.5 (524.2) µg/L at Month 3, 156.5 (291.3) µg/L at Month 6, 176.5 (376.8) µg/L at Month 12, 71.7(86.7) µg/L at Month 18, and 89.2 (162.2) µg/L at Month 30.

In RET positive patients, the mean (SD) CEA value at baseline was 348.9 (643.3) µg/L, 237.6 (520.5) µg/L at Month 3, 144.7 (179.1) µg/L at Month 6, 166.3 (357.0) µg/L at Month 12, 70.0 (86.7) µg/L at Month 18, and 80.0 (152.7) µg/L at Month 30.

In RET negative patients, the mean (SD) CEA value at baseline was 352.9 (697.1) µg/L, 217.8 (557.8) µg/L at Month 3, 185.6 (476.5) µg/L at Month 6, 202.4 (440.9) µg/L at Month 12, 75.6 (91.9) µg/L at Month 18, and 111.3 (192.1) µg/L at Month 30.

Figure 7. Plot of carcinoembryonic antigen (CEA) through Week 144 - Evaluable population



n at weeks	0	1	3	6	12	24	36	48	60	72	84	96	108	120	132	144
RET +	53	0	32	33	34	32	28	28	24	21	18	20	19	19	8	3
RET -	18	1	12	13	12	13	12	11	10	9	8	8	8	8	4	4

Source: Figure 14.2.5.2
RET = Rearranged during transfection
Data graphed through Week 144.

Safety results

Extent of exposure

Of the 97 patients enrolled, a total of 91 patients received at least 1 dose of vandetanib and were included in the safety analyses, 64 of whom were RET positive and 27 of whom were RET negative. Of these, the median exposure to vandetanib was 24.8 months overall; 23.4 months and 27.6 months for RET positive and RET negative patients, respectively; see Table 19.

Table 19. Extent of exposure to vandetanib (months) - Overall safety population

	RET mutation positive			RET mutation negative				
Exposure to andetanib	Prospective (N=28)	D4200C00058 (N=36)	All (N=64)	Prospective (N=7)	D4200C00058 (N=11)	Retrospective (N=9)	All (N=27)	Overall (N=91)
Overall (months)								
Number	28	36	64	7	11	7	25	89
Mean (StdD)	26.36 (20.616)	22.91 (12.026)	24.42 (16.294)	29.88 (24.702)	27.35 (12.269)	25.10 (25.297)	27.43 (19.457)	25.27 (17.180)
Median	20.96	30.49	23.43	24.57	30.98	15.05	27.60	24.84
Min, Max	0.9, 74.5	0.9, 39.4	0.9, 74.5	5.3, 69.4	1.8, 39.6	1.5, 63.6	1.5, 69.4	0.9, 74.5

Source: Table 14.3.1.1
Max = Maximum; Min = Minimum; RET = Rearranged during transfection; StdD = Standard deviation

Summary of adverse events

An overview of patients with TEAEs is provided in Table 20.

Table 20. Overview of treatment-emergent adverse events - Safety population

Parameter	RET mutation positive			RET mutation negative				Overall (N=91) n (%)
	Prospective (N=28) n (%)	D4200C00058 (N=36) n (%)	All (N=64) n (%)	Prospective (N=7) n (%)	D4200C00058 (N=11) n (%)	Retrospective (N=9) n (%)	All (N=27) n (%)	
TEAE	27 (96.4)	36 (100.0)	63 (98.4)	7 (100.0)	11 (100.0)	6 (66.7)	24 (88.9)	87 (95.6)
Treatment-Related TEAE	26 (92.9)	33 (91.7)	59 (92.2)	7 (100.0)	11 (100.0)	6 (66.7)	24 (88.9)	83 (91.2)
TEAE leading to disc. of study medication	7 (25.0)	2 (5.6)	9 (14.1)	1 (14.3)	1 (9.1)	3 (33.3)	5 (18.5)	14 (15.4)
TEAE leading to disc. from study	9 (32.1)	1 (2.8)	10 (15.6)	1 (14.3)	2 (18.2)	3 (33.3)	6 (22.2)	16 (17.6)
Serious TEAE	8 (28.6)	12 (33.3)	20 (31.3)	1 (14.3)	5 (45.5)	0	6 (22.2)	26 (28.6)
Treatment-Related Serious TEAE	3 (10.7)	5 (13.9)	8 (12.5)	0	0	0	0	8 (8.8)
Serious TEAE leading to disc. of study medication	2 (7.1)	0	2 (3.1)	0	0	0	0	2 (2.2)
Serious TEAE leading to disc. from study	3 (10.7)	1 (2.8)	4 (6.3)	0	1 (9.1)	0	1 (3.7)	5 (5.5)
TEAE by grade[a]								
Mild	3 (10.7)	6 (16.7)	9 (14.1)	2 (28.6)	0	0	2 (7.4)	11 (12.1)
Moderate	14 (50.0)	11 (30.6)	25 (39.1)	4 (57.1)	4 (36.4)	5 (55.6)	13 (48.1)	38 (41.8)
Severe	9 (32.1)	16 (44.4)	25 (39.1)	1 (14.3)	7 (63.6)	1 (11.1)	9 (33.3)	34 (37.4)
Life-threatening or Disabling	0	2 (5.6)	2 (3.1)	0	0	0	0	2 (2.2)
Death	1 (3.6)	1 (2.8)	2 (3.1)	0	0	0	0	2 (2.2)

Source: Table 14.3.2.1
AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; RET = Rearranged during transfection
A TEAE is any AE that has onset or any pre-existing AE that has worsened in severity on or after the first dose of study medication.
Adverse Event data for D4200C00058 and OBS14778 were recoded/coded respectively using MedDRA V22.1.
a TEAE by grade reflects the initial CTCAE grades. A patient was counted once at the maximum CTCAE grade.

Analysis of adverse events

Pre-treatment adverse events

Pre-treatment AEs were observed in 17 (18.7%) patients, with 29 events overall (11 [17.2%] patients who were RET positive and 6 [22.2%] patients who were RET negative). The majority of pre-treatment AEs were in the SOCs of musculoskeletal and connective tissue disorders (4 [4.4%] patients with 6 events) and gastrointestinal disorders (4 [4.4%] patients with 5 events).

Treatment-emergent adverse events

Of the 91 patients exposed to vandetanib, 87 patients (95.6%) reported 993 TEAEs, 63 (98.4%) RET positive patients (687 TEAEs) and 24 (88.9%) RET negative patients (306 TEAEs).

- The most commonly reported SOCs (≥10.0% of patients) were as follows:
  - Skin and subcutaneous tissue disorders: 70.3% overall (RET positive 75.0%, RET negative 59.3%)
  - Gastrointestinal disorders: 68.1% overall (RET positive 68.8%, RET negative 66.7%)
  - Investigations: 46.2% overall (RET positive 48.4%, RET negative 40.7%)
  - Infections and infestations: 45.1% overall (RET positive 46.9%, RET negative 40.7%)
  - Metabolism and nutrition disorders: 36.3% overall (RET positive 34.4%, RET negative 40.7%)
  - General disorders and administration site conditions: 35.2% overall (RET positive 37.5%, RET negative 29.6%)
  - Nervous system disorders: 35.2% overall (RET positive 31.3%, RET negative 44.4%)

  - Musculoskeletal and connective tissue disorders: 34.1% overall (RET positive 34.4%, RET negative 33.3%)
  - Vascular disorders: 29.7% overall (RET positive 32.8%, RET negative 22.2%)
  - Respiratory, thoracic and mediastinal disorders: 25.3% overall (RET positive 25.0%, RET negative 25.9%)
  - Psychiatric disorders: 23.1% overall (RET positive 28.1%, RET negative 11.1%)
  - Renal and urinary disorders: 20.9% overall (RET positive 14.1%, RET negative 37.0%)
  - Eye disorders: 19.8% overall (RET positive 18.8%, RET negative 22.2%)
  - Reproductive system and breast disorders: 11.0% overall (RET positive 10.9%, RET negative 11.1%)
- At the PT level, all grade TEAEs reported in ≥10% of patients were as follows:
  - Diarrhea: 56.0% overall (RET positive 56.3%, RET negative 55.6%)
  - Rash: 31.9% overall (RET positive 34.4%, RET negative 25.9%)
  - Hypertension: 23.1% overall (RET positive 23.4%, RET negative 22.2%)
  - Nausea: 17.6% overall (RET positive 17.2%, RET negative 18.5%)
  - Hypocalcaemia: 16.5% overall (RET positive 18.8%, RET negative 11.1%)
  - Decreased appetite: 16.5% overall (RET positive 15.6%, RET negative 18.5%)
  - Dermatitis acneiform: 16.5% overall (RET positive 18.8%, RET negative 11.1%)
  - Headache: 15.4% overall (RET positive 18.8%, RET negative 7.4%)
  - Asthenia: 15.4% overall (RET positive 18.8%, RET negative 7.4%)
  - Insomnia: 14.3% overall (RET positive 17.2%, RET negative 7.4%)
  - ECG QT prolonged: 14.3% overall (RET positive 17.2%, RET negative 7.4%)
  - Fatigue: 14.3% overall (RET positive 9.4%, RET negative 25.9%)
  - Abdominal pain: 12.1% overall (RET positive 15.6%, RET negative 3.7%)
  - Cough: 11.0% overall (RET positive 10.9%, RET negative 11.1%)
  - Erythema: 11.0% overall (RET positive 10.9%, RET negative 11.1%)
  - ALT increased: 11.0% overall (RET positive 10.9%, RET negative 11.1%)
  - AST increased: 11.0% overall (RET positive 10.9%, RET negative 11.1%)
  - Weight decreased: 11.0% overall (RET positive 12.5%, RET negative 7.4%)
- The most commonly reported severe and life-threatening or disabling TEAEs by SOC (≥5%) were the following:
  - Infections and infestations (11.0%; RET positive 9.4%, RET negative 14.8%)
  - Gastrointestinal disorders (7.7%; RET positive 9.4%, RET negative 3.7%) overall.
- The most commonly reported severe and life-threatening or disabling TEAEs by PT (≥2%) were the following:
  - Diarrhea (4.4%; RET positive 4.7%, RET negative 3.7%)
  - Rash (4.4%; RET positive 4.7%; RET negative 3.7%)
  - Hypertension (2.2%, RET positive 3.1%. RET negative 0%)
  - Pneumonia (2.2%; RET positive 0%, RET negative 7.4%)
  - Decreased appetite (2.2%; RET positive 1.6%, RET negative 3.7%)
  - Cough (2.2%; RET positive 3.1%, RET negative 0%)
  - Dysphagia (2.2%; RET positive 3.1%, RET negative 0%)

Treatment-related adverse events

Overall, 83 (91.2%) patients exposed to vandetanib reported 476 TEAEs that were considered related to Investigational Medicinal Product (IMP), 59 (92.2%) RET positive and 24 (88.9%) RET negative patients.

- The most commonly reported SOCs (reported in ≥10.0% of patients) that were considered related to IMP were the following:

  - Skin and subcutaneous tissue disorders: 68.1% overall (RET positive 73.4%, RET negative 55.6%)
  - Gastrointestinal disorders: 48.4% overall (RET positive 51.6%, RET negative 40.7%)
  - Investigations: 36.3% overall (RET positive 37.5%, RET negative 33.3%)
  - Metabolism and nutrition disorders: 22.0% overall (RET positive 20.3%, RET negative 25.9%)
  - Vascular disorders: 22.0% overall (RET positive 25.0%, RET negative 14.8%)
  - General disorders and administration site conditions: 19.8% overall (RET positive 20.3%, RET negative 18.5%)
  - Eye disorders: 18.7% overall (RET positive 18.8%, RET negative 18.5%)
  - Infections and infestations: 15.4% overall (RET positive 15.6%, RET negative 14.8%)
  - Renal and urinary disorders: 14.3% overall (RET positive 9.4%, RET negative 25.9%)
  - Nervous system disorders: 11.0% overall (RET positive 7.8%, RET negative 18.5%)
- The most common TEAEs by PT (reported in ≥10% of patients) that were considered related to IMP were the following:
  - Diarrhea: 44.0% overall (RET positive 45.3%, RET negative 40.7%)
  - Rash: 29.7% overall (RET positive 31.3%, RET negative 25.9%)
  - Hypertension: 18.7% overall (RET positive 20.3%, RET negative 14.8%)
  - Dermatitis acneiform: 16.5% overall (RET positive 18.8%, RET negative 11.1%)
  - ECG QT prolonged: 13.2% overall (RET positive 17.2%, RET negative 3.7%)
  - Nausea: 12.1% overall (RET positive 12.5%, RET negative 11.1%)

Serious adverse events

Overall, 26 patients (28.6%) exposed to vandetanib reported 44 serious TEAEs, regardless of relationship with study treatment, 20 (31.3%) RET positive patients (31 serious TEAEs) and 6 (22.2%) RET negative patients (13 serious TEAEs). These serious TEAEs are summarized by SOC and PT, overall and by RET mutation status in Table 21.

Table 21. Serious TEAEs by primary system organ class and preferred term - Overall safety population

	RET mutation positive		RET mutation negative			
	All (N=64)		All (N=27)		Overall (N=91)	
Primary System Organ Class/ Preferred Term	n (%)	Evt	n (%)	Evt	n (%)	Evt
Any Serious TEAE	20 (31.3)	31	6 (22.2)	13	26 (28.6)	44
Infections and infestations	6 (9.4)	7	5 (18.5)	6	11 (12.1)	13
Pneumonia	0	0	2 (7.4)	3	2 (2.2)	3
Urinary tract infection	0	0	2 (7.4)	2	2 (2.2)	2
Aspergilloma	1 (1.6)	1	0	0	1 (1.1)	1
Clostridium difficile infection	1 (1.6)	1	0	0	1 (1.1)	1
Colonic abscess	1 (1.6)	1	0	0	1 (1.1)	1
Dermatitis infected	0	0	1 (3.7)	1	1 (1.1)	1
Diverticulitis	1 (1.6)	1	0	0	1 (1.1)	1
Gastroenteritis	1 (1.6)	1	0	0	1 (1.1)	1
Pyelonephritis	1 (1.6)	1	0	0	1 (1.1)	1
Soft tissue infection	1 (1.6)	1	0	0	1 (1.1)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (3.7)	1	1 (1.1)	1
Breast cancer	0	0	1 (3.7)	1	1 (1.1)	1
Blood and lymphatic system disorders	1 (1.6)	1	0	0	1 (1.1)	1
Lymphadenopathy	1 (1.6)	1	0	0	1 (1.1)	1
Metabolism and nutrition disorders	1 (1.6)	1	0	0	1 (1.1)	1
Decreased appetite	1 (1.6)	1	0	0	1 (1.1)	1
Psychiatric disorders	1 (1.6)	1	0	0	1 (1.1)	1
Depression	1 (1.6)	1	0	0	1 (1.1)	1
Nervous system disorders	0	0	1 (3.7)	1	1 (1.1)	1
Transient ischaemic attack	0	0	1 (3.7)	1	1 (1.1)	1
Cardiac disorders	2 (3.1)	3	0	0	2 (2.2)	3
Arrhythmia	1 (1.6)	1	0	0	1 (1.1)	1
Bradycardia	1 (1.6)	1	0	0	1 (1.1)	1
Cardiac failure acute	1 (1.6)	1	0	0	1 (1.1)	1
Vascular disorders	2 (3.1)	2	0	0	2 (2.2)	2
Accelerated hypertension	1 (1.6)	1	0	0	1 (1.1)	1
Hypertensive crisis	1 (1.6)	1	0	0	1 (1.1)	1
Respiratory, thoracic and mediastinal disorders	1 (1.6)	2	1 (3.7)	1	2 (2.2)	3
Haemothorax	1 (1.6)	2	0	0	1 (1.1)	2
Pneumonia aspiration	0	0	1 (3.7)	1	1 (1.1)	1
Gastrointestinal disorders	4 (6.3)	4	1 (3.7)	1	5 (5.5)	5
Diarrhoea	1 (1.6)	1	0	0	1 (1.1)	1
Dysphagia	1 (1.6)	1	0	0	1 (1.1)	1
Faecaloma	1 (1.6)	1	0	0	1 (1.1)	1
Gastritis	0	0	1 (3.7)	1	1 (1.1)	1
Nausea	1 (1.6)	1	0	0	1 (1.1)	1
Hepatobiliary disorders	3 (4.7)	3	0	0	3 (3.3)	3
Cholecystitis	2 (3.1)	2	0	0	2 (2.2)	2
Jaundice	1 (1.6)	1	0	0	1 (1.1)	1
Musculoskeletal and connective tissue disorders	2 (3.1)	2	0	0	2 (2.2)	2
Back pain	1 (1.6)	1	0	0	1 (1.1)	1
Bone pain	1 (1.6)	1	0	0	1 (1.1)	1
Renal and urinary disorders	1 (1.6)	1	1 (3.7)	1	2 (2.2)	2
Nephrolithiasis	1 (1.6)	1	0	0	1 (1.1)	1
Renal colic	0	0	1 (3.7)	1	1 (1.1)	1
General disorders and administration site conditions	3 (4.7)	3	1 (3.7)	1	4 (4.4)	4
Disease progression	3 (4.7)	3	0	0	3 (3.3)	3
Fatigue	0	0	1 (3.7)	1	1 (1.1)	1
Investigations	1 (1.6)	1	0	0	1 (1.1)	1
Electrocardiogram QT prolonged	1 (1.6)	1	0	0	1 (1.1)	1
Injury, poisoning and procedural complications	0	0	1 (3.7)	1	1 (1.1)	1
Venomous bite	0	0	1 (3.7)	1	1 (1.1)	1

Source: Table 14.3.2.7
AE= Adverse event; Evt = Event; RET = Rearranged during transfection; SOC = System Organ Class; TEAE = Treatment-emergent adverse event
A TEAE is any AE that has onset or any pre-existing AE that had worsened in severity on or after the first dose of study medication
Data was sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
Patients were counted once within a system organ class and once for each unique preferred term.
Adverse Event data for D4200C00058 and OBS14778 were recoded/coded respectively using MedDRA V22.1.

Adverse events leading to discontinuations

A total of 14 (15.4%) patients had 15 TEAEs leading to treatment discontinuation, 9 (14.1%) RET positive patients (9 TEAEs) and 5 (18.5%) RET negative patients (6 TEAEs). The TEAEs leading to treatment discontinuation are summarized in Table 23.

Table 22. TEAEs leading to discontinuation of study medication by primary system organ class and preferred term - Safety population

	RET mutation positive				RET mutation negative					
	Prospective (N=28)		D4200C00058 (N=36)		Prospective (N=7)		D4200C00058 (N=11)		Retrospective (N=9)	
Primary System Organ Class/ Preferred Term	n(%)	Evt	n(%)	Evt	n(%)	Evt	n(%)	Evt	n(%)	Evt
Any TEAE leading to disc. of study medication	7 (25.0)	7	2 (5.6)	2	1 (14.3)	1	1 (9.1)	2	3 (33.3)	3
Infections and infestations	1 (3.6)	1	0	0	1 (14.3)	1	0	0	0	0
Empyema	0	0	0	0	1 (14.3)	1	0	0	0	0
Pyelonephritis	1 (3.6)	1	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1 (3.6)	1	0	0	0	0	1 (9.1)	2	0	0
Nausea	1 (3.6)	1	0	0	0	0	1 (9.1)	1	0	0
Vomiting	0	0	0	0	0	0	1 (9.1)	1	0	0
Skin and subcutaneous tissue disorders	2 (7.1)	2	2 (5.6)	2	0	0	0	0	0	0
Rash	2 (7.1)	2	2 (5.6)	2	0	0	0	0	0	0
Renal and urinary disorders	1 (3.6)	1	0	0	0	0	0	0	3 (33.3)	3
Chronic kidney disease	0	0	0	0	0	0	0	0	2 (22.2)	2
Acute kidney injury	1 (3.6)	1	0	0	0	0	0	0	0	0
Oedematous kidney	0	0	0	0	0	0	0	0	1 (11.1)	1
General disorders and administration site conditions	1 (3.6)	1	0	0	0	0	0	0	0	0
Pain	1 (3.6)	1	0	0	0	0	0	0	0	0
Investigations	1 (3.6)	1	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	1 (3.6)	1	0	0	0	0	0	0	0	0

Source: Table 14.3.2.12
AE = Adverse event; Evt = Event; PT= Preferred term; RET = Rearranged during transfection; SOC = System Organ Class
A TEAE was any AE that had onset or any pre-existing AE that had worsened in severity on or after the first dose of study medication
Data were sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
Patients were counted once within an SOC and once for each unique preferred term.
Adverse event data for D4200C00058 and OBS14778 were recoded/coded respectively using MedDRA V22.1.

A total of 16 (17.6%) patients had 22 TEAEs leading to discontinuation from the study, as summarized in Table 24. A higher proportion of patients with RET negative mutation (6 [22.2%] patients, 8 TEAEs) experienced TEAEs that led to discontinuation from study in comparison to patients with RET positive mutation (10 [15.6%] patients, 14 TEAEs).

Table 23. TEAEs leading to discontinuation from study by system organ class and preferred term - Safety population

	RET mutation positive				RET mutation negative					
	Prospective (N=28)		D4200C00058 (N=36)		Prospective (N=7)		D4200C00058 (N=11)		Retrospective (N=9)	
Primary System Organ Class/ Preferred Term	n(%)	Evt	n(%)	Evt	n(%)	Evt	n(%)	Evt	n(%)	Evt
Any TEAE leading to disc. from study	9 (32.1)	13	1 (2.8)	1	1 (14.3)	1	2 (18.2)	4	3 (33.3)	3
Infections and infestations	0	0	0	0	1 (14.3)	1	0	0	0	0
Empyema	0	0	0	0	1 (14.3)	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.6)	1	0	0	0	0	0	0	0	0
Cancer pain	1 (3.6)	1	0	0	0	0	0	0	0	0
Nervous system disorders	1 (3.6)	1	0	0	0	0	0	0	0	0
Hypoaesthesia	1 (3.6)	1	0	0	0	0	0	0	0	0
Cardiac disorders	0	0	1 (2.8)	1	0	0	0	0	0	0
Arrhythmia	0	0	1 (2.8)	1	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	1 (9.1)	1	0	0
Pneumonia aspiration	0	0	0	0	0	0	1 (9.1)	1	0	0
Gastrointestinal disorders	0	0	0	0	0	0	1 (9.1)	3	0	0
Diarrhoea	0	0	0	0	0	0	1 (9.1)	1	0	0
Nausea	0	0	0	0	0	0	1 9.1)	1	0	0
Vomiting	0	0	0	0	0	0	1 (9.1)	1	0	0
Skin and subcutaneous tissue disorders	2 (7.1)	2	0	0	0	0	0	0	0	0
Rash	2 (7.1)	2	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (3.6)	2	0	0	0	0	0	0	0	0
Back pain	1 (3.6)	1	0	0	0	0	0	0	0	0
Musculoskeletal pain	1 (3.6)	1	0	0	0	0	0	0	0	0
Renal and urinary disorders	1 (3.6)	1	0	0	0	0	0	0	3 (33.3)	3
Chronic kidney disease	0	0	0	0	0	0	0	0	2 (22.2)	2
Acute kidney injury	1 (3.6)	1	0	0	0	0	0	0	0	0
Oedematous kidney	0	0	0	0	0	0	0	0	1 (11.1)	1
General disorders and administration site conditions	4 (14.3)	4	0	0	0	0	0	0	0	0
Disease progression	3 (10.7)	3	0	0	0	0	0	0	0	0
Pain	1 (3.6)	1	0	0	0	0	0	0	0	0
Investigations	2 (7.1)	2	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	1 (3.6)	1	0	0	0	0	0	0	0	0
Weight decreased	1 (3.6)	1	0	0	0	0	0	0	0	0

Source: Table 14.3.2.16
AE = Adverse event; Evt = Event; PT= Preferred term; RET = Rearranged during transfection; SOC = System Organ Class
A TEAE was any AE that has onset or Any pre-existing AE that had worsened in severity on or after the first dose of study medication
Data were sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
Patients were counted once within an SOC and once for each unique preferred term.
Adverse Event data for D4200C00058 and OBS14778 were recoded/coded respectively using MedDRA V22.1.

Deaths

In all, 27 (29.1%) patients died during the study; of these, 23 deaths were not due to an AE and 4 deaths were due to an AE. The 27 patients consisted of 20 RET positive patients and 7 RET negative patients. A summary of all 27 patients who died during the study is provided in Table 25.

Of the 4 patients who died due to an AE:

- Two RET mutation positive patients had an AE with fatal outcome per the initial CTCAE grade.
  - One patient experienced an AE of disease progression, unrelated to vandetanib
  - The other patient, previously reported in Study D4200C00058, experienced AEs of cardiac failure acute and arrhythmia, both of which were considered related to vandetanib.
- One RET mutation negative patient, previously reported in Study D4200C00058, had an AE with fatal outcome following a CTCAE grade change; this patient experienced an AE of pneumonia aspiration, unrelated to vandetanib.
- One RET mutation positive patient) had an AE of disease progression with a maximum CTCAE grade of "severe"; this AE was unrelated to vandetanib.

Of the 23 patients for which the cause of death was not reported as an AE, 17 were RET positive and 6 were RET negative. For these 23 patients, the reported primary causes of death were MTC (5 patients), underlying disease (1 patient), and respiratory insufficiency (secondary cause of death: disease progression) (1 patient); for the other 16 patients, the primary cause of death was unknown.

Table 24. Summary of primary cause of death - Safety Population

	RET mutation positive			RET mutation negative				
	Prospective D4200C00058 (N=28) n(%)	(N=36) n(%)	All (N=64) n(%)	Prospective D4200C00058 (N=7) n(%)	(N=11) n(%)	Retrospective (N=9) n(%)	All (N=27) n(%)	Overall (N=91) n(%)
Total Deaths	11 (39.3)	9 (25.0)	20 (31.3)	2 (28.6)	1 (9.1)	4 (44.4)	7 (25.9)	27 (29.7)
Fatal TEAE[a]	2 (7.1)	1 (2.8)	3 (4.7)	0	1 (9.1)	0	1 (3.7)	4 (4.4)
Medullary thyroid cancer	1 (3.6)	4 (11.1)	5 (7.8)	0	0	0	0	5 (5.5)
Underlying disease	0	1 (2.8)	1 (1.6)	0	0	0	0	1 (1.1)
Respiratory insufficiency	0	1 (2.8)	1 (1.6)	0	0	0	0	1 (1.1)
Unknown	8 (28.6)	2 (5.6)	10 (15.6)	2 (28.6)	0	4 (44.4)	6 (22.2)	16 (17.6)

Source: Table 14.3.2.21
RET = Rearranged during transfection; TEAS = Treatment-emergent adverse event
a A fatal TEAE is a treatment-emergent AE that had a fatal outcome. A patient was counted once if a patient had at least 1 fatal TEAE.
Deaths were reported as a Fatal TEAE if death was reported as a TEAE. Otherwise, death was reported by primary cause of death (if collected) or unknown if only death date was available.

Investigations

A total of 13 patients (14.3%) experienced TEAEs of electrocardiogram QT prolonged (11 RET positive [17.2%] and 2 RET negative [7.4%] patients); in 12 (13.2%) the TEAE was assessed as related to vandetanib. In 6 of the 13 cases, the event was mild, in 5 moderate, and in 2 severe. These events resolved for all but 3 patients, who had mild/moderate cases and were lost to follow-up (one due to disease progression, one due to withdrawal from study related to a different AE, and one due to study closure in July 2020). One patient (RET positive) experienced a serious TEAE of electrocardiogram QT prolonged, which resolved.

The mean QTc (Bazett) showed similar mean QTc intervals for RET positive and RET negative patients through Week 144 (generally ranging from 436 – 456 ms).

A total of 8 patients experienced a QTc interval >500 ms (associated with increased risk of ventricular arrhythmia), 7 of whom were RET positive and 1 of whom was RET negative, and 6 of whom were originally enrolled in Study D4200C00058. Of these 8 patients, 2 experienced other cardiac-related TEAEs (E2301002 and E2301006); all of these TEAEs resolved except for an ongoing mild left bundle branch block (E2301002) and the fatal TEAEs of arrythmia and cardiac failure, considered related to vandetanib (as noted above, this patient case has already been reported in the D4200C00058 CSR and

labeled). The QT prolongation is an expected adverse drug reaction of vandetanib along with ventricular arrhythmia labeled in the vandetanib SmPC.

There was no significant difference between the RET positive and negative patients in reference to the laboratory parameters and vital signs.

Assessment of the MAH's response

In the response, the MAH provided the final CSR for study D4200C00104 (OBS14778) as requested. In this CSR data were pooled from the observational D4200C00104 study (prospectively and retrospectively enrolled patients) and the phase 3 D4200C00058 study (reanalyzed samples that were previously categorized as RET mutation "unknown"). This is in line with the SOB formulated after variation II/0028 to enroll 20-25 RET mutation positive and 20-25 RET mutation negative patients including retrospective enrollment in study D4200C00104 and re-analysis of samples in the pivotal study D4200C00058. The study population analyzed in the CSR consisted of the following three groups:

1. 40 patients prospectively recruited (30 patients with RET positive mutation, 7 patients with RET negative mutation, 3 patients with unknown RET status)
2. 10 RET negative patients retrospectively recruited
3. 47 patients from the randomized study D4200C00058 who had their RET status reanalyzed (36 patients with RET positive mutation, 11 patients with RET negative mutation).

As part of the study was specifically recruiting RET negative patients, a higher than expected percentage of all patients had a RET negative status.

Regarding efficacy, tumor response was evaluated in 55 RET positive patients and 20 RET negative patients. In the RET negative population, 1 patient from study D4200C00058 had no evaluable baseline RECIST assessment. In addition, 7 patients were not evaluable in the retrospective RET negative cohort in study D4200C00104: 1 did not meet eligibility criteria, 1 did not take at least 1 dose of vandetanib, and 5 had no evaluable baseline RECIST assessment. For response analysis, there was no central review of imaging in the prospective and retrospective cohorts. The ORR was 41.8% (95% CI: 28.7-55.9) for RET positive patients and 5.0% (n=1 [PR]; 95% CI: 0.1-24.9) for RET negative patients. More RET positive patients experienced CR and PR compared to RET negative patients (CR: 3.6% versus 0%; PR: 38.2% versus 5.0%, respectively). The one patient achieving a PR in the RET negative cohort was from study D4200C00058. Compared to the preliminary analysis provided before, there is one patient less achieving a response in the RET negative population. Based on the information provided previously the patients with a response in the RET negative population had a RAS mutation and the MAH is requested to confirm that the one patient in the final CSR with a response in the RET negative population had a RAS mutation and to describe this in the SmPC (**OC**), as this might mechanistically explain activity in a RET negative tumor. SD was reported in 43.6% of the RET positive patients and 85.0% of the RET negative patients. For PD these numbers were 7.3% in RET positive patients and 5.0% in RET negative patients, respectively. DCR (CR, PR, or SD) was 85.5% in the cohort with RET positive patients and 90% in the cohort with RET negative patients. Median DOR was 24.9 months in the RET positive patients and for the 1 RET negative patient this was 5.3 months. Median PFS (95% CI) was 24.6 months (95% CI: 15.6-31.8) in RET positive patients and 24.6 months (95% CI: 9.9-59.5) in RET negative patients. There were 4 deaths (11.1%) in RET positive patients and 2 (14.3%) in RET negative patients. Time dependent outcomes are difficult to interpret in this non-randomized, observational study. ORR in the RET positive patients was comparable to that shown in study D4200C0058 (i.e. 45%). However, the response rate of 5% in RET negative patients was substantially lower than the response rate of 35% in the cohort of 46 patients who were classified as RET negative (i.e. "with no M918T mutation and no other identified mutation") and treated with vandetanib in the registration study. This discrepancy is as yet unexplained. Also, which RET mutations were investigated at the time of approval besides the M918T in that population

is not clear. As a consequence, the B/R in the RET negative patients may be impacted. The MAH is, therefore, requested to elaborate on the differences in response rate reported at the time of the CMA and the currently provided data, including a clarification on the performed RET mutation analysis at the time of approval in comparison to the currently provided re-analysis. Next, the MAH should confirm that all of the 46 patients classified at the time of approval as RET-negative would still be RET-negative following re-analysis. Finally, the MAH should discuss the impact of this additional information on the B/R in the RET-negative patients (**MO**).

Regarding safety, 91 patients received at least 1 dose of vandetanib (64 RET positive and 27 RET negative) with a median exposure of around 2 years. Based on the provided results, a higher rate of AEs (98 vs 89%) and serious AEs (31 vs 22%) were reported in the RET positive compared to the RET negative patients. Most common AEs observed were diarrhea, rash, and hypertension. It is agreed with the MAH that the reported AEs are consistent with the known safety profile of vandetanib. It is noted that the toxicity profile is substantial and should be weighed against the benefit in RET negative patients.

In conclusion, data from a total of 20 RET negative patients treated with vandetanib were available. This is in line with the SOB formulated after variation II/0028 to enroll 20-25 RET mutation positive and 20-25 RET mutation negative patients including retrospective enrollment in study D4200C00104 and re-analysis of samples in the pivotal study D4200C00058. The activity in the RET negative patients is low with only 1 responder in 20 efficacy evaluable patients. Combined with the currently identified uncertainties on the efficacy in the patients previously classified as RET-negative and the known substantial toxicity, the B/R in RET negative patients is uncertain (**MO**). The B/R balance for the RET positive population remains positive.

Based on the provided response to the MO, the indication might have to be restricted to RET positive patients. Therefore, possible consequences to section 4.1 and 4.4 of the SmPC can currently not be assessed. It is, in principle, agreed to update section 5.1 with the data provided. Regarding the text in section 5.1 textual changes are proposed (please refer to the SmPC assessment; **OC**). A final conclusion can be made pending the B/R in the RET negative patients.

Based on the provided CSR the MAH considers that the SOB001 is fulfilled and can be lifted from the Marketing Authorisation in order to convert it from a conditional to a standard MA. As the final CSR is currently submitted confirming the efficacy and safety in Caprelsa in 20 RET negative patients, it is agreed that the SOB is, in principle, fulfilled pending the response to the LoQ. However, based on the provided data the B/R in RET negative patients is uncertain (**MO**).

Of note, as written in a previous communication with and agreed by the EMA in 2020, the MAH is not providing an updated RMP, it will be provided in another variation upon approval of the current type II labelling variation at a later stage.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

12. Attachments

Please refer to Attachment 1 which includes the Product Information.

13. Request for supplementary information 2

13.1. Major objections

Clinical aspects

1. The response rate of 5% in RET negative patients was lower than the reported response rate of 35% in the cohort of 46 patients classified as RET negative (i.e. "with no M918T mutation and no other identified mutation") in the registration study. This discrepancy is unexplained and B/R in the RET negative patients may be impacted. Also, which RET mutations were investigated at the time of approval besides the M918T in that population is not clear. Therefore, the MAH is requested to:

    a. elaborate on the differences in response rate reported at the time of the CMA and the currently provided data, including a clarification on the performed RET mutation analysis at the time of approval in comparison to the currently provided re-analysis and details on subjects disposition and patient flow specific to RET mutation status (re-)classification over time;

    b. the MAH should confirm that all of the 46 patients classified and treated with vandetanib at the time of approval as RET-negative would still be RET-negative following re-analysis;

    c. subsequently, discuss the B/R in the RET negative population given the known substantial toxicity profile.

13.2. Other concerns

Clinical aspects

- The MAH is requested to confirm that the one patient in the final CSR with a response in the RET negative population had a RAS mutation and to describe this in the SmPC.
- Regarding the text in section 5.1 textual changes are proposed (please refer to the SmPC assessment).

14. Assessment of the responses to the request for supplementary information 2

14.1. Major objections

Clinical aspects

Question 1

The response rate of 5% in RET negative patients was lower than the reported response rate of 35% in the cohort of 46 patients classified as RET negative (i.e. "with no M918T mutation and no other identified mutation") in the registration study. This discrepancy is unexplained and B/R in the RET negative patients may be impacted. Also, which RET mutations were investigated at the time of approval besides the M918T in that population is not clear. Therefore, the MAH is requested to:

a. *elaborate on the differences in response rate reported at the time of the CMA and the currently provided data, including a clarification on the performed RET mutation analysis at the time of approval in comparison to the currently provided re-analysis and details on subjects disposition and patient flow specific to RET mutation status (re-)classification over time;*

b. *the MAH should confirm that all of the 46 patients classified and treated with vandetanib at the time of approval as RET-negative would still be RET-negative following re-analysis;*

c. *subsequently, discuss the B/R in the RET negative population given the known substantial toxicity profile.*

Summary of the MAH's response

Question 1a

The differences in objective tumor response rates are explained by progresses made by the science in determining *RET* status in patients with medullary thyroid cancer (MDT):

- At the time of the CMA (February 2012), the response rate in 46 patients treated with vandetanib and having no M918T mutation in study D4200C00058 was 35%, based on a blinded central review of imaging.
- At that time, it was hypothesized that patients having no M918T mutation by amplification refractory mutation system (ARMS) analysis had a high probability (86%) to have no additional *RET* mutation detected (Elisei et al., J Clin Endocrinol Metab, 2008) (see also Appendix 1 below for detailed description of the methodology and results obtained).
- In December 2018, as part of the variation procedure no. EMEA/H/C/002315/II/0028, the MAH proposed to re-analyze the mutation status of patients enrolled in study D4200C00058 using new technologies. Using these new technologies only 11 out of 46 patients (23.9%) treated with vandetanib were confirmed to be *RET*-negative. All other patients were reclassified as being *RET*-positive (see Appendix 1 below for detailed description of the methodology and results obtained).
- Recruitment of *RET*-negative patients in the observational study OBS14778/D4200C00104 was difficult. It was thus agreed to pool *RET*-negative patients newly identified from re-analysis of study D4200C00058 (with patients enrolled in study OBS14778).
  Study OBS14778 thus analyzed 10 *RET*-negative patients from study D4200C00058 (1 patient was excluded because RECIST evaluation at baseline was lacking), 7 *RET*-negative patients recruited prospectively and 3 *RET*-negative patients recruited retrospectively.

Objective responses were exclusively found in patients from study D4200C00058. Therefore, the objective response (ORR) in *RET*-negative patients of Study OBS14778 was as follows:

- 5% (1/20) as per investigator evaluation of tumor response in study D4200C00058 (listing used for the analysis of Study OBS14778)
- 10% (2/20) as per blinded centralized review of tumor response in study D4200C00058 (listing not used for the analysis of Study OBS14778)

The fact that no objective tumor response was observed in patients recruited either prospectively or retrospectively in study OBS14778 may be partly explained by the observational design of the study (lack of central review of tumor response, frequency of monitoring visits left at the discretion of the treating physician, no centralized determination of *RET* status).

Based on the above information, the MAH believes that the ORR rate observed following the reanalysis of *RET* status in Study D4200C00058 (18.2%) is more reliable, since it was a randomized placebo-controlled trial with a blinded central review of imaging. Results of this reanalysis of are provided below (see Appendix 2 below):

- Of the 69 patients lacking mutation M918T and who had their *RET* status re-analyzed, 17 were confirmed to be *RET*-negative (11 in the vandetanib arm and 6 in the placebo arm) and 52 were reclassified at *RET*-positive, leading to a total of 239 *RET*-positive patients (172 in the vandetanib arm and 67 in the placebo arm).
- Two (2) out of 11 *RET*-negative patients (18.2%) treated with vandetanib had an objective tumor response versus 0 out of 6 patients treated with placebo (Table 26).
- At 2 years, 90% of *RET*-negative patients treated with vandetanib had no disease progression versus 50% of *RET*-negative patients treated with placebo (Table 27).

Table 25. Objective response rate and disease control rate by updated RET status on study D4200C00058 (full analysis set)

					RET-					
	RET+ (N=239)		All *RET-* (N=17)		*RAS- BRAF-* (N=2)		*RAS+* (N=14)		*BRAF+* (N=1)	
Parameter	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Objective Response Rate (ORR)	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Disease Control Rate (DCR)	149 (86.6%)	45 (67.2%)	8 (72.7%)	6 (100%)	0	1 (100%)	7 (77.8%)	5 (100%)	1 (100%)	0

All *RET*-negative (*RET*-) patients included: patients *RET-/ RAS-/ BRAF-*; patients *RET-/ RAS+* and patients *RET-/ BRAF+*

Table 26. Progression-free survival in study D4200C00058 by updated RET status (full analysis set)

	RET+ (N = 239)		All *RET-* (N = 17)		*RET-*					
	Vandetanib (N = 172)	Placebo (N = 67)	Vandetanib (N = 11)	Placebo (N = 6)	RAS-BRAF- Vandetanib (N = 1)	RAS-BRAF- Placebo (N = 1)	RAS+ Vandetanib (N = 9)	RAS+ Placebo (N = 5)	BRAF+ Vandetanib (N = 1)	BRAF+ Placebo (N = 0)
Number of events, n (%)	60 (34.9%)	38 (56.7%)	1 (9.1%)	3 (50.0%)	0	1 (100.0%)	1 (11.1%)	2 (40.0%)	0 (0.0%)	0
Median PFS (months)	NC	18.0	NC	NC	-	11.5	NC	NC	NC	-
Percentage of patients at 6 months	90.9	71.2	90.0	100	-	100	88.9	100	100	-
Percentage of patients at 1 year	83.3	61.9	90.0	66.7	-	0.0	88.9	80.0	100	-
Percentage of patients at 2 years	55.7	40.1	90.0	50.0	-	0.0	88.9	60.0	100	-

All *RET* negative (*RET*-) patients included: patients *RET-/ RAS-/ BRAF-*; patients *RET-/ RAS+* and patients *RET-/ BRAF+*; NC: Not calculable due to an insufficient number of events; PFS: Progression-free survival

Interestingly, a vast majority of *RET*-negative patients in study D4200C00058 were found to have a concomitant *RAS* mutation (14/17, 82.4%). In a recent series of 209 patients with MTC analyzed by next-generation sequencing (Ciampi et al., iScience, 2019), *RAS* mutations were observed in approximately 30% of cases and were mutually exclusive with *RET* mutations. Both *RET*-negative patients having an objective tumor response with vandetanib had a concomitant *RAS* mutation.

Appendix 1: History of RET mutation analysis

Initial RET mutation statis determination in study D4200C00058 (phase III study)

Initial *RET* mutation status was determined by AstraZeneca's Tissue Bank Reception (Alderley Park, Macclesfield, Cheshire UK) by sequencing the 6 most commonly mutated exons in MTC (10, 11, 13, 14, 15 and 16) and by looking for the M918T mutation using an ARMS analysis.

- A *RET*-positive mutation status was defined as having a mutation either observed from the sequencing or ARMS assay.
- A *RET*-negative mutation status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons plus the ARMS assay negative for a M918T mutation.
- A *RET* "Unknown" mutation status was documented when 1 or more sequencing assay was unsuccessful (non-informative) and none of the successful assays demonstrated a mutation.

Based on this methodology, 331 patients enrolled in the Study D4200C00058 were classified as follows:

- 187 patients (56.5%) were found to be *RET*-positive
- 8 patients (2.4%) were found to be *RET*-negative
- 136 patients (41.1%) had an "unknown" *RET*-status

Proposed new classification of patients (based on absence of M918T mutation) in November 2011

In November 2011, in the frame of response to second outstanding issues - clinical (sequence 0010), the applicant suggested a less stringent classification of patients with MTC, based on presence or absence of M918T mutation. This was based on a publication by Elisei (Elisei et al., J Clin Endocrinol Metab, 2008) suggesting that 86% of patients having no M918T mutation had no additional *RET* mutation identified.

In study D4200C00058, 79 patients (8 patients initially classified as *RET*-negative and 71 patients initially classified as *RET* "unknown") had no mutation M918T. It was extrapolated that these patients would be *RET*-negative. Of them, 46 received vandetanib with a response rate of 35% (Table 28).

Table 27. Efficacy endpoints in RET mutation positive patients and 79 patients with no M918T mutation and no other RET mutation identified

Efficacy end-point	*RET* Mutation positive (n=187)*	Patients with no M918T mutation and no other identified mutation (n=79)
PFS hazard ratio [95% confidence interval]	0.45 [0.26-0.78]	0.57 [0.29-1.13]
Predicted median PFS (vandetanib vs placebo)	29 vs 18 months	28 vs 18 months
Objective response rate (vandetanib arm)	52%	35%
Duration of response	22 months	18 months

**RET* mutation positive hereditary and sporadic medullary thyroid cancer patients; PFS: Progression-free survival

Appendix 2:

In December 2018, as part of the variation procedure no. EMEA/H/C/002315/II/0028 (sequence 0114), the MAH proposed to re-analyze the mutation status of patients enrolled in study D4200C00058 using new technologies.

Of 79 patients with no mutation M918T mutation and thus considered *RET*-negative at the time of approval, 69 had enough tissue for *RET* status re-analysis.

Of these 69 patients re-analyzed, only 17 were found to be *RET*-negative and 52 were reclassified at *RET*-positive. A vast majority of *RET*-negative patients had a concomitant *RAS* mutation (14/17, 82.4%) (Table 29).

Table 28. Overall disposition of patients enrolled in study D4200C00058 following re-analysis of RET status

					RET -					
	RET+ (N = 239)		All *RET-* (N=17)		*RAS- BRAF-* (N=2)		*RAS+* (N=14)		*BRAF+* (N=1)	
	Vandetanib (N = 172)	Placebo (N = 67)	Vandetanib (N = 11)	Placebo (N = 6)	Vandetanib (N = 1)	Placebo (N = 1)	Vandetanib (N = 9)	Placebo (N = 5)	Vandetanib (N = 1)	Placebo (N = 0)
Patients randomized	172	67	11	6	1	1	9	5	1	0
Patients who received double-blind treatment	172 (100%)	66 (98.5%)	11 (100%)	6 (100%)	1 (100%)	1 (100%)	9 (100%)	5 (100%)	1 (100%)	0
Patients who received open-label treatment	65 (37.8%)	50 (74.6%)	7 (63.6%)	4 (66.7%)	0	1 (100%)	6 (66.7%)	3 (60.0%)	1 (100%)	0

All *RET* negative (*RET-*) patients included: patients *RET-/ RAS-/ BRAF-*; patients *RET-/ RAS+* and patients *RET-/ BRAF+*

Among these 17 *RET*-negative patients, 11 received vandetanib with an ORR rate 18.2% (2/11) (Table 30). These 2 patients were *RET*-negative/ *RAS*-positive and had a duration of response of 38 and 96 weeks, respectively.

Table 29. Efficacy endpoints in RET mutation positive patients and RET mutation negative patients following re-analysis of RET mutational status

Efficacy end-point	*RET* mutation positive (n = 239)	*RET* mutation negative (n = 17)
Objective response rate (vandetanib arm vs placebo)	51.7% vs 14.9%	18.2% vs 0%
2-year PFS rate	55.7% vs 40.1%	90.0% vs 50.0%

PFS: Progression-free survival

Study OBS14778 (D4200C00104)

In parallel, the observational study OBS14778 was conducted to fulfill the specific obligation linked to the CMA of vandetanib.

Only 10 evaluable *RET*-negative patients could be recruited at study sites (7 enrolled prospectively and 3 enrolled retrospectively). Because recruitment of *RET*-negative patients was difficult, it was agreed to pool these 10 patients with 10 *RET*-negative patients newly identified from re-analysis of study D4200C00058 (1 patient was excluded because he was lacking RECIST evaluation at baseline).

Among patients enrolled in prospective and retrospective cohorts, none had an ORR. Objective responses were exclusively found in patients from study D4200C00058. Therefore, the ORR in *RET*-negative patients of study OBS14778 was:

• 5% (1/20) as per investigator evaluation of tumor response in study D4200C00058 (listing used for the analysis of study OBS14778)

• 10% (2/20) as per blinded centralized review of tumor response in study D4200C00058 (listing not used for the analysis of Study OBS14778)

Question 1b

Of 46 patients considered *RET*-negative at the time of approval and treated with vandetanib, 11 patients were confirmed to be *RET*-negative, and 35 patients were reclassified as *RET*-positive.

Of these 11 *RET*-negative patients:

- 9 patients were *RET*-negative/*RAS*-positive
- 1 patient was *RET*/*RAS*/*BRAF*-negative
- 1 patient was *RET*-negative/*BRAF*-positive

Question 1c

No new safety signal was observed in *RET*-negative patients. Based on the cumulative evidence and the detailed results from re-analysis in Study D4200C00058, the B/R in *RET*-negative patients is still considered positive by the MAH.

Figure 8. Value tree of key benefits and risk outcomes for vandetanib in MTC

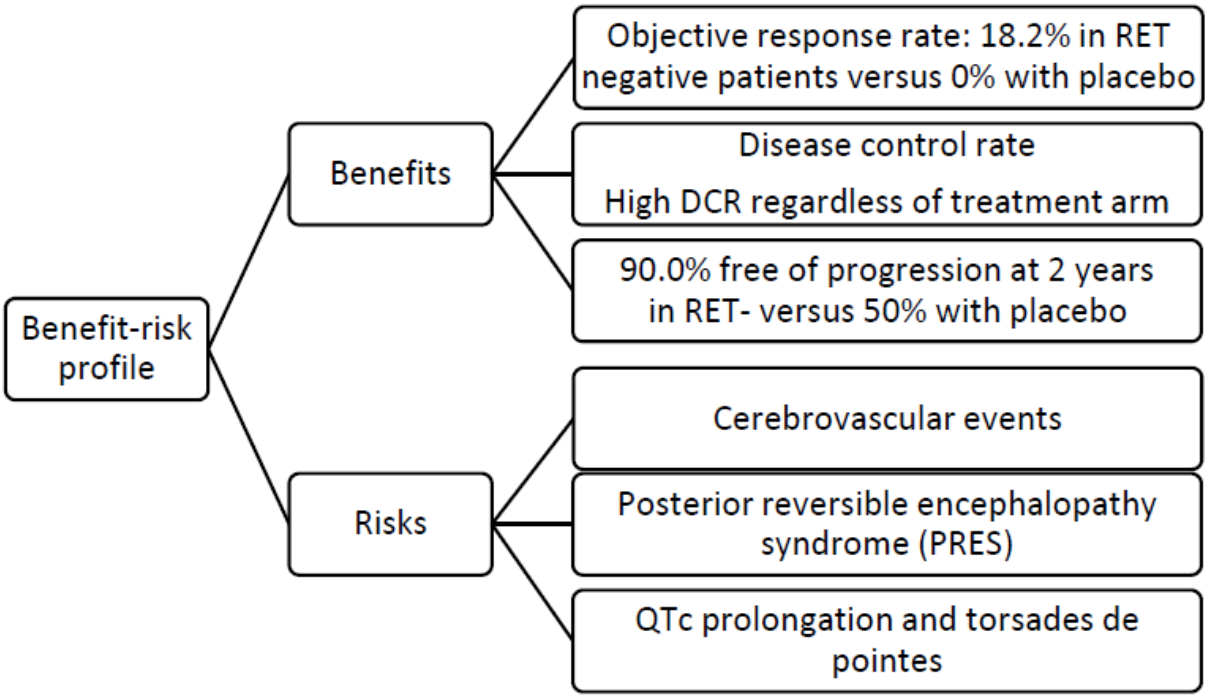


Table 30. Benefit-risk assessment table for vandetanib in the treatment of aggressive and symptomatic MTC in RET-negative patients with unresectable locally advanced/metastatic disease

	Evidence and uncertainties	Conclusion and reasons
Analysis of condition	MTC is a rare cancer (2.1% of all types of thyroid cancers). Of the overall MTC cases, only 10% patients are *RET* mutation negative, making it very rare population. Most *RET* negative patients have a concomitant mutation in *RAS* gene. In routine clinical practice, *RET* and *RAS* mutation status is rarely evaluated prior to treatment initiation.	*RET*-negative patient population is very limited in MTC patients. Most *RET*-negative have a concomitant mutation of *RAS* gene.
Current treatment options	For resectable MTC, surgery is the primary treatment For unresectable, recurrent or symptomatic and progressing MTC, preferred options are vandetanib and cabozantinib as per international guidelines There is no head-to-head study comparing vandetanib versus cabozantinib	Vandetanib is an effective first-line treatment option for unresectable, advanced metastatic MTC. There are limited treatment options in *RET*-negative patients.
Benefits	In *RET*-negative patients, vandetanib shows an objective tumor response of 18.2% (versus 0% with placebo) and 90% of patients are free from progression at 2 years (versus 50% with placebo). *RET*-negative patients having an objective response with vandetanib had a concomitant *RAS* mutation Limitations: There was a low number of *RET*-negative patients enrolled in Study D4200C00058.	Based on the findings and study limitations, efficacy of vandetanib is acceptable in the *RET*-negative patients.
Risks and risk management	Adverse events in *RET*-negative patients are in agreement with the known safety profile vandetanib. No new safety findings were identified in *RET*-negative patients.	Acceptable safety profile was observed in *RET*-negative patients with MTC. Current risk management strategy is appropriate to minimize the risks.

Conclusion

Considering the post-hoc re-analysis of the pivotal study D4200C00058 the B/R profile of vandetanib is considered acceptable in *RET*-negative patients with unresectable locally advanced or metastatic MTC with an ORR of 18.2% with vandetanib versus 0% with placebo and a PFS rate at 2 years of 90% with vandetanib versus 50% with placebo.

Interestingly, *RET*-negative patients having an objective tumor response with vandetanib had a concomitant *RAS* mutation. These patients represent the majority of *RET*-negative patients.

No new safety signal was observed in *RET*-negative patients.

Thus, the MAH believes that the B/R balance of vandetanib remains positive in the currently approved indication regardless of the *RET* status and vandetanib should not be contraindicated in *RET*-negative patients with MTC.

The MAH proposes to provide addendum reports to the 2 studies (OBS14778 and D4200C00058) as soon as possible and, based on the re-analysis of *RET* mutation status recently performed, to update more adequately the section 5.1 of the Summary of Product Characteristics (SmPC) regarding the RET-negative patients.

Assessment of the MAH's response

The positive B/R for vandetanib including RET negative patients at time of CMA was based on a response rate per blinded central review of 35% in study D4200C00058 in 46 vandetanib-treated patients that had no M918T mutation. RET mutation status was determined by sequencing the 6 most commonly mutated exons in MTC (exon 10, 11, 13, 14, 15, and 16) and by amplification refractory mutation system (ARMS) analysis. A RET negative mutation status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons plus the ARMS assay negative for a M918T mutation. According to the MAH, it was anticipated at that time that patients with no M918T mutation had a high probability to have no additional RET mutation.

Using new technologies, part of the samples in study D4200C00058 were reanalysed, which confirmed RET negative status in only 11 of 46 patients previously classified as RET negative at time of CMA. The remaining 35 patients were reclassified as RET positive. The new technologies used were a custom Taqman assay to genotype the RET M918T mutation and, when adequate material was available, sequencing using Illumina technology to reveal any other RET mutations.

RET negative patients as confirmed by new mutation analysis technologies from study D4200C00058 were pooled with RET negative patients from the observational study OBS14778/D4200C00104 in order to provide a higher number of RET negative patients to confirm the positive B/R as SOB. The pooled RET negative pool consisted of 10 patients from study D4200C00058 and 10 patients from study OBS14778/D4200C00104 (7 recruited prospectively and 3 patients retrospectively). One of the patients from the D4200C00058 was excluded from the pooled analysis, because RECIST evaluation at baseline was lacking. The MAH is requested to confirm this concerns the assessment by investigator and the reason why this was not performed or resolved during the study (**OC**). In the pooled set of 20 RET negative patients, in one patient from study D4200C00058 a PR was observed, leading to an ORR per investigator of 5%.

The MAH is of the opinion that the analysis of RET negative patients in the D4200C00058 is more reliable than the pooled analysis as this was a randomised placebo-controlled study using blinded central review of tumour responses. According to the MAH, the observational design of study OBS14778/D4200C00104 can partly explain the lack of responses in the study, as there was a lack of central review of tumour response, the frequency of monitoring visits was left at the discretion of the treating physician, and there

was no centralised determination of RET status. When looking specifically at the D4200C00058 data, an ORR per central review was observed of 18.2% (2 out of 11 patients). Of note, both patients had a RAS positive status.

Based on the response rate in study D4200C00058 after post-hoc re-analysis of the samples, the B/R profile of vandetanib is considered acceptable in RET negative patients in view of the MAH with an ORR of 18.2% with vandetanib versus 0% with placebo and a PFS rate at 2 years of 90% with vandetanib versus 50% with placebo. Combined with the observation that no new safety signals were reported in RET negative patients, the MAH believes that the B/R balance of vandetanib remains positive in the currently approved indication regardless of the RET status and vandetanib should not be contraindicated in RET negative patients with MTC.

By changing the primary population from the pooled set of the randomised placebo-controlled study D4200C00058 and the observational study OBS14778/D4200C00104 to only the D4200C00058 study, two questions arise. The first question is whether it is valid to leave out the patients from the observational study and the second question is whether the SOB can be considered fulfilled based on only the D4200C00058 RET negative population. Regarding the first question, the MAH is not supported that the patients from the observational study should be disregarded. In the D4200C00058 RET negative population, only 1 response (or 2 pending on the used tumour assessment) was observed in 10 patients. It cannot be concluded that this is much higher than no responses in the 10 RET negative patients from OBS14778/D4200C00104 and to leave out the observational study population. In addition, by excluding the patients from study OBS14778/D4200C00104, only 11 RET negative patients are included which does not correspond with the 20-25 RET negative patients as defined in the SOB.

An even more important question is whether efficacy and safety is now confirmed in RET negative patients, which was the goal of the SOB. The activity in the RET negative patients is low with only 1 (or 2) responder(s) in 20 efficacy evaluable patients. The response rate of 35% in the group with "no M918T mutation and no other RET mutation identified" at time of the CMA now appears to be based on inaccurate data, as the majority of patients was actually RET positive. It is unlikely that the reported response rate of 5% in 20 RET negative patients will translate into a clinical benefit. Combined with the known substantial toxicity, the B/R in RET negative patients cannot be considered positive. Therefore, the indication should be restricted to RET positive patients (**MO**). The B/R balance for the RET positive population remains positive.In addition to the concerns described above, discrepancies were noted for the number reported in the D4200C00058 study. One of the discrepancies concerns the number of patients that had "unknown" RET status at time of CMA based on initial RET analysis. According to the EPAR this number was 138, but Appendix 1 reports 136 patients with "unknown" RET status. Another discrepancy that is noted, is the number of RET negative patients after the re-analysis. The MAH describes that re-analysis was performed for RET mutation status "unknown" samples (n=67), previously RET negative samples (n=2), and previously RET positive (n=4). The reanalysis confirmed the four previously RET positive patients to be RET positive, and 1 of 2 previously RET negative patients was found to be RET positive. Out of the 67 RET unknown patients re-analyzed, 52 were reclassified as RET positive and 15 were found to be RET negative. In total, 17 patients were found to be RET negative according to the MAH. However, the number of 17 RET negative patients is not understood as 15 RET negative samples out of the previously unknown set and 1 RET negative patients out of the previously RET negative set adds up to 16. The MAH is requested to clarify these discrepancies, adjust the numbers if needed, and to discuss the consequences for the interpretation of the results (**OC**).

Of note, it was agreed with the EMA that an updated SmPC will be submitted at a later stage of the procedure as the MAH had to generate additional statistical reports from the clinical study and these new tables will not be available before the end of the year/beginning 2022. Therefore, the SmPC will be assessed in the next round (see also question 3).

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

14.2. Other concerns

Clinical aspects

Question 2

The MAH is requested to confirm that the one patient in the final CSR with a response in the RET negative population had a RAS mutation and to describe this in the SmPC.

Summary of the MAH's response

It is confirmed that the RET-negative patient (E1201002) in the CSR of study OBS14778 with a response was RAS-positive. This patient was coming from study D4200C00058 and the ORR was determined using the investigator evaluation on site.

According to the blinded central review of study D4200C00058, 2 RET-negative patients (E1001011 and E1701002) had an objective tumour response and patient E1201002 had a stable disease. These data were not reported in the CSR. Patients E1001011 and E1701002 had also a RAS mutation.

The MAH agrees to describe this information in the SmPC. However, no updated product information is proposed yet, waiting for the addendum reports of studies OBS14778 and D4200C00058 to update more adequately the section 5.1 of the SmPC regarding the RET-negative patients.

Assessment of the MAH's response

The MAH confirmed that that the RET-negative patient (E1201002) in the CSR of study OBS14778 with a response was RAS-positive.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 3

Regarding the text in section 5.1 textual changes are proposed (please refer to the SmPC assessment).

Summary of the MAH's response

The MAH endorses the Rapporteur's comments. However, no updated product information is proposed yet, waiting for the addendum reports of studies OBS14778 and D4200C00058 to update more adequately the section 5.1 of the SmPC regarding the *RET*-negative patients.

Assessment of the MAH's response

It was agreed with the EMA that an updated SmPC will be submitted at a later stage of the procedure as the MAH had to generate additional statistical reports from the clinical study and these new tables will not be available before the end of the year/beginning 2022. Therefore, the SmPC will be assessed in the next round (**OC**).

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

15. Request for supplementary information 3

15.1. Major objections

Clinical aspects

1. Efficacy of Caprelsa has not been established in patients with RET negative status. Having in mind the known substantial toxicity, the B/R balance is negative for these patients. The MAH is requested to restrict the indication to RET positive patients.

15.2. Other concerns

Clinical aspects

2. The pooled RET negative sample consisted of 10 patients from study D4200C00058 and 10 patients from study OBS14778/D4200C00104 (7 recruited prospectively and 3 patients retrospectively). One of the patients from the D4200C00058 was excluded from the pooled analysis, because RECIST evaluation at baseline was lacking. The MAH is requested to confirm this concerns the assessment by investigator and the reason why this was not performed or resolved during the study.
3. Discrepancies were noted for the number reported in the D4200C00058 study. One of the discrepancies concerns the number of patients that had "unknown" RET status at time of CMA based on initial RET analysis. According to the EPAR this number was 138, but Appendix 1 reports 136 patients with "unknown" RET status. Another discrepancy that is noted, is the number of RET negative patients after the re-analysis. The MAH describes that re-analysis was performed for RET mutation status "unknown" samples (n=67), previously RET negative samples (n=2), and previously RET positive (n=4). The reanalysis confirmed the four previously RET positive patients to be RET positive, and 1 of 2 previously RET negative patients was found to be RET positive. Out of the 67 RET unknown patients re-analyzed, 52 were reclassified as RET positive and 15 were found to be RET negative. In total, 17 patients were found to be RET negative according to the MAH. However, the number of 17 RET negative patients is not understood as 15 RET negative samples out of the previously unknown set and 1 RET negative patients out of the previously RET negative set adds up to 16. The MAH is requested to clarify these discrepancies, adjust the numbers if needed, and to discuss the consequences for the interpretation of the results.

16. Assessment of the response to the request for supplementary information 3

16.1. Major objections

Clinical aspects

Question 1

Efficacy of Caprelsa has not been established in patients with RET negative status. Having in mind the known substantial toxicity, the B/R is negative for these patients. The MAH is requested to restrict the indication to RET positive patients.

Summary of the MAH's response

The MAH agrees that the activity of Caprelsa in patients lacking a RET mutation (M918T or other) is less pronounced than in RET "positive patients". However, there is additional information in the two clinical study reports (CSR) joined to this response (addendum to Study D4500C00058 CSR, addendum of Study OBS14778 CSR) suggesting that Caprelsa remains a treatment option for RET "negative patients".

Reanalysis of RET status in Study D4500C00058 "An International, Phase III, Randomized, Double-Blinded, Placebo-controlled, Multi-center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer"

- In study D4500C00058, 79 patients had no M918T mutation identified. Of these 79 patients, 69 had enough tissue sample to allow a reanalysis of RET mutation status based on new available assays. Most patients were reclassified as RET positive (52/69) and a minority (17/69 patients) were found to have no RET mutation (M918T or other) detected.
- Of these 17 patients RET negative patients, 11 were treated with Caprelsa and 6 were treated with placebo. The activity of Caprelsa appeared lower than in RET positive patients but remained numerically higher than placebo (Table 32):
  - The progression-free survival (PFS) hazard ratio (HR) was 0.21 [95% CI 0.03-1.53] with a 2-year PFS rate of 90% in patients treated with Caprelsa versus 50% in patients treated with placebo.
  - An objective tumor response was observed in 18.2% (2/11) treated with Caprelsa versus none of those treated with placebo (n=6).
  - Both patients with an objective response carried a RAS mutation and had a concomitant decline of carcinoembryonic antigen (ACE) and/or calcitonin (CTN) serum levels.
  - The only RET negative patient who died from thyroid cancer received the placebo.

Table 31. Efficacy endpoints in RET positive patients and 17 patients with no RET mutation (M918T or other) identified

Efficacy end-point (Caprelsa vs placebo)	RET mutation positive (n=239)	Patients with no RET mutation (M918T or other) detected (n=17)
Objective response rate	51.7% vs 14.9%	18.2% vs 0%
PFS HR [95% CI]	0.46 [0.29-0.74]	0.21 [0.03-1.56]
2-year PFS rate	55.7% vs 40.1%	90.0% vs 50.0%

- The safety profile of Caprelsa in RET "negative" patients was generally consistent with what was observed in the overall population of Study D4500C00058 and in patients having a RET mutation. No new safety signal was observed in RET "negative" patients.

CSR amendment of Study OBS14778 (D4200C00104)

Because Study OBS14778 was observational, the evaluation of objective response provided in the CSR was based on investigator assessment of imaging for all patients, including those coming from Study D4200C00058. Since the primary analysis of Study D4200C00058 was based on a blinded central review of imaging, the MAH thought it was more rigourous to reanalyse the objective response in Study OBS14778 using the blinded central review dataset of study D4200C00058.

Using this blinded central review data, 79 patients (instead of 75) were evaluable for analysis in Study OBS14778, 58 RET positive patients (instead of 55) and 21 RET negative patients (instead of 20).

The objective response rate with Caprelsa remained lower in RET negative patients (9.5%) than in RET positive patients (39.7%). However, the median duration of treatment (24.42 months for RET negative vs 25.10 months for RET positive patients), the disease control rate (DCR, 85.7% for RET negative vs 94.4% for RET positive patients) and the median PFS (35.71 months for RET negative vs 35.71 months for RET positive patients) did not seem influenced by the RET status. Treatment with Caprelsa was associated with a decrease in CTN, which was delayed in RET negative versus RET positive patients. There was also a decrease in CEA which was comparable in both RET negative and RET positive patients. At 2 years, 21% of RET negative patients and 43% of RET positive patients were estimated to have disease progression. At the end of the follow-up period, one RET negative patient treated with Caprelsa had died due to disease progression (4.8%) versus 8 RET positive patients (13.8%). Lastly, the adverse event profile in RET negative patients was in agreement with that of RET positive patients and no new safety signal was identified.

The MAH also performed a literature review related to Caprelsa, RET status and medullary thyroid cancer MTC. Several European academic teams published their own experience with Caprelsa in advanced MTC and noted that 27.6% to 68.3% of patients were long-term responders (median PFS values ranging from 73.2 to 87 months) [1-2]. Although RET negative status determined by next generation sequencing appears uncommon in sporadic MTC [3], long-term responders to Caprelsa are described in such patients [2]. Other institutions reported similar outcomes between RET negative and RET positive patients [4-5] but the high percentage of RET negative patients in these publications suggests the use of less advanced technologies for RET testing.

Considering the above-mentioned clinical and literature data, discrepancies in RET testing quality between institutions as well as the lack of standard of care for RET negative patients, the MAH believes that Caprelsa should remain a treatment option for patients with aggressive, symptomatic, unresectable, locally advanced or metastatic MTC. The activity of Caprelsa may be less pronounced than that observed in RET positive patients in terms of objective response but remains numerically higher than placebo with an acceptable safety profile.

References

[1] Ramos HE, Hecht F, Berdelou A, Borget I, Leboulleux S, Baudin E, et al. Long-term follow-up and safety of vandetanib for advanced medullary thyroid cancer. Endocrine. 2021 Feb;71(2):434-42

[2] Valerio L, Bottici V, Matrone A, Piaggi P, Viola D, Cappagli V, et al. Medullary thyroid cancer treated with vandetanib: predictors of a longer and durable response. Endocr Relat Cancer. 2020 Jan 20;27(2):97-110.

[3] Sciampi R, Romei C, Ramone T, Prete A, Tacito A et al. Genetic landscape of somatic mutations in a large cohort of sporadic medullary thyroid carcinomas studied by next-generation targeted sequencing. iScience 2019 Oct 25;20:324-336.

[4] Prabhu M, Shakya S, Ballal S, Ahmed Shamim S, Bal C. RET gene mutation analysis and long-term clinical outcomes of medullary thyroid cancer patients. Nucl Med Commun 2020 Nov;41(11):1136-1142.

[5] Kim M, Yoon JH, Ahn J, Jeon MJ, Kim HK, Lim DJ, et al. Vandetanib for the management of advanced medullary thyroid cancer: A Real-World Multicenter Experience. Endocrinol Metab (Seoul). 2020 Sep;35(3):587-94.

Assessment of the MAH's response

In the response, the MAH refers to two additional CSR addendum. The first addendum concerns study D4500C00058 and most results were already described in the response to MO1 in the request for supplementary information 2. In study D4500C00058, 17 RET negative patients were treated with either vandetanib (n=11) or placebo (n=6). The second addendum concerns study D4200C00104, the observational study analysing pooled data from the D4500C00058 study and the observational data. In the previous data analysis from study D4200C00104 ORR was based on investigator assessment for all patients, as there were only investigator assessments available for the observational patients. In the addendum, the MAH provided analyses based on blinded central review for the D500C00058 patients, the data from the patients included in the observational part did not change. Using the blinded central review data for the D500C00058 patients, 79 patients (instead of 75) were evaluable for analysis: 58 RET positive patients (instead of 55) and 21 RET negative patients (instead of 20).

In addition, the MAH refers to literature publications to support an indication for vandetanib irrespective of RET status. Below, the main efficacy data for the addenda to CSRs for D4500C00058 and D4200C00104 will be presented. Next, the provided literature references will be reviewed, followed by the Rapporteur's assessment.

Addendum CSR D4500C00058 (randomized controlled trial; pivotal at the time of MAA):

Please also refer to the previously provided PFS (Table 8) and response data (Table 9).

Table 32. Summary of primary analysis of PFS - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Number of events n(%)	60 (34.9%)	38 (56.7%)	1 (9.1%)	3 (50.0%)	0	1 (100%)	1 (11.1%)	2 (40.0%)	0	0
Hazard Ratio	0.46		0.21				0.29			
95% CI	(0.29 - 0.74)		(0.03 - 1.56)				(0.03 - 3.04)			

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
PFS was derived from all available central read RECIST assessments
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_prim_pfs.sas OUT=EXPLO/OUTPUT/retaddl_prim_pfs_r_t_i.rtf (13DEC2021 - 17:10)

Table 33. Summary of predicted median PFS - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Number of events	60 (34.9%)	38 (56.7%)	1 (9.1%)	3 (50.0%)	0	1 (100%)	1 (11.1%)	2 (40.0%)	0	0
Predictive median PFS (months)	28.3	17.2	621.7	20.9	-	-	441.0	25.8	-	-

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
PFS was derived from all available central read RECIST assessments
Predicted median PFS was determined by fitting a Weibull model with different shape parameters in the two treatment arms
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_predict_pfs.sas OUT=EXPLO/OUTPUT/retaddl_predict_pfs_r_t_i.rtf (13DEC2021 - 17:11)

Table 34. Summary of primary analysis of objective response rate - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
Parameter	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Objective Response Rate (ORR)	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Odds Ratio	6.11									
95% CI	(3.04 - 13.43)									

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
The analysis was performed using a logistic regression model with treatment as the only factor.
Best objective tumor response was derived from all available central read RECIST assessments collected prior to the first progression as determined from the central read assessments.
Objective response rate is the proportion of patients with a best objective response of complete response or partial response.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_resp_orr.sas OUT=EXPLO/OUTPUT/retaddl_resp_orr_r_t_i.rtf (13DEC2021 - 17:12)

Table 35. Summary of primary analysis of disease control rate - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
Parameter	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Disease Control Rate (DCR)	149 (86.6%)	45 (67.2%)	8 (72.7%)	6 (100%)	0	1 (100%)	7 (77.8%)	5 (100%)	1 (100%)	0
Odds Ratio	3.17									
95% CI	(1.61 - 6.23)									

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
The analysis was performed using a logistic regression model with treatment as the only factor.
Best objective tumor response was derived from all available central read RECIST assessments collected prior to the first progression as determined from the central read assessments.
Disease control is a best objective response of complete response, partial response or stable disease at 24 weeks.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_resp_dcr.sas OUT=EXPLO/OUTPUT/retaddl_resp_dcr_r_t_i.rtf (13DEC2021 - 17:13)

Table 36. Summary of objective tumour response - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
Response status Best objective response	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Response										
Total	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Complete Response	0	0	0	0	0	0	0	0	0	0
Partial Response	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
No response										
Total	83 (48.3%)	57 (85.1%)	9 (81.8%)	6 (100%)	1 (100%)	1 (100%)	7 (77.8%)	5 (100%)	1 (100%)	0
Stable Disease ≥ 8 weeks	73 (42.4%)	44 (65.7%)	7 (63.6%)	6 (100%)	0	1 (100%)	6 (66.7%)	5 (100%)	1 (100%)	0
Progressive Disease	7 (4.1%)	11 (16.4%)	1 (9.1%)	0	0	0	1 (11.1%)	0	0	0
Not Evaluable	3 (1.7%)	2 (3.0%)	1 (9.1%)	0	1 (100%)	0	0	0	0	0

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
Best objective tumor response was derived from all available central read RECIST assessments collected prior to the first progression as determined from the central read assessments
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_tumor.sas OUT=EXPLO/OUTPUT/retaddl_tumor_r_t_i.rtf (13DEC2021 - 17:13)

Table 37. Summary of the predicted median DOR - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Number of responders	89 (51.7%)	10 (14.9%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Predictive median DOR (months)	20.2	16.6	-	-	-	-	-	-	-	-

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
Best objectitve tumor response was derived from all available central read RECIST assessments collected prior to the first progression as determined from the central read assessments
A patient who has a response is defined as a patient with a best objective response of complete or partial response. Only patients who had a response are included in this plot
Duration of response is calculated from the date of onset of the response.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retadd_predict_dor.sas OUT=EXPLO/OUTPUT/retadd_predict_dor_r_t_i.rtf (13DEC2021 - 17:11)

Table 38. Summary of survival status - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Survival status										
Dead	39 (22.7%)	15 (22.4%)	1 (9.1%)	1 (16.7%)	0	0	1 (11.1%)	1 (20.0%)	0	0
Continuing follow-up for survival	4 (2.3%)	0	0	0	0	0	0	0	0	0
Withdrawn from study prior to death	22 (12.8%)	6 (9.0%)	1 (9.1%)	0	1 (100%)	0	0	0	0	0
Voluntary discontinuation	15 (8.7%)	2 (3.0%)	1 (9.1%)	0	1 (100%)	0	0	0	0	0
Lost to follow-up	1 (0.6%)	0	0	0	0	0	0	0	0	0
Severe non-compliance to protocol	3 (1.7%)	2 (3.0%)	0	0	0	0	0	0	0	0
Safety reasons	2 (1.2%)	0	0	0	0	0	0	0	0	0
Other	1 (0.6%)	2 (3.0%)	0	0	0	0	0	0	0	0
Unknown status	107 (62.2%)	46 (68.7%)	9 (81.8%)	5 (83.3%)	0	1 (100%)	8 (88.9%)	4 (80.0%)	1 (100%)	0

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
Unknown: Investigator was unable to establish survival status of patient.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retadd_survivalstat.sas OUT=EXPLO/OUTPUT/retadd_survivalstat_r_t_i.rtf (13DEC2021 - 17:14)

Table 39. Summary of duration of follow up - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Duration of follow-up (weeks)										
Number	112	46	9	5	0	1	8	4	1	0
Mean (SD)	144.5 (13.1)	146.7 (14.0)	148.9 (14.1)	143.3 (17.8)		149.9 (NC)	147.5 (14.4)	141.7 (20.1)	160.0 (NC)	
Median	144.1	148.4	148.3	133.9		149.9	144.9	132.9	160.0	
Min : Max	116 : 170	122 : 171	133 : 172	129 : 172		150 : 150	133 : 172	129 : 172	160 : 160	

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retadd_duration.sas OUT=EXPLO/OUTPUT/retadd_duration_r_t_i.rtf (13DEC2021 - 17:17)

Table 40. Summary of 6 months, 1 year and 2 years OS - Full analysis set

	RET + (N= 239)		All RET - (N= 17)		RET-					
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	RAS-BRAF- Vandetanib (N=1)	RAS-BRAF- Placebo (N=1)	RAS+ Vandetanib (N=9)	RAS+ Placebo (N=5)	BRAF+ Vandetanib (N=1)	BRAF+ Placebo (N=0)
Number of events, n(%)	39 (22.7%)	15 (22.4%)	1 (9.1%)	1 (16.7%)	0	0	1 (11.1%)	1 (20.0%)	0	0
Median OS (months)	NC	NC	NC	NC	NC	NC	NC	NC	NC	
Probability of surviving										
- at 6 months	97.0	91.0	100	100	100	100	100	100	100	
- at 1 year	94.0	91.0	100	100	100	100	100	100	100	
- at 2 years	84.9	84.8	90.0	83.3	100	100	88.9	80.0	100	

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
NC: not calculable due to an insufficient number of events
Percentage of patients alive at 6 months, 1 year and 2 years calculated using Kaplan-Meier techniques.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retadd_6months.sas OUT=EXPLO/OUTPUT/retadd_6months_r_t_i.rtf (13DEC2021 - 17:15)

Table 41. Summary of primary analysis of CTN biochemical response rate - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Number (%) of responses	137 (79.7%)	1 (1.5%)	1 (9.1%)	0	0	0	1 (11.1%)	0	0	0
Odds ratio	258.34	-	-	-	-	-	-	-	-	-
95% CI	(54.07 - 4638.18)	-	-	-	-	-	-	-	-	-

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
The analysis was performed using a logistic regression model with treatment as the only factor.
Complete response (CR) - complete normalization of CTN, confirmed by a repeat assessment > 4 weeks later.
Partial response (PR) - decrease of > 50% in CTN from baseline, confirmed by a repeat assessment > 4 weeks later.
Progressive disease (PD) - increase of > 50% in CTN from baseline.
Stable disease (SD) - change in CTN from baseline does not meet the criteria for CR, PR or PD.
Baseline is defined as the average of up to 4 levels for blood samples taken on the same date prior to randomization.
The CTN biochemical response rate is the proportion of patients with a best CTN response of CR or PR.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_ctn.sas OUT=EXPLO/OUTPUT/retaddl_ctn_r_t_i.rtf (13DEC2021 - 17:15)

Table 42. Summary of primary analysis of CEA biochemical response rate - Full analysis set

	RET + (N=239)		All RET - (N=17)		RET - RAS - BRAF - (N=2)		RET - RAS + (N=14)		RET - BRAF + (N=1)	
	Vandetanib (N=172)	Placebo (N=67)	Vandetanib (N=11)	Placebo (N=6)	Vandetanib (N=1)	Placebo (N=1)	Vandetanib (N=9)	Placebo (N=5)	Vandetanib (N=1)	Placebo (N=0)
Number (%) of responses	100 (58.1%)	1 (1.5%)	2 (18.2%)	0	0	0	2 (22.2%)	0	0	0
Odds ratio	91.67	-	-	-	-	-	-	-	-	-
95% CI	(19.53 - 1636.32)	-	-	-	-	-	-	-	-	-

All RET - included: patients RET - / RAS - / BRAF - ; patients RET - / RAS + and patients RET - / BRAF +
The analysis was performed using a logistic regression model with treatment as the only factor.
Complete response (CR) - complete normalization of CEA, confirmed by a repeat assessment > 4 weeks later.
Partial response (PR) - decrease of > 50% in CEA from baseline, confirmed by a repeat assessment > 4 weeks later.
Progressive disease (PD) - increase of > 50% in CEA from baseline.
Stable disease (SD) - change in CEA from baseline does not meet the criteria for CR, PR or PD.
Baseline is defined as the average of up to 4 levels for blood samples taken on the same date prior to randomization.
The CEA biochemical response rate is the proportion of patients with a best CEA response of CR or PR.
PGM=PRODOPS/SAR390530/D4200C00058/SAFETY_UPDATE/EXPLO/PGM/retaddl_cea.sas OUT=EXPLO/OUTPUT/retaddl_cea_r_t_i.rtf (13DEC2021 - 17:16)

<u>Addendum CSR D4200C00104 (observational study; planned to provide confirmatory evidence for RET-negative patients as SpecOB)</u>:

Because study D4200C00104 study was observational, the objective response was based on the investigator assessment of imaging for all participants, including those from study D4200C00058. However, the primary analysis of study D4200C00058 was based on a blinded central review. The MAH provided this addendum to present the results of the objective response from the blinded central review (in addition to the analysis per investigator assessment), in line with original CSR of study D4200C00058.

Overall, 97 patients were screened and enrolled in the study: 37 patients prospectively enrolled (30 patients with RET positive mutation and 7 patients with RET negative mutation) and 57 patients retrospectively enrolled (47 patients coming from D4200C00058 randomised study with re-evaluated RET mutation status [36 RET positive and 11 RET negative], and 10 patients with RET negative mutation retrospectively enrolled at the site level). Of the 97 patients enrolled, 79 patients were evaluable for efficacy (81.4%) (all enrolled and eligible [i.e. exposed to vandetanib with known RET mutation status] and RECIST assessment evaluable at baseline). The remaining 18 patients (18.6%) were non-evaluable (11 [11.3%] patients had no evaluable baseline RECIST assessment, 6 [6.2%] patients did not meet eligibility criteria, and 1 [1.0%] patients did not take at least 1 dose of vandetanib). Of the 79 evaluable patients, there were 58 RET positive and 21 RET negative patients included in the analysis.

Below the main efficacy tables will be shown. Compared to the previous results, there were 3 additional evaluable patients in the RET positive population and one additional evaluable patient in the RET negative population from study D4200C0058. The median duration of treatment with vandetanib was 23.4 months in the RET positive population and 27.6 months in the RET negative population. ORR in the RET positive population was 39.7% (compared to 41.8% previously) and in the RET negative population ORR was 9.5% due to one additional responder in study D4200C0058 (compared to 5.0% previously) when using

blinded central review of for the patients in study D4200C0058. In total 2 out of 21 RET negative patients had a partial response, no complete responses were reported. Per investigator evaluation of tumour response, ORR was 5.0% in the RET negative population with one responder. DCR was 87.9% (n=51) for RET positive patients and 85.7% (n=18) for RET negative participants. The median time to response was 5.52 months (range: 2.8 to 16.6 months) in RET positive patients and 5.52 months for RET negative patients. The median DOR was 19.6 months for RET positive and not estimable for RET negative patients. The median PFS was 25.4 months RET positive patients and 35.7 months in RET negative patients. At 12 months, 22% of RET positive patients and 21% of RET negative patients were estimated to have progressed; at 24 months, 43% of RET positive patients and 21% of RET negative patients were estimated to have progressed. Treatment with vandetanib was associated with a decrease in calcitonin (CTN), which appeared more rapidly in RET positive than in RET negative patients. There was also a decrease in carcinoembryonic antigen (CEA) levels which was comparable in both RET positive and RET negative participants.

Table 43. Analysis populations - Enrolled population

	RET mutation positive			RET mutation negative				
Population	Prospective	D4200C00058	All	Prospective	D4200C00058	Retrospective	All	Overall*
Enrolled	30 (100.0%)	36 (100.0%)	66 (100.0%)	7 (100.0%)	11 (100.0%)	10 (100.0%)	28 (100.0%)	97 (100.0%)
Evaluable (Study 58 Central Read)	22 (73.3%)	36 (100.0%)	58 (87.9%)	7 (100.0%)	11 (100.0%)	3 (30.0%)	21 (75.0%)	79 (81.4%)
Safety	28 (93.3%)	36 (100.0%)	64 (97.0%)	7 (100.0%)	11 (100.0%)	9 (90.0%)	27 (96.4%)	91 (93.8%)
Non-Evaluable (Study 58 Central Read)	8 (26.7%)	0	8 (12.1%)	0	0	7 (70.0%)	7 (25.0%)	18 (18.6%)
Did not meet eligibility criteria	2 (6.7%)	0	2 (3.0%)	0	0	1 (10.0%)	1 (3.6%)	6 (6.2%)
Did not take at least one dose of Vandetanib	0	0	0	0	0	1 (10.0%)	1 (3.6%)	1 (1.0%)
No evaluable baseline RECIST assessment	6 (20.0%)	0	6 (9.1%)	0	0	5 (50.0%)	5 (17.9%)	11 (11.3%)

Percentages are based on the number of patients in the Enrolled population.
Evaluable population (Study 58 Central Read) consists of all enrolled and eligible patients with a known RET mutation test status (positive or negative) treated with at least one dose of vandetanib and who have an evaluable baseline RECIST assessment.
Safety population consists of enrolled population who have received at least one dose of vandetanib.
Non-evaluable population consists of enrolled patients who failed to meet the criteria for Evaluable population (Study 58 Central Read).
*The following 3 enrolled patients, who did not meet eligibility criteria, do not have a ret mutation status and are counted in overall column only: 3101003, 4401002 and 4401003.
Program: table_14_01_01_01_01.sas Worldwide Clinical Trials 10FEB2022:08:43

Table 44. Objective response rate, disease control rate, duration of response and time to response - Evaluable population (Study 58 Central Read)

	RET mutation positive			RET mutation negative				
Parameter	Prospective (N=22)	D4200C00058 (N=36)	All (N=58)	Prospective (N=7)	D4200C00058 (N=11)	Retrospective (N=3)	All (N=21)	Overall (N=79)
Duration of Follow-up[1] (months)								
Number	18	36	54	7	10	3	20	74
Mean (SD)	26.30 (17.608)	16.41 (7.460)	19.71 (12.583)	28.40 (23.779)	19.99 (7.445)	31.38 (44.245)	24.64 (20.848)	21.04 (15.263)
Median	20.86	19.30	19.32	24.21	20.96	6.21	20.96	19.35
Min, Max	3.1, 63.7	2.6, 28.8	2.6, 63.7	2.8, 66.3	2.7, 28.1	5.5, 82.5	2.7, 82.5	2.6, 82.5
Objective Response Rate (ORR)								
n (%)	5 (22.7)	18 (50.0)	23 (39.7)	0	2 (18.2)	0	2 (9.5)	25 (31.6)
95% CI	(7.8, 45.4)	(32.9, 67.1)	(27.0, 53.4)	(NE, NE)	(2.3, 51.8)	(NE, NE)	(1.2, 30.4)	(21.6, 43.1)
Best Objective Response (BOR), n (%)								
CR	1 (4.5)	0	1 (1.7)	0	0	0	0	1 (1.3)
PR	4 (18.2)	18 (50.0)	22 (37.9)	0	2 (18.2)	0	2 (9.5)	24 (30.4)
SD	11 (50.0)	17 (47.2)	28 (48.3)	6 (85.7)	7 (63.6)	3 (100.0)	16 (76.2)	44 (55.7)
PD	2 (9.1)	1 (2.8)	3 (5.2)	1 (14.3)	1 (9.1)	0	2 (9.5)	5 (6.3)
NE	4 (18.2)	0	4 (6.9)	0	1 (9.1)	0	1 (4.8)	5 (6.3)
Missing	0	0	0	0	0	0	0	0
Disease Control Rate (DCR)								
n (%)	16 (72.7)	35 (97.2)	51 (87.9)	6 (85.7)	9 (81.8)	3 (100.0)	18 (85.7)	69 (87.3)
95% CI	(49.8, 89.3)	(85.5, 99.9)	(76.7, 95.0)	(42.1, 99.6)	(48.2, 97.7)	(29.2, 100.0)	(63.7, 97.0)	(78.0, 93.8)
Duration of Response[2] (months)								
Number	3	10	13	0	0	0	0	13
Mean (SD)	27.75 (5.593)	10.06 (4.837)	14.14 (9.107)					14.14 (9.107)
Median	28.35	10.17	11.30					11.30
Min, Max	21.9, 33.0	5.1, 19.6	5.1, 33.0					5.1, 33.0
Time to Response[3] (months)								
Number	5	18	23	0	2	0	2	25
Mean (SD)	5.60 (2.308)	6.97 (4.015)	6.67 (3.709)		5.52 (0.000)		5.52 (0.000)	6.58 (3.566)
Median	5.45	5.67	5.52		5.52		5.52	5.52
Min, Max	2.8, 9.2	2.8, 16.6	2.8, 16.6		5.5, 5.5		5.5, 5.5	2.8, 16.6

1: Duration follow-up is based on last RECIST assessment date - first dose date of study medication + 1.
2: Duration of Response (number of months from time of response until the first date of either of PD or death) for responders. Does not include Responders who does not progress or die.
3: Time to Response (number of months from start date of study medication to first documentation of response) is only calculated for responders.
Program: table_14_02_01_01_01.sas Worldwide Clinical Trials 04FEB2022:12:05

Table 45. Time to response and duration of response, Kaplan Meier - Evaluable population (Study 58 Central Read)

Parameter Statistics	RET mutation positive (N=58)	RET mutation negative (N=21)
Number of responders		
Responders, n (%)	23 (39.7)	2 (9.5)
Non-responders, n (%)	35 (60.3)	19 (90.5)
Time to response (months)		
Median (95% CI)	5.52 (4.797, 8.279)	5.52 (NE, NE)
1st quartile (95% CI)	3.15 (2.760, 5.454)	5.52 (NE, NE)
3rd quartile (95% CI)	8.31 (5.782, 11.138)	5.52 (NE, NE)
Min, Max*	2.8, 16.6	5.5, 5.5
Number of responders for duration[1]		
Experienced the event[2], n (%)	13 (56.5)	0
Censored, n (%)	10 (43.5)	2 (100.0)
Duration of response (months)		
Median (95% CI)	19.58 (11.236, 28.353)	NE (NE, NE)
1st quartile (95% CI)	11.24 (5.092, 13.897)	NE (NE, NE)
3rd quartile (95% CI)	28.35 (19.581, NE)	NE (NE, NE)
Min, Max*	5.1, 33.0	

NE = Not Estimable
*Based on actual (that is, non-censored) values only
1: Percentages are based on the number of responders.
2: Responders who progressed or died.
Program: table_14_02_02_01_01.sas Worldwide Clinical Trials 04FEB2022:12:05

Figure 9. Waterfall plot - Largest percentage change in sum of the longest diameters of the target lesions from baseline - Evaluable population (Study 58 Central Read)

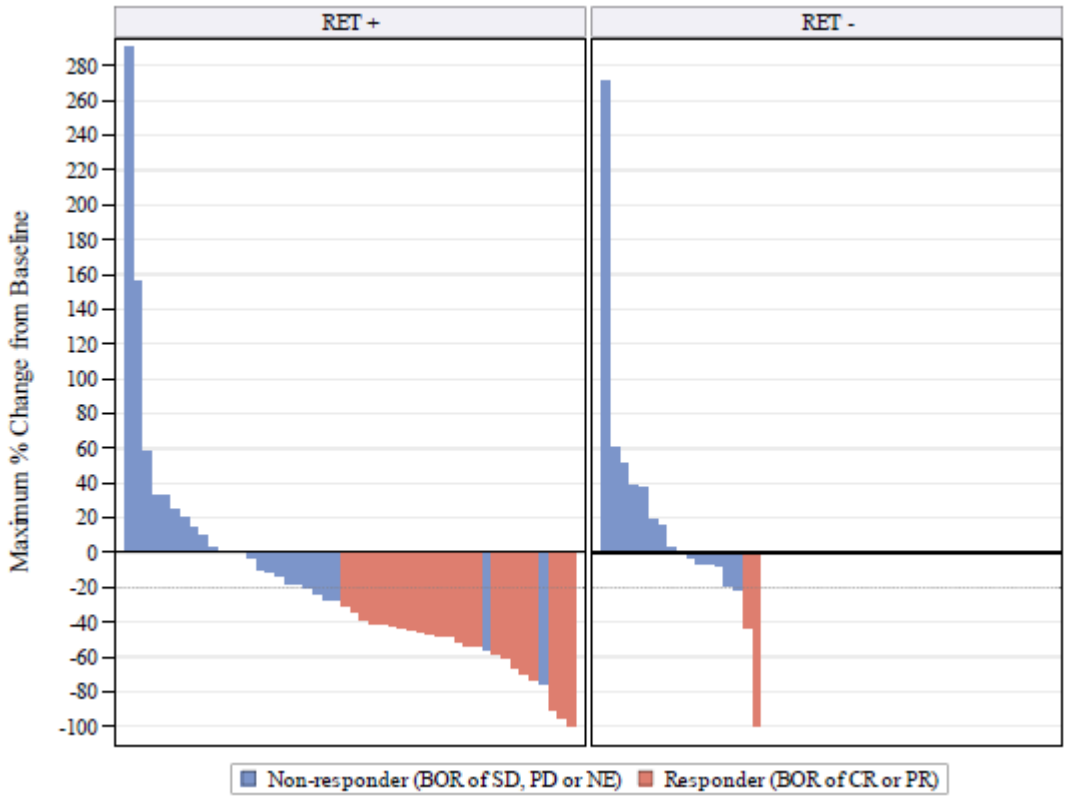


Table 46. Progression status at end of study

Parameter	RET mutation positive			RET mutation negative				Overall (N=79)
	Prospective (N=22)	D4200C00058 (N=36)	All (N=58)	Prospective (N=7)	D4200C00058 (N=11)	Retrospective (N=3)	All (N=21)	
Progression, n (%)								
Total	14 (63.6)	16 (44.4)	30 (51.7)	6 (85.7)	1 (9.1)	2 (66.7)	9 (42.9)	39 (49.4)
RECIST-Based[1]	12 (54.5)	10 (27.8)	22 (37.9)	5 (71.4)	1 (9.1)	2 (66.7)	8 (38.1)	30 (38.0)
Death[2]	2 (9.1)	6 (16.7)	8 (13.8)	1 (14.3)	0	0	1 (4.8)	9 (11.4)
No progression, n (%)								
Alive and withdrawn prior to progression	8 (36.4)	20 (55.6)	28 (48.3)	1 (14.3)	10 (90.9)	1 (33.3)	12 (57.1)	40 (50.6)
Missing	0	0	0	0	0	0	0	0

1: RECIST guidelines 1.1 was used for study D4200C00104 (Investigator's assessment); RECIST guidelines 1.0 was used for study D4200C00058 (Central reader's assessment).
2: Death, in the absence of RECIST progression.
Program: table_14_02_04_02_01.sas

Worldwide Clinical Trials 04FEB2022:12:05

Results for biochemistry were not changed compared to previously reported results *(*Figure 6*,* Figure 7*).*

Regarding safety, the safety profile was unaffected by the addendum.

Literature:

Lastly, the MAH refers to literature publications related to the use of vandetanib in MTC and RET status.

The first publication by Ramos et al., 2020 is a retrospective clinical file review in a single center of 76 patients treated with vandetanib. According to the authors, twelve patients (17.9%) had a known germline RET mutation and the genetic status was undiscovered in eight patients. No further information is provided regarding RET status.

Valerio et al., 2020, analysed medical records for 79 patients in a single center. In 72/79 patients, tumour tissues were available for RET genetic analysis which was performed according to standard protocols (Elisei et al., 2019). In this study, the RET mutation gene was present in 100% of patients with the hereditary form and in almost 90% of sporadic cases. Among all RET mutations, the somatic RET Met918Thr mutation was the most represented. In the presented series, the presence of RET mutations was not a predictor of longer and/or better response to vandetanib. However, the very high prevalence of RET mutated cases and the correspondent low prevalence of non-mutated cases probably would require a much larger number of samples to reach statistical power according to the authors. Of note, the referred to publication by Elisei et al., 2019, describes RET analysis investigating RET mutations in eight exons (5, 8, 10, 11, 13, 14, 15 and 16).

Ciampi et al., 2019 studied 181 cases of MTC by deep sequencing to define the mutational landscape. This analysis showed that 55.8% of cases harbored RET genetic alterations, confirming that RET, particularly the M918T mutation, is the main driver oncogene in MTC. The second main driver oncogene has been confirmed to be RAS, particularly HRAS and KRAS genes, which were altered in 24.3% of MTC cases. Only a small subgroup, representing only 1.6% of cases, showed other types of uncommon mutations whose driver role remains unclear. The prevalence of complete negative cases in this series was 18.3% of cases, which increased up to 19.9% if the subgroup with the uncommon mutations was included. The authors found a strong correlation between the presence of RET mutations and a worse patient outcome, and the survival of Kaplan-Meier curves confirmed that patients with MTC harboring the RET mutation had a higher rate of cancer-related deaths than patients harboring RAS mutations.

Pradhu et al., 2020, describe data from a single institution retrieved through a prospectively maintained thyroid cancer database from 1998 to June 2019. RET gene mutation status (exon 10–16) was assessed. Out of 149 peripheral blood samples, 42 were positive for RET gene mutation (prevalence of 28.1%). The authors did not find a statistically significant difference between RET positive and RET negative groups concerning OS and PFS.

The last publication was by Kim et al. 2020 and was already provided previously (see response to MO1 the request for supplementary information 1). RET genetic screening was performed in nine patients (75%), and the majority of patients (8/9, 89%) were not carrying a RET mutation. A germline mutation in the RET gene (p.D878Y) was identified in one patient. Efficacy results were not provided separately for RET positive or RET negative patients. Partial response was observed in five patients (ORR, 42%).

Assessment:

The MAH concludes that based on the provided clinical and literature data, discrepancies in RET testing quality between institutions as well as the lack of standard of care for RET negative patients, vandetanib should remain a treatment option for patients with aggressive, symptomatic, unresectable, locally advanced or metastatic MTC.

In the response, the MAH provided the appendices to CSRs of both the RCT D4200C0058 and the observational study D4200C00104. Study D4200C00104 includes data from the RET negative population of the RCT D4200C0058 and from retrospectively collected RET negative patients. Due to the study design of D4200C00104, it is considered that ORR and DoR should be the focus as efficacy measures, because of the difficulties interpreting time-dependent endpoints of a non-controlled observational study. Furthermore, the focus will be on the activity in RET negative patients as a comparison between RET positive and RET negative patients is considered to be less relevant. Even a lower activity in RET negative patients compared to RET positive patients could still be relevant and it should be assessed whether the activity in RET negative patients specifically is clinically relevant for a positive B/R balance.

In study D4200C0058, objective tumour response was observed in 18.2% (2/11) RET-negative patients treated with vandetanib versus none of those treated with placebo (0/6). Both responders had a partial response and were RAS mutation positive. Disease control rate was 72.7% (8/11) in vandetanib and 100% (6/6) in the placebo group. Median DOR could not be predicted in RET negative patients.

As agreed previously, the data from the RET negative population in study D4200C0058 will be pooled with the RET negative patients from the observational study, in study D4200C00104 to provide a sufficient number of patients in order to be able to fulfill the SOB. In the pooled RET negative population ORR was 9.5% using central assessment of the patients in study D4200C0058 (2/21 with PR) or 5.0% using investigator assessment of the patients in study D4200C0058 (1/20 PR). Median DOR was not estimable for the RET negative population. The one responder per investigator assessment is different (E1201002) than the two responders per central review (E1001011 and E1701002). Per central review, patient E1201002 had stable disease (see response to OC#2 in the previous round). It should also be noted that for the patients in the observational part, only investigator assessment is available. It is, therefore, preferred to analyse all patients per investigator assessment.

Regarding the literature overview provided by the MAH, it is unknown how the literature review was performed, for example the search and selection strategy are not described. In addition, the methods of RET testing differed between the literature articles and, therefore, the provided literature cannot be considered supportive to determine on a positive B/R in RET negative patients.

As discussed previously, the low number of patients in the RET negative group make it difficult to compare with the RET positive subgroup. It seems that vandetanib treatment is at least not more toxic in RET negative patients compared to RET positive patients.

Summarising, the B/R of the RET negative population at time of CMA was based on a population that was mainly not RET negative after re-analysis. In a pooled set of 21 or 20 RET-negative patients depending on the used tumour assessment, the response rate is at best 9.5% and DOR is not estimable. It is unlikely that the reported response rate of 9.5 or 5% in RET negative patients will translate into a clinical benefit. Combined with the known toxicity profile of vandetanib and that RET testing is expected

to play a more and more important role in MTC given the developments in treatments specifically targeting RET, the benefits do not outweigh the risks in the RET negative population and the indication should be restricted to RET positive patients (**MO**), in which the B/R remains positive.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

16.2. Other concerns

Clinical aspects

Question 2

The pooled RET negative sample consisted of 10 patients from study D4200C00058 and 10 patients from study OBS14778/D4200C00104 (7 recruited prospectively and 3 patients retrospectively). One of the patients from the D4200C00058 was excluded from the pooled analysis, because RECIST evaluation at baseline was lacking. The MAH is requested to confirm this concerns the assessment by investigator and the reason why this was not performed or resolved during the study.

Summary of the MAH's response

As explained in the answer to question 1, the MAH reanalyzed study OBS14778 using the blinded central review listing of Study D4200C00058.

Using this dataset, all 11 RET negative patients treated with Caprelsa in Study D4200C00058 are now evaluable for efficacy analysis.

Assessment of the MAH's response
The MAH did not reply to the question directly, but refers to the MO where a re-analysis based on blinded central review is presented. This issue will not be pursued further.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 3

Discrepancies were noted for the number reported in the D4200C00058 study. One of the discrepancies concerns the number of patients that had "unknown" RET status at time of CMA based on initial RET analysis. According to the EPAR this number was 138, but Appendix 1 reports 136 patients with "unknown" RET status. Another discrepancy that is noted, is the number of RET negative patients after the re-analysis. The MAH describes that re-analysis was performed for RET mutation status "unknown" samples (n=67), previously RET negative samples (n=2), and previously RET positive (n=4). The reanalysis confirmed the four previously RET positive patients to be RET positive, and 1 of 2 previously RET negative patients was found to be RET positive. Out of the 67 RET unknown patients re-analyzed, 52 were reclassified as RET positive and 15 were found to be RET negative. In total, 17 patients were

found to be RET negative according to the MAH. However, the number of 17 RET negative patients is not understood as 15 RET negative samples out of the previously unknown set and 1 RET negative patients out of the previously RET negative set adds up to 16. The MAH is requested to clarify these discrepancies, adjust the numbers if needed, and to discuss the consequences for the interpretation of the results.

Summary of the MAH's response

Of 331 patients randomized in Study D4200C00058, all but 2 patients (ie n=329) provided an archived tissue sample for RET mutation analysis. As mentioned on page 38 of the EPAR (EMA128076, dated 17 November 2011), RET mutation status was determined to be positive in 187 (56.5%) patients, negative in 8 patients (2.4%), and unknown in 136 (41.1%) patients. The 2 patients who had no tissue available are included in those 136 patients with unknown RET status (they should not be added to them).

Of 79 patients lacking M918T mutation in Study D4200C00058, 69 had enough tissue for RET status reanalysis (2/8 patients previously classified as RET negative and 67/71 patients previously classified as RET "unknown"):

• Among RET "unknown" patients reanalyzed (n=67), 51 (instead of 52) were reclassified as RET positive and 16 (instead of 15) were found to be RET negative.

• Among RET negative patients reanalyzed (n=2), one was confirmed to be RET negative and the other one was reclassified as RET positive.

Thus, in total, 17 patients (16 plus 1) were found to be RET negative and 52 patients (51 plus 1) were reclassified as RET positive.

The MAH does apologize for the mistake.

Assessment of the MAH's response

The number of patients with "unknown" RET status at time of CMA based on initial RET analysis is clarified: 136 had unknown RET status and 2 had not enough tissue to assess the RET status.

Regarding the number of RET negative patients, there was apparently a mistake and in total 17 patients had RET negative status in study D4200C00058. Of the patients with RET "unknown" status, 16 (instead of the previously reported 15) were RET negative. In addition, 1 of the RET negative patients was confirmed to be RET negative. Of the 17 RET negative patients, 11 were treated with vandetanib and 6 with placebo. The mistake does not impact the efficacy data.

The discrepancies are explained and the issue will not be further pursued.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

17. Request for supplementary information 4

17.1. Major objections

Clinical aspects

1. Efficacy of vandetanib has not been established in patients with RET negative status. Having in mind the known substantial toxicity, the B/R balance is negative for these patients. The MAH is requested to restrict the indication to RET mutant patients.

18. Assessment of the response to the request for supplementary information 4

18.1. Major objections

Clinical aspects

Question 1

Efficacy of vandetanib has not been established in patients with RET negative status. Having in mind the known substantial toxicity, the B/R balance is negative for these patients. The MAH is requested to restrict the indication to RET mutant patients.

Summary of the MAH's response

The MAH acknowledges the CHMP conclusion that the positive benefit/risk profile of vandetanib established in RET mutant patients with aggressive and symptomatic medullary thyroid cancer (MTC), is not sufficiently demonstrated in RET negative patients after reviewing the data from:

- The re-analysis of the RET status in 69 patients lacking M918T mutation in the double-blind, randomized, placebo-controlled Study D4500C00058 (also referred as Study 58). Of these 69 patients, 52 were reclassified as RET mutant and only 17 patients were confirmed to be RET negative (14 of them being RAS mutant).
- The observational PASS study (OBS14778), which enrolled 21 evaluable RET negative patients treated with vandetanib, 11 coming from the randomized Study 58.

With reference to our response to previous request for supplementary information, despite the overall low number of RET negative patients described above, the MAH considers that the benefit/risk balance of vandetanib remains positive, regardless of RET status, for the following reasons:

- Vandetanib is indicated for patients with aggressive and symptomatic MTC which is unresectable, locally advanced or metastatic.
- The objective tumor response rate with vandetanib was numerically higher than placebo in the randomized Study 58:
  - 2/11 patients (18.2%) treated with vandetanib had an objective tumor response versus 0/6 patients (0%) treated with placebo.
  - Both RET negative patients having an objective response with vandetanib were RAS mutant (ie 22.2% of all RAS mutant patients treated with vandetanib).
- Progression-free survival (PFS) was longer in RET negative than in RET mutant patients, in Study 58 as in the PASS Study:
  - In Study 58, hazard ratio (HR) for PFS (primary end-point) was 0.21 [95% CI, 0.03-1.56] in RET negative patients versus 0.46 [95% CI, 0.29-0.74] in RET mutant patients. At 2 years, 10% of RET negative patients and 44% of RET mutant patients had progressed with vandetanib.
  - In the PASS Study, PFS with vandetanib was 35.7 months in RET negative patients versus 25.4 months in RET mutant patients. At 2 years, 21% of RET negative patients and 43% of RET mutant patients had progressed with vandetanib.
- Disease control rate and duration of treatment were comparable in RET negative and RET positive patients.

- In Study 58, the only RET negative patient who died from thyroid cancer received the placebo. In the PASS Study, cancer death was lower in RET negative patients (4.8%) than in RET mutant patients (13.8%).
- The safety profile of vandetanib was not influenced by RET status in Study 58 as in the PASS Study.

Whilst acknowledging the CHMP request to restrict the indication to RET mutant patients, the MAH would like to highlight the following important implications for patients with MTC:

- Many European countries do not have any treatment alternative to vandetanib for MTC. Indeed, cabozantinib is registered in Europe regardless of RET status but is not reimbursed for MTC in most European countries (see table below).

Country	Is Cabozantinib reimbursed for medullary thyroid cancer?
Austria	YES
Belgium	NO (Cabozantinib reimbursed for kidney cancer only)
Cyprus	Access via a named patient program only
Czech Republic	NO
Finland	YES
France	NO (Cabozantinib reimbursed for kidney cancer only)
Germany	YES
Greece	NO
Hungary	NO
Ireland	NO
Italy	NO
Netherlands	YES
Norway	YES
Poland	NO
Portugal	NO
Romania	NO
Spain	NO
Sweden	YES
UK	YES

- Most recent technologies to determine RET status are not available or not reimbursed everywhere since RET testing is not yet standard practice in Europe.

MAH would like to also specify that it has been made aware that a network in France is currently conducting a retrospective study evaluating clinical outcomes in RET negative patients with unresectable metastatic or locally advanced MTC. It is estimated that 200-250 patients have metastatic MTC will be enrolled in the database and data is collected from 2000 to 2020.

MAH believes that this retrospective study could provide valuable information in completion of the available data to support the benefit/risk of vandetanib in RET negative patients.

However, considering the results of the study is presently not available, MAH accepts the CHMP request to restrict the indication to RET mutant patients in order, to close the current procedure and to lift the SOB and the conditional MA in EU.

Once the study results become available, the MAH will review the data to assess a potential new variation submission to update the indication.

Assessment of the MAH's response

The MAH restricted the indication to RET mutant positive patients as requested. In the population with RET mutant positive patients, the B/R is considered to remain positive. With reference to the assessment of all available data in the previous round(s), in the RET mutant negative patients the benefits do not outweigh the risks. In a pooled set of 21 or 20 patients, pending on the used tumour assessment, the response rate is at best 9.5% and DOR is not estimable. It is unlikely that the reported response rate of 9.5 or 5% in RET mutation negative patients will translate into a clinical benefit. Combined with the known toxicity profile of vandetanib, this renders the B/R negative in the RET mutation negative population.

The retrospective study in unresectable metastatic or locally advanced MTC is noted. Noting that RET testing is expected to play a more and more important role in MTC and given the developments in treatments targeting RET, the results from this study are considered of interest. Whether the results will be able to support a positive B/R in RET mutation negative patients will in the end be a matter of assessment and pending on, amongst others, the sample size, used method of RET mutation testing and tumour assessment, and predefined statistical analysis plan.

Issue resolved, pending resolution of the remaining SmPC comments. Please refer to the separate SmPC assessment.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Updated assessment

The MAH provided an updated SmPC that resolved part, but not all of the issues, while an additional comment is made that the PIL should also reflect the restricted indication. Please refer to the separate updated SmPC assessment.

In addition, the MAH was requested to provide a draft DHPC and communication plan regarding the restricted indication. The assessment of the DHPC and communication plan is provided in the separate documentation. The Co-Rapp's assessment (in the lead for this procedure) is endorsed by the CHMP and PRAC Rapp.