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 a non-interventional post-authorization safety study (PASS) 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 negative and RET positive participants with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC).

Only 10 evaluable RET negative participants could be recruited at study sites (7 enrolled prospectively and 3 enrolled retrospectively). Because recruitment of RET-negative participants was difficult, it was agreed to pool these 10 participants with 11 confirmed RET-negative participants identified from re-analysis of Study D4200C00058.

Because OBS14778 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. This addendum provides the results of the objective response from the blinded central review (in addition to the analysis per investigator assessment), in line with original clinical study report (CSR) of study D4200C00058.

Research question and objectives of the Study

This addendum of the PASS report OBS14778 provides the objective response of participants from Study D4200C00058 according to the blinded central review (in addition to the analysis per investigator assessment), in line with the original CSR of study D4200C00058.

The objectives of the study were as follows:

- To determine the Objective Response Rate (ORR) for participants treated with vandetanib who were RET positive and participants treated with vandetanib who were RET negative.
- To determine the Disease Control Rate (DCR) for participants treated with vandetanib who were RET positive and participants treated with vandetanib who were RET negative.
- To assess the duration of response and time to response for participants treated with vandetanib who were RET positive and participants treated with vandetanib who were RET negative.
- To explore the clinical outcomes (including, but not limited to, progression free survival (PFS) and ORR) among RET negative participants 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 participants receiving vandetanib who were RET positive and RET 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 participants treated with vandetanib who were RET positive to participants treated with vandetanib who were RET negative.

Study design

The full description of the study design is provided in the original PASS report.

Setting

Details describing the setting is available in the original PASS report.

Participants and study size, including dropouts

The full description of the participants and study size can be found in the original PASS report.

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 considerations, please refer to the final Statistical Analysis Plan.
- **Variables and evaluation criteria:**

  Efficacy evaluation

  - Objective Response Rate (ORR), defined as the percentage of participants 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 as per investigator assessment and RECIST 1.0 for D4200C00058 [originating data] as per central review and investigator assessment).
  - Variable and evaluation criteria for DCR, PFS, time to response, duration of response, duration of follow up, and other efficacy evaluations are provided in the original PASS report.

  Safety evaluation

  Detailed of the safety evaluation is provided in the original PASS report.

- **Data analyses:**

  Efficacy Analyses

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

  - Objective Response Rate, DCR

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

  - Time to Response, DOR, PFS, and other outcomes are provided in the original PASS report.

Results

- **Overall participation status:** Overall, 97 participants were screened and enrolled in the study: 37 participants prospectively enrolled (30 participants with RET positive mutation and 7 participants with RET negative mutation) and 57 participants retrospectively enrolled (47 participants coming from D4200C00058 randomized study with re-evaluated RET mutation status [36 RET positive and 11 RET negative], and 10 participants with RET negative mutation retrospectively enrolled at the site level). Of the 97 participants enrolled in the study, 79 were evaluable for efficacy and 18 participants were non evaluable (including 3 participants who had no RET mutation status available). Of the 79 evaluable participants, there were 58 RET positive participants and 21 RET negative participants included in this analysis.
- **Participation per period of the study:** Of the 97 participants enrolled, 79 participants were evaluable for efficacy (81.4%) (all enrolled and eligible [ie exposed to vandetanib with known RET mutation status] and RECIST assessment evaluable at baseline). The remaining 18 participants (18.6%) were non evaluable (11 [11.3%] participants had no

evaluable baseline RECIST assessment, 6 [6.2%] participants did not meet eligibility criteria, and 1 [1.0%] participant did not take at least 1 dose of vandetanib). Of these 79 participants, 43 (54.4%) participants withdrew prematurely (34 [58.6%] RET positive and 9 [42.9%] RET negative).

- **Descriptive data:**
  - Baseline characteristics: Overall, 81.4% (N = 79) of the participants were evaluable, 58 RET positive participants (mainly due to mutation in Exon 16 [M918T]) and 21 RET negative participants. The median age of participants was 50.0 years (range: 20 to 77 years), higher for RET negative participants compared to RET positive (58.0 years versus 45.0 years). A total of 63.3% (N = 50) were males and 36.7% (N = 29) were females. Most participants (92.3% [N = 72]) were white.
  - The median time from MTC diagnosis to first dose of vandetanib was 69.91 months overall (65.15 months and 80.46 months for RET positive and RET negative participants, respectively); the median time from diagnosis of sporadic, unresectable, locally advanced/metastatic MTC to first dose of vandetanib was 10.25 months overall (5.45 months and 17.02 months for RET positive and RET negative participants, respectively); the median time from last disease progression to first dose of vandetanib was 2.37 months overall (1.82 months and 6.05 months for RET positive and RET negative participants, respectively). Most participants had stage IVc disease at baseline (83.3% [N = 65] of the participants overall, 82.8% [N = 48] were RET positive, and 85.0% [N = 17] were RET negative). Metastases were mainly located in lymph nodes, liver, and lung.
  - Overall, 84.8% (N = 67) had a prior thyroidectomy, 38.0% (N = 30) had prior radiotherapy, and 10.1% (N = 8) received prior chemotherapy.
  - Efficacy: The median duration of treatment with vandetanib was 23.4 months in RET positive participants and 27.6 months in RET negative participants. The objective response rate (CR+PR) for RET positive participants was 39.7% (N = 23), 9.5% (N = 2) for RET negative participants per blinded centralized review of tumor response, and 5.0% (N = 1) for RET negative participants as per investigator evaluation of tumor response. DCR was 87.9% (N = 51) for RET positive participants 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 participants and 5.52 months for RET negative participants. The median DOR was 19.58 months for RET positive and not estimable for RET negative participants. The median PFS was 25.36 months RET positive participants and 35.71 months in RET negative participants. At 12 months, 22% of RET positive participants and 21% of RET negative participants were estimated to have progressed; at 24 months, 43% of RET positive participants and 21% of RET negative participants 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 participants. There was also a decrease in carcinoembryonic antigen (CEA) levels which was comparable in both RET positive and RET negative participants.
  - The safety profile of vandetanib is unaffected by this addendum. All other safety data descriptions are available in the original PASS report.

Discussion

- Interpretation: The purpose of the addendum was to provide, for participants coming from Study D4200C00058, the results of the objective response according to the blinded central review, in addition to the tumor response per investigator assessment. Although RET negative participants had a lower tumor response than RET positive participants (9.5% versus 39.7%), DCR and PFS were comparable between both groups and a decrease in CTN and CEA levels was observed in both groups. At the end of the follow-up period, one RET negative participant treated with vandetanib had died due to disease progression (4.8%) versus 8 RET positive participants (13.8%). The safety profile was unaffected in this addendum. The major limitations of these results are the low number of RET negative participants (N = 21) and the fact that, there was no central review of the tumor response in participants enrolled in prospective and retrospective observational cohorts.

  Despite the potential limitations, the study design was typical for an observational analysis and reflected specific adaptations to align with the real-world situation for these participants. Objective assessments were employed to reduce bias, although there was no central review of imaging (except for participants coming from Study D4200C00058).
- Generalizability: This study utilized a typical observational study design with adjustments made to better recruit and assess RET negative participants. However, generalizability of the results is limited by the low number of RET negative participants in daily clinical practice.
- Conclusion: The OBS14778 study was an observational study where the objective response was based on the investigator assessment of imaging for all participants, including those from Study D4200C00058. Since, the analysis of imaging in Study D4200C00058 was primarily based on a blinded central review, this addendum provides the results of the objective response from the blinded data set, in line with the original CSR of study D4200C00058. Although RET negative participants showed a lower objective tumor response than RET positive participants, DCR and PFS were comparable between both groups and a decrease in CTN and CEA was observed in both groups. At the end of the follow-up period, one RET negative participant had died due to disease progression (4.8%) versus 8 RET positive participants (13.8%). There was a slightly higher rate of AEs and serious TEAEs among the RET positive participants compared to the RET negative participants but overall, reported AEs were consistent with the known safety profile of vandetanib and were unaffected by this addendum.

  Considering the results and limitations of this observational study, the positive benefit/risk profile of vandetanib already established in RET positive participants is confirmed. Considering the absence of standard of care for RET negative MTC, the benefit/risk of vandetanib is considered acceptable for RET negative participants with progressive and symptomatic unresectable locally advanced or metastatic MTC.

Marketing Authorization Holder(s)

Genzyme Corporation, a Sanofi company
50 Binney Street
Cambridge, MA, 02142
UNITED STATES

Study Personnel

This report was prepared by:

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.