AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib (ZD6474)
Study Code	D4200C00097
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An International, Randomised, Double-Blind, Two-Arm Study to Evaluate the Safety and Efficacy of Vandetanib 150 and 300 mg/day in Patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma with Progressive or Symptomatic Disease

Study dates: First subject enrolled: 08 June 2012
Last subject last visit: 02 April 2014 (Part A only)

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centers

This study was performed at 29 sites in 9 countries: Czech Republic, India, Israel, Italy, Netherlands, Poland, Russia, UK and USA.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the objective response rate (ORR) for 2 starting doses of vandetanib, 150 mg and 300 mg, in patients with unresectable locally advanced or metastatic MTC having progressive or symptomatic disease.	ORR (ORR = CR or PR as defined by RECIST 1.1)
Secondary	Safety	To evaluate the safety and tolerability of vandetanib 150 mg and 300 mg	AEs Physical examination Vital signs (BP and pulse) ECG parameters Opthalmologic exam Laboratory parameters (clinical chemistry, hematology and urinalysis)
Secondary	Efficacy	To evaluate the time to objective response, duration of objective response, and the best percentage change in target lesion size	BOR, tumor size, duration of and time to response
Secondary	Pharmacokinetics	To evaluate the PK of vandetanib at 150 mg and 300 mg in this patient population	Maximum plasma concentration (C_{max}), area under the plasma concentration time curve from zero to the last measurable time point (AUC) and apparent plasma clearance following oral administration (CL/F). Other parameters could be determined as deemed appropriate.

Study design

This was a randomized, double-blind, international study to evaluate the safety and efficacy of vandetanib 150 and 300 mg/day in patients with unresectable locally advanced or metastatic MTC with progressive or symptomatic disease. The study consisted of a double-blind

randomized phase (Part A) and an unblinded phase (Part B). Patients were followed for efficacy only during the double-blind randomized phase (Part A) of the study that continued for a maximum of 14 months. No further efficacy data will be collected in Part B, but safety evaluations will continue in Part B until each patient has received vandetanib for a total (Parts A and B) of 2 years, or for 60 days following permanent discontinuation of vandetanib if prior to 2 years. The results presented in this Clinical Study Report (CSR) are for Part A only. Part B of the study is currently ongoing and results will be presented in an addendum to the CSR.

Target subject population and sample size

It was planned that approximately 10% of the patients were enrolled in the US, and the remaining 90% from Rest of World countries. Approximately 35 centers were planned. It was expected that each center will recruit 2 to 3 patients with previously confirmed histological diagnosis of unresectable, locally advanced or metastatic, hereditary or sporadic medullary thyroid carcinoma (MTC) over an 18-month recruitment period.

AstraZeneca and FDA agreed that a sample size of 40 patients per arm (80 in total) would allow the ORR in each treatment arm to be estimated with adequate precision. For example, if 8/40 patients respond, the ORR would be 20%. The corresponding 95% confidence interval using the Wilson score method would be (10.5%, 34.8%), which lies entirely to the right of zero, thus providing evidence that the ORR for this treatment group was likely to be greater than zero. The proposed sample size for this study was therefore 80 patients in total, with 40 patients to be randomized in each treatment group.

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

Vandetanib 300 mg arm: Patients randomized to the 300 mg arm began on once daily vandetanib at 300 mg using one 300 mg vandetanib tablet, one 100 mg placebo tablet and one 50 mg placebo tablet.

Vandetanib 150 mg arm: Patients randomized to the 150 mg arm began on once daily vandetanib at 150 mg using one 100 mg vandetanib tablet, one 50 mg vandetanib tablet and one 300 mg placebo tablet.

Duration of treatment

Patients were followed for efficacy only during the double-blind randomized phase (Part A) of the study that continued for a maximum of 14 months. No further efficacy data will be collected in Part B, but safety evaluations will continue in Part B until each patient has received vandetanib for a total (Parts A and B) of 2 years, or for 60 days following permanent discontinuation of vandetanib if prior to 2 years.

Statistical methods

For the primary endpoint (ORR) estimates of the ORR within the first 14 months after randomization were calculated, along with 2-sided 95% confidence intervals (CI) per

treatment group. The Wilson score method was to be used for the calculation of the CI. As the aim of the study was to provide additional information on the likely range of response rates with a starting dose of either 150 mg or 300 mg, there was no formal hypothesis testing to compare the ORR between the 2 treatment groups.

For tumor lesion size, the best percentage change was to be defined as the maximum percentage decrease relative to baseline or the minimum percentage increase relative to baseline for patients who had not experienced a decrease. If no RECIST data were available for a specific patient, then these data were assumed to be missing completely at random and the patient was to be excluded from the waterfall plot.

The best overall objective tumor response within the first 14 months after randomization was to be summarized by treatment group, using counts and percentages.

The median duration of response and median onset of response were to be summarized with corresponding 95% CIs split by treatment arm. Only patients who had a response within the first 14 months after randomization were to be included in these summary tables.

Safety data were listed and summarised using descriptive statistics.

This study report contains data from Part A of the study only. Part B of the study is currently ongoing and results will be presented in an addendum to the CSR.

Subject population

A total of 80 patients were planned to be recruited and 81 were randomized at a 1:1 ratio (40 in the vandetanib 150 mg group and 41 in the vandetanib 300 mg group) at 29 sites in 9 countries. Overall, 30.9% (25/81) randomized patients who received vandetanib had objective disease progression prior to 14 months with more patients (45.0% [18/40]) in the vandetanib 150 mg group. A total of 24.7% [20/81] patients discontinued treatment in Part A (12.5% in the vandetanib 150 mg group and 36.6% in the vandetanib 300 mg group). The main reason for discontinuation from study treatment was AEs. Demographic and patient characteristics were similar between the 2 treatment groups and representative of the intended patient population. Most patients had a surgical or medical procedure and this was considered to be consistent with the known treatments for MTC.

Summary of efficacy results

Overall, 25% of patients had objective response by 14 months; 20% of patients had objective response in the vandetanib 150 mg group (8 partial response [PR]) and 29% of patients had objective response in the vandetanib 300 mg group (11 PR and 1 complete response [CR]). Most patients had a reduction in target lesion size with more reductions seen in the 300 mg group. Duration of response was similar between treatment groups; a slightly longer median was observed of 9.8 months in the vandetanib 150 mg group. Time to onset of response was similar between treatment groups. A slightly higher proportion of patients had responded by 6 months in the vandetanib 300 mg group.

Summary of pharmacokinetic results

Clearance was similar for the 150 mg group at 10.4 L/h and the 300 mg group at 11.1 L/h. Mean maximum plasma concentration at steady state ($Cmax_{ss}$) was estimated to be 486 ng/ml for the 150 mg group and 885 ng/ml for the 300 mg group. Mean area under the plasma concentration time curve at steady state (AUC_{ss}) was estimated to be 8250 ng.h/ml for the 150 mg group and 14804 ng.h/ml for the 300 mg group. Steady state exposure was approximately 2-fold higher for the 300 mg group than for the 150 mg group.

The mean population parameters for the baseline, maximum change from baseline (Emax) and plasma concentration resulting in 50% of Emax (EC50) were 450 ± 1.09 ms, 52.5 ± 7.47 ms and 578 ± 194 ng/mL, respectively.

Summary of safety results

In the safety analysis set, AEs were reported by a total of 79 patients (97.5%). The number and type of AEs reported during this study were consistent with what would be expected for this patient population and the safety profile for vandetanib. The most frequently reported AEs in the vandetanib 150 mg group were diarrhea (37.5%), blood thyroid stimulating hormone increased (27.5%), rash (20.0%), hypocalcemia (20.0%), hypertension (20.0%) and fatigue (20.0%); the most frequently reported AEs in the vandetanib 300 mg group were diarrhea (43.9%), electrocardiogram QT prolonged (34.1%), rash (31.7%), keratopathy (31.7%), hypocalcemia (29.3%), hypertension (26.8%) and blood thyroid stimulating hormone increased (22.0%). The proportion of patients reporting SAEs was similar between the 2 groups although the only AEs leading to death (2) were reported in the 300 mg group (pulmonary embolus and epileptic attack). Neither of these was thought to be related to vandetanib in the investigators opinion. More patients in the vandetanib 300 mg group discontinued vandetanib due to an AE (DAE) (2 in the vandetanib 150 mg group and 5 in the vandetanib 300 mg group). Three of these patients had DAEs that were considered to be causally related to study treatment: in the vandetanib 150 mg group 1 patient had angina pectoris; in the vandetanib 300 mg group 1 patient had peripheral motor neuropathy and 1 patient had cholecystitis. Numerically, a higher proportion of patients reported AEs of Grade 3 or higher in the vandetanib 300 mg group, the most common being hypertension.

There were values recorded outside the normal reference ranges for the majority of laboratory parameters. CTCAE grade changes of 2 or higher were not common, occurring in a small number of patients in each treatment group. QTcF prolongations (>450 ms) occurred sooner and more frequently in the 300 mg group and multiple prolongations (>450 ms) also occurred more frequently in the 300 mg group. This is consistent with the current safety profile of vandetanib.