1 ABSTRACT

Title

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

Keywords

- Caprelsa (vandetanib)
- RET mutation
- Benefit/risk evaluation
- Symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer
- Non-interventional observational study

Rationale and background

Study OBS14778 (D4200C00104) was conducted to fulfill the post authorization specific obligation linked to the conditional marketing authorization of vandetanib. It was conducted to confirm, in real-life conditions, the benefit/risk of vandetanib 300 mg, both in RET mutation negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC). The clinical benefit of vandetanib 300 mg has previously been established in Study D4200C00058 on the basis of a clinically and statistically significant advantage in progression free survival (PFS), supported by a high response rate and substantial duration of response (DOR).

A non-interventional study (NIS) was the appropriate approach because this type of study may provide information on the clinical benefit/risk between these groups of patients based on the actual clinical practice of physicians who are prescribing vandetanib. Moreover, it was important for the study objectives that the management of the disease was not modified in comparison to standard of care. Therefore, no delays of vandetanib treatment initiation time and no extra procedures, interventions, or extra visits over and above the standard of care were required for study purposes. Conducting this real-world NIS as described above may lead to a more thorough understanding of the benefit/risk profile of vandetanib in RET mutation positive and negative patients based on the actual clinical practice with vandetanib. An NIS is a study in which no additional diagnostic or monitoring procedures shall be applied to the patients.

Of note, study OBS14778 was initiated by AstraZeneca under the study code D4200C00104. The first patient in for the study occurred on 17 February 2014. In 2015, the rights for clinical development of vandetanib were granted from AstraZeneca to Genzyme Corporation. Since that point, the Sanofi-Genzyme code OBS14778 has been used and the study has been conducted under the sponsorship of Genzyme Corporation.

Research question and objectives of the Study

The objectives of the study were as follows:

- 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.

Study design

This was a prospective multinational, multicenter, non-interventional (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 taken 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.

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 population 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 an European Medical Agency (EMA) agreement on 28 February 2019. In Amended Protocol 02 dated 21 June 2019, the sample size of 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. In addition to the besides prospective recruitment of RET-negative and RET-positive patients at study sites, the protocol amendment included the following changes:
(1) retrospective enrollment of RET-negative patients at study sites was allowed, and
(2) the prospective and retrospective data collection was enriched with patients from the randomized Phase 3 study D4200C00058 who had an initially unknown RET status and were subsequently reclassified RET-positive or RET-negative following re-analysis of archived tumor samples.

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.

Setting

- Site and participant selection:
  - Key site selection criteria: The study was initiated under the Sponsorship of AstraZeneca, and, in 2015, the territory rights for the clinical development and commercialization of vandetanib were granted to Genzyme Corporation. AstraZeneca had identified the participating sites based on their use of vandetanib. All appropriate sites had a remote Pre-Study Site Visit performed by AstraZeneca; further information is not available.
  - Key participant selection criteria:
    a) Histological diagnosis of MTC
    b) Symptomatic and aggressive sporadic MTC, who have unresectable, locally advanced/metastatic disease
    c) Measurable disease
    d) Known RET mutation status
    e) No contraindications to vandetanib
- Overall participation status: The study was conducted across 30 sites in 8 countries including 4 sites specifically involved in the retrospective data collection. Among the 30 sites, 18 sites responded that they did not have any RET negative patient to contribute to the retrospective data collection effort. A total of 47 patients from Study D4200C00058 were retrospectively included for the present analysis.
- Data collection: Data were recorded on electronic case report forms (eCRFs) using a Web-based Data Capture (WBDC) system
- Safety data collection: AEs (including SAEs), ECGs, vital signs, and laboratory data (electrolytes, thyroid stimulating hormone [TSH], renal function, and hepatic function) were collected beginning at the screening/enrollment or baseline time point, and at follow-up visits thereafter for patients prospectively (RET mutation positive or negative) and retrospectively (RET mutation negative) recruited. All safety data were recorded in the eCRF.

Participants and study size, including dropouts

Participation per period of the study: A total of 97 patients were screened for inclusion and enrolled in this study. Of these, 75 (77.3%) patients were evaluable (eligibility criteria for efficacy analysis met), and 91 (93.8%) patients were included in the safety population (6 patients were not exposed to vandetanib). A total of 22 (22.7%) patients were non-evaluable (eligibility criteria for efficacy analysis not met). 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 evaluable patients, 41 (54.7%) patients withdrew prematurely.

Variables and data sources

- **Data management, review, validation:** Data entered in the WBDC system were immediately saved to a central database and changes tracked to provide an audit trail.

  Data lock occurred at the time of the final statistical analysis (17 December 2020).

  The Company responsible for the WBDC and the whole data management process is Worldwide Clinical Trials (WCT), 1st Floor Waterfront House, Beeston Business Park, Beeston, Nottingham, NG9 1LA, United Kingdom.
- **Statistical considerations:** For detailed statistical consideration, please refer to the final Statistical Analysis Plan.
- **Variables and evaluation criteria:**

  Efficacy evaluation

  - Objective Response Rate (ORR), defined as the percentage of patients with a best objective response (BOR) of complete response (CR) or partial response (PR), using Response Evaluation Criteria in Solid Tumors (RECIST) assessment (RECIST 1.1 for OBS14778 and RECIST 1.0 for D4200C00058).
  - Disease Control Rate (DCR), defined as the percentage of patients with CR or PR or stable disease, using RECIST assessment (RECIST 1.1 for OBS14778 and RECIST 1.0 for D4200C00058).
  - Progression free survival (PFS), defined as the number of days from the treatment start date to the date of objective progression or death (by any cause in the absence of progression), whichever was earlier.
  - Time to response, defined as the number of days from treatment start date to first documented of response, and calculated only for patients who had a response.
  - Duration of response, defined as number of days from CR or PR (whichever status was recorded first) until the first date of progressive disease (PD) was documented (as defined by the Investigator based on RECIST guidelines) or death.
  - Duration of follow-up defined as the last RECIST assessment date - date of first dose of study medication + 1.

  Other efficacy evaluations included RECIST assessment, progression status at end of study, calcitonin (CTN) and carcinoembryonic antigen (CEA) levels, and symptoms throughout the study.

Safety evaluation

Safety was assessed based on AEs, vital signs, ECG data, and laboratory data.

All AEs were recorded and were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 22.1)

- Pre-treatment AEs: events which occurred between the informed consent sign and the first dose of the study treatment
- Treatment-emergent adverse events (TEAEs): any AE that had an onset on or after the first dose of study medication or any pre-existing AE that had worsened in severity on or after the first dose of study medication

Vital signs (heart rate, systolic and diastolic blood pressure, temperature throughout the study

ECG: QTc interval throughout the study (QTcB, QTcF, QTc [Bazett, Fredericia, Framingham, Hodges, and other])

Laboratory results: electrolytes, TSH, hepatic, and renal function throughout the study

- **Data analyses:**

Efficacy Analyses

All efficacy analyses were performed on the evaluable population (ie, all patients exposed to vandetanib with a RET status positive or negative and an evaluable RECIST assessment at baseline).

- Objective Response Rate and DCR

  Estimates of ORR and DCR for RET positive and RET negative patients were summarized as a qualitative variable with corresponding 95% confidence interval by RET mutation status, by study and overall.

  A waterfall plot of the largest percentage change in the sum of the longest diameters of the target lesions from baseline was produced by RET mutation status.
- Time to Response and DOR

  Time to response and DOR for RET positive and RET negative patients were summarized descriptively and as time-to-event data. Kaplan Meier estimator was used to estimate the quartiles of time to response and duration and Kaplan Meier survival curves were presented.
- Progression Free Survival

  Median PFS was presented in RET positive and RET negative patients. The proportion of patients who had PFS at 3, 6, 9, 12, 18, and 24 months after the start of treatment was summarized by RET mutation status. A Kaplan-Meier plot of PFS split by RET mutation status was provided.
- Other outcome evaluations (including CTN and CEA) were presented descriptively.

Safety Analyses

Safety data were presented by RET mutation status and by study on the safety population.

- Extent of exposure

  Extent (or duration) of exposure was defined as number of days of exposure to study medication [last dose date - first dose date +1]). Duration of exposure was summarized descriptively by RET mutation/study and overall.

- Adverse events

  All AEs (including SAEs) were coded to LLT, PT, HLT, HLGT, and associated primary system organ class (SOC) using MedDRA version 22.1.

  The number and percentage of patients with TEAEs were presented by the internationally agreed SOC order and decreasing frequency of PT within each SOC. Multiple occurrences of the same event in the same patients was counted only once in the tables. The denominator for computation of percentages was the safety population with RET mutation status. The same presentation was done for pre-treatments AEs, SAEs, treatment-related TEAEs, TEAEs leading to discontinuation of study medication, TEAEs leading to discontinuation from study, TEAEs by grade, and TEAE leading to death.

  The AE incidence table was provided by RET mutation status, study, and overall for all types of TEAEs.

- Other safety evaluations including vital signs, ECG, and laboratory data were summarized descriptively.

Results

- **Overall participation status:** As of 17 December 2020 (date of database lock), a total of 30 sites in 8 countries were participating, including 4 sites specifically involved in the retrospective data collection effort on RET negative patients. Among these 30 sites, 18 sites responded that they did not have any RET negative patient to contribute to the retrospective data collection effort. Overall, 97 patients were enrolled in the study: 3 patients did not meet eligibility criteria and did not have RET mutations status, 37 patients (30 patients with RET positive mutation and 7 patients with RET negative mutation) prospectively enrolled in OBS14778 study and 57 patients retrospectively enrolled (47 patients coming from D4200C00058 randomized 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).
- **Participation per period of the study:** Of the 97 patients enrolled, 75 patients were evaluable for efficacy (77.3%) (all enrolled and eligible patients exposed to vandetanib with known RET mutation status and RECIST assessment evaluable at baseline). Of these 75 patients, 41 (54.7%) patients withdrew prematurely: 14 (18.7%) due to disease progression, 5 (6.7%) patients due to AEs (cutaneous rash, n=2; acute kidney injury, n=1; empyema, n=1; alanine aminotransferase increased, n=1); 1 (1.3%) patient each due to disease progression (recorded also as safety reason) and 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 and led to premature withdrawal from the study. Twenty-two (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).

- **Descriptive data:**
  - Baseline characteristics: Overall, 75/97 (77.3%) patients were evaluable, 55 RET positive patients (mainly due to mutation in Exon 16 [M918T]) and 20 RET negative patients. 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.

    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); the 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); 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). Most patients had stage IVc disease at baseline (62 [83.8%] patients overall, 46 [83.6%] patients with RET positive status, and 16 [84.2%] patients with RET negative status). Metastases were mainly located in lymph nodes, liver, and lung.

    Overall, 63 (84.0%) patients had a prior thyroidectomy, 28 (37.3%) had prior radiotherapy, and 8 (10.7%) received prior chemotherapy.
  - Efficacy: The median duration of treatment with vandetanib was 23.4 months in RET positive patients and 27.6 months in RET negative patients. The objective tumor response rate (CR+PR) for RET positive patients was 41.8% (23 out of 55), and 5.0% (1 patient out of 20) for RET negative patients; however, the DCR was 85.5% for RET positive patients and 90.0% for RET negative patients. The median DOR in RET positive patients was 21.9 months and median time to response was 5.5 months (range: 2.7 to 30.7 months). The RET negative patient with a PR had a DOR of 5.3 months and time to response of 8.3 months. 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. Treatment with vandetanib was associated with a decrease in CTN, which appeared more rapidly in RET positive than in RET negative patients. There was also a decrease in CEA which was comparable in both RET positive and RET negative patients.
  - Safety: 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. The median exposure to vandetanib was 23.4 months for RET positive patients and 27.6 months for RET negative patients. A slightly higher percentage of RET positive patients compared to RET negative patients experienced TEAEs (98.4% versus 88.9%) and serious TEAEs (31.3% versus 22.2%). As expected, the most common TEAEs (in ≥20% patients) with vandetanib were diarrhea (56.0%), rash (31.9%), and hypertension (23.1%). A total of 14 (15.4%) patients had 15 TEAEs

leading to treatment discontinuation, 9 (14.1%) patients were RET positive (9 TEAEs) and 5 (18.5%) patients were RET negative (6 TEAEs). A total of 16 (17.6%) patients had 22 TEAEs leading to discontinuation from the study; 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). Overall, 4 patients died due to TEAEs, 2 of whom have been previously reported in the D4200C00058 study; 1 RET positive patient had fatal AEs of arrhythmia and cardiac failure acute (from D4200C00058), 1 RET negative patient had a fatal AE of inhalation pneumonia (from D4200C00058), and 2 RET positive patients had a fatal AE of disease progression (both enrolled in OBS14778). There were no clinically meaningful differences between the RET positive and RET negative patients with regard to the incidence of QTc prolongation and associated risks for QTc prolongation, and no new safety findings were identified.

Discussion

- Interpretation: RET negative patients had a lower objective tumor response rate than RET positive patients but DCR and PFS were comparable between both groups. There was also a slightly higher rate of AEs and serious TEAEs among the RET positive patients compared to the RET negative patients but AEs were in agreement with the known safety profile of vandetanib. The major limitations of these results is the low number of RET negative patients (n=20) and the fact that, as for any other observational study, there was no central review of the tumor response.

  Despite the potential limitations, the study design is typical for an observational analysis and reflects specific adaptations to align with the real-world situation for these patients. Objective assessments were employed to reduce bias, although there was no central review of imaging.
- Generalizability: This study utilized a typical observational study design with adjustments made to better recruit and assess RET negative patients. Therefore, the data collected and presented in analyses of this report are considered to reflect the real-world use of vandetanib in these populations.
- Conclusion: 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 patients. 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.

Marketing Authorization Holder

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This report was prepared by:

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The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

Names and affiliations of Principal Investigators

Not applicable.

National coordinators

Not applicable.