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AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib (ZD6474)
Study Code	D4200C00088
Edition Number	1
Date	13 September 2013
EudraCT Number	2010-023428-26

A Randomized, International, Open-Label, Multi-Center, Phase III Study to Assess the Effect of a Patient Outreach Program on the Percentage of Time Patients with Locally Advanced or Metastatic Medullary Thyroid Cancer Experience Grade 2 or Higher Adverse Events During the First 12 Months of Treatment with Vandetanib

Study dates:	First subject enrolled: 25 February 2011 Last subject enrolled: 27 April 2012
Phase of development:	Therapeutic confirmatory (IIIb)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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Study centers

This multi-center study was conducted in 33 international centers across 20 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Study objectives and outcome variables are summarized in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To demonstrate a decrease in the percentage of time patients with locally advanced or metastatic medullary thyroid cancer experience AE of CTCAE Grade 2 or higher in the first 12 months of receiving vandetanib with the use of a patient outreach program	Percentage of time a patient experienced at least 1 AE of CTCAE Grade 2 or higher in the first 12 months of receiving vandetanib
Secondary	Safety	To collect additional information on the safety and tolerability of vandetanib in patients with locally advanced or metastatic medullary thyroid cancer	AEs, vital signs, clinically significant laboratory abnormalities, ECG abnormalities (including QTc)
Exploratory[a]	PRO	To investigate patient health status index during the first 12 months of treatment with vandetanib by assessment of EQ-5D in patients with locally advanced or metastatic medullary thyroid cancer	EQ-5D self-classified health state

[a] The results from the exploratory objective were not reported in the abbreviated CSR and CSR synopsis.
AE Adverse events; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Event; ECG Electrocardiogram; EQ-5D EuroQol 5 Dimension instrument; QTc QT interval corrected for heart rate by the Bazett's method; PRO Patient-reported outcomes.

Study design

This was an international, randomized, open-label, multi-center study to assess the effect of a patient outreach program on the percentage of time patients, with locally advanced or metastatic medullary thyroid cancer (MTC) experienced Common Terminology Criteria for Adverse Event (CTCAE) Grade 2 or higher adverse events (AEs) during the first 12 months of treatment with vandetanib. Eligible patients were randomized in a 1:1 ratio to either the experimental arm (inclusion in patient outreach program) or the control arm (standard AE monitoring schedule) using an integrated voice/web recording system.

Target subject population and sample size

Male and female patients aged ≥18 years, with previously histologically confirmed unresectable locally advanced or metastatic MTC and performance status of 0 to 2 (World Health Organization [WHO] or Eastern Cooperative Oncology Group [ECOG]) and for whom no standard therapy was available, were enrolled in this study.

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Assuming a 2-sided 5% significance level, 1:1 randomization, a true prevalence of 60% in the control arm, a true absolute difference in means of 15% (ie, H1 would correspond to a true prevalence of 45% in the experiment arm), and a standard deviation (SD) of 33%, a total of 206 patients (approximately 103 patients per arm) were required to achieve a 90% power.

Investigational product and comparator(s): Dosage, mode of administration, and batch numbers

Vandetanib was available in a 100 mg tablet form and was administered orally, once daily, preferably in the morning at the same time of the day. Patients with screening creatinine clearance ≥50 mL/min started vandetanib at a dose of 300 mg (3x100 mg vandetanib tablets) once daily whereas patients with moderate renal impairment, defined as screening creatinine clearance ≥30 mL/min to <50 mL/min, started vandetanib at a reduced dose of 200 mg (2x100 mg vandetanib tablets) once daily.

Batch numbers of vandetanib used in this study were TS27094, TX28134, TX28135, ES2012008, TX28132, and TX28135.

Duration of treatment

The patients were subjected to a screening period to determine eligibility. Once randomized, the patients were followed for 52 weeks unless they met any criteria for discontinuation. At the completion of 52 weeks on the study treatment, patients had the option to either permanently discontinue the study (no longer receive vandetanib) or continue taking the study treatment. The patients who permanently discontinued the study treatment had a discontinuation visit and were contacted 60 days later for follow-up for AEs/serious adverse events (SAEs), after which they were considered to have completed the study.

Patients, who at the completion of 52 weeks wished to remain on therapy, had to complete a final analysis visit and were contacted every 13 weeks (Visit 10, Visit 11, etc) thereafter for collection of SAE information and drug accountability until being permanently discontinued. Patients who permanently discontinued the study had a final discontinuation visit (Visit 85) and were contacted 60 days later for SAE follow-up (Visit 90). These patients were then considered to have completed the study.

Patients could discontinue the study at any time and for any reason. The patients who discontinued the study prior to 52 weeks for any reason had a discontinuation visit (Visit 75) and were contacted 60 days following that visit for AE/SAE follow-up (Visit 80). These patients were then considered to have completed the study.

Statistical methods

The statistical analysis was performed when recruitment had ended and all randomized patients were either terminated from the study or reached Week 52.

The primary comparison of interest was between patients who participated in the patient outreach program and patients who did not participate in the patient outreach program.

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The primary endpoint was the percentage of time a patient experienced at least 1 AE of CTCAE Grade 2 or higher in the first 12 months of treatment with vandetanib. The primary endpoint was analyzed using a student's independent 2-sample t-test.

Subject population

A total of 205 patients were randomized in 1:1 ratio to the vandetanib 300 mg arm+outreach program arm or the vandetanib 300 mg arm. In total, 205 patients received the study treatment (103 patients in the vandetanib 300 mg+outreach program arm and 102 patients in the vandetanib 300 mg arm). Of the 205 patients, 155 (75.6%) patients received the study treatment for 12 months whereas 50 (24.4%) patients discontinued the treatment prior to 12 months. The reasons for discontinuation of the treatment prior to 12 months were: Condition under investigation worsened (27 [13.2%] patients), other (10 [4.9%] patients), AE (7 [3.4%] patients), subject decision (4 [2.0%] patients), severe non-compliance to protocol (1 [0.5%] patient), and subject lost to follow-up (1 [0.5%] patient). Of the 103 patients who were randomized to the vandetanib 300 mg+outreach program arm, all except 1 patient took part in the patient outreach program.

The demographic characteristics in the overall population were well balanced between the 2 treatment arms. There was a balance between the 2 treatment arms with respect to WHO/ECOG performance status at study entry. All 205 (100.0%) patients had a WHO/ECOG performance status between 0 and 2, inclusive.

Summary of safety results

Overall, the mean total duration of treatment in the vandetanib 300 mg+outreach program arm (14.84 months for total treatment exposure and 14.13 months for actual treatment exposure) was numerically higher than that for the vandetanib 300 mg arm (14.36 months for total exposure and 13.87 months for actual exposure).

The mean (SD) percentage of time a patient experienced an AE of CTCAE Grade 2 or higher for the vandetanib 300 mg+outreach program arm was 51.65 (35.548), which was higher compared with the vandetanib 300 mg arm (45.19 [36.347]). However, this difference was not statistically significant (T-statistic: 1.29; 95% CI -3.44% to 16.37%; p-value=0.199) and likely reflects an ascertainment bias associated with the more frequent patient contacts in the outreach arm. The most frequently reported preferred terms (PTs) with CTCAE Grade 2 or higher were hypertension (33.3% patients in the vandetanib 300 mg+outreach program arm versus 23.3% patients in the vandetanib 300 mg arm), diarrhea (26.5% patients in the vandetanib 300 mg+outreach program arm versus 24.3% patients in the vandetanib 300 mg arm), and dermatitis acneiform (11.8% patients in the vandetanib 300 mg+outreach program arm versus 9.7% patients in the vandetanib 300 mg arm).

Overall, the number of patients who reported at least 1 AE was higher in the vandetanib 300 mg+outreach program arm (101 [99.0%] patients) compared with the vandetanib 300 mg arm (93 [90.3%] patients). Of the 194 (94.6%) patients who experienced AEs during the study, 179 (87.3%) patients had a drug-related AE. There were a higher number of patients with CTCAE Grade 3 or higher AEs in the vandetanib 300 mg+outreach program arm

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(54 [52.9%] patients) compared with the vandetanib 300 mg arm (47 [45.6%] patients). AEs with an outcome of death were noted in 6 (2.9%) patients. Serious adverse events (SAEs) were noted in 57 (27.8%) patients, of which 21 (10.2%) patients had drug-related SAEs. A total of 11 (5.4%) patients discontinued treatment due to AEs. AEs leading to dose reduction and dose interruption of vandetanib were noted in 77 (37.6%) patients and 50 (24.4%) patients, respectively.

The most common AEs by PT, with a frequency >10%, were diarrhea, hypertension, rash, and nausea. These AEs were consistent with the known safety profile of vandetanib and the mechanism of action of vascular endothelial growth factor receptor (VEGFR) and endothelial growth factor receptor (EGFR) inhibition.

Clinically significant laboratory abnormalities, vital sign abnormalities, and electrocardiogram changes observed in the study were consistent with the known safety profile of vandetanib.

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