Clinical Study Report Synopsis

Drug Substance	Vandetanib (ZD6474)
Study Code	D4200C00098
Edition Number	1

A Phase I/II, Open-Label Study to Evaluate the Safety and Tolerability of Vandetanib 300 mg/Day in Japanese Patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma

Study dates:	First patient enrolled: 12 November 2012 Last patient enrolled: 18 June 2013 Data cut-off: 10 December 2013
Phase of development:	Clinical pharmacology (I)/Therapeutic exploratory (II)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives and outcome variables for the study are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety and tolerability in Japanese patients with unresectable locally advanced or metastatic MTC treated with 300 mg/day of vandetanib	AEs; vital signs; laboratory data, ECG, chest X-ray and SpO_2; ophthalmologic evaluation; and PE
Secondary	Efficacy	To evaluate the ORR in Japanese patients treated with 300 mg/day of vandetanib if a patient has measurable or assessable lesion(s)	ORR
	PK/Pharmacodynamic	To assess the PK and PK/pharmacodynamic relationship using data from this study	PK parameters: $C_{ss\ max}$, $t_{ss\ max}$, AUC_{ss}, and CL/F, PK/pharmacodynamic relationship
	Efficacy	To evaluate PFS in Japanese patients treated with 300 mg/day of vandetanib	PFS

AE Adverse event; AUC_{ss} Area under the plasma concentration-time curve during any dosing interval at steady-state; CL/F Total body clearance of drug from plasma after an oral dose; $C_{ss\ max}$ Maximum steady-state plasma concentration; ECG Electrocardiogram; MTC Medullary thyroid carcinoma; ORR Objective response rate; PE Physical examination; PFS Progression-free survival; PK Pharmacokinetic; SpO_2 Arterial oxygen saturation; $t_{ss\ max}$ Time to maximum steady-state concentration.

Study design

This was a Phase I/II multi-center, non-randomized, open-label study to evaluate the safety and tolerability of vandetanib 300 mg/day in Japanese patients with unresectable locally advanced or metastatic, hereditary or sporadic medullary thyroid carcinoma (MTC). Patients were to be recruited until data for 10 patients who received vandetanib for ≥24 weeks (and therefore had safety follow-up of ≥24 weeks) were accumulated and all patients with measurable disease had been followed until progressive disease (PD) or for 56 weeks, whichever occurred first.

Study visits schedule were to include visits at screening (Day -28 to Day -1), registration (Day 1), and Days 8, 15, 22, 29, and every 28 days until Day 253. After Day 253, study visits were to be scheduled every 84 days except for Visit 16, where data for Week 56 were collected.

Target patient population and sample size

The target population included Japanese female and male patients aged ≥20 years with unresectable, locally advanced or metastatic, hereditary or sporadic MTC, with WHO performance status of 0 to 2, and a life expectancy of ≥6 months.

At least 10 patients were to be registered and at least 24-week safety data were to be obtained from them. In addition, all patients with measurable lesion were to be followed up until progressive disease (PD) or for 56 weeks, to obtain the efficacy data of vandetanib.

Investigational product: Dosage, mode of administration, and batch numbers

Details of the investigational product (IP) are given in Table S2.

Table S2 Details of investigational product

IP	Dosage form and strength	Manufacturer	Batch number
Vandetanib	Tablet; 100 mg	AstraZeneca Pharmaceuticals	12269.1/1 12269.3/1

IP Investigational product.

Patients were dosed with vandetanib 300 mg (3x100 mg tablets) orally, once daily. The starting dose for patients with moderate renal impairment (creatinine clearance ≥30 mL/minute to <50 mL/minute) was 200 mg/day. If required, the dose was to be reduced to 200 mg/day (2x100 mg tablets) or to 100 mg/day (1x100 mg tablet). Two dose reductions were allowed in the study.

Duration of treatment

Vandetanib treatment was to be given until objective disease progression was documented or any other criterion for discontinuation (eg, toxicity, withdrawal of consent) was met.

Statistical methods

In this study, efficacy data were to be summarized and analyzed on the efficacy analysis set. Safety data were to be summarized and analyzed on the safety analysis set. Pharmacokinetics (PK) data were to be analyzed separately using the PK analysis set.

Summary on dose reductions, dose interruptions, duration of exposure, duration of vandetanib by each dose, dose intensity of vandetanib, and summary of overall study treatment compliance were to be provided. Patients showing overall study treatment compliance, date and time of dose and duration of exposure were to be listed.

Any treatment emergent adverse events (TEAEs) occurring after the first dose of vandetanib and within 60 days after discontinuation of vandetanib treatment (AEs considered as TEAEs) were to be included in the adverse event (AE) summaries. It was recommended that any clinically significant prolongation of the interval between Q-wave and T-wave (QT interval)

on electrocardiogram (ECG) or other clinically significant abnormal findings on ECG were to be reported as an AE.

Laboratory data were to be descriptively summarized and listed by patients. Laboratory parameters actual values and changes from baseline were to be summarized by time point and by scheduled visit.

ECG and vital signs assessments were to be summarized and listed based on the protocol scheduled times. Ophthalmologic examination results (slit lamp examination) were to be summarized. Respiratory tests (chest X-ray and arterial oxygen saturation [SpO_2]) were to be listed.

The analysis of the ORR within the first 56 weeks after registration was to be done via point estimate and 2-sided exact 95% confidence interval. For patients with measurable lesion, a waterfall plot (bar charts) representing the individual patients' best percentage change from baseline in tumor size over the first 56 weeks on study was to be presented. For patients who had a response within the first 56 weeks after the first dose of vandetanib, time to response and the individual duration of response were to be documented from the date of the first visit of complete response or partial response until:

- Date of progression or death (in the absence of disease progression)

OR

- Last evaluable Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessment (for patients who did not show progression).

The best overall objective tumor response within the first 56 weeks after registration was summarized for patients with measurable lesion. A Kaplan-Meier plot of progression-free survival (PFS) was also presented. The PFS was to be calculated from the date of registration until the date of objective disease progression or death (by any cause in the absence of progression), provided death was within 12 weeks from the last evaluable RECIST assessment.

Non-compartmental PK parameters, maximum steady state plasma concentration ($C_{ss\ max}$) and time to maximum steady state concentration ($T_{ss\ max}$) were to be determined by inspection of the concentration-time profiles. Area under the plasma concentration-time curve during any dosing interval at steady state (AUC_{ss}) was to be calculated using the linear trapezoidal rule. Following multiple dosing, total body clearance of drug from plasma after an oral dose at steady state (CL_{ss}/F) was to be determined from the ratio of dose/AUC_{ss}.

A population PK analyses were to be performed using non-linear mixed effects modeling. A PK data analyses plan was prepared prior to the commencement of this analysis. The PK, QT interval corrected by Fridericias' formula (QTcF) and QT interval corrected by Bazzet's correction (QTcB) data from this Study 98 (N=14) was combined with data from Western patients with similar disease conditions Study 58 (ZETA) (N=230) to allow the data to be

modelled effectively. The combined data analyses were conducted based on the established population PK and PK-corrected electrocardiogram QT interval (QTc) models from Study 58 (ZETA).

Interim analyses were conducted at minimum of 24 weeks after the last recruited patient started on the IP. Data analyses were performed and the Clinical Study Report (CSR) is drafted on the results of interim analyses.

Subject population

This is an interim report for which the data cut-off was 10 December 2013; by this time, all patients (except for patients who discontinued the study or treatment prematurely) had completed at least 24 weeks of treatment.

Patient disposition is presented in Table S3. Of the 16 enrolled patients, 14 patients were registered and received treatment. Thirteen patients received vandetanib 300 mg/day, while 1 patient with moderate renal impairment received a reduced dose of vandetanib ie, 200 mg/day.

All patients enrolled into the study were Japanese female or male patients with half of the population (7 [50.0%] patients) from the ≥50 to <65 years age group. There were equal number of male and female patients enrolled into the study (7 [50.0%] male and 7 [50.0%] female patients).

The study population was generally representative of the intended target population ie, patients with unresectable, locally advanced or metastatic, hereditary or sporadic MTC.

Table S3 Patient disposition (All patients)

	Number (%) of patients
	Vandetanib 300 mg
Patients enrolled[a]	16
Patients registered	14
Patients who received treatment	14 (100.0)
Patients ongoing study treatment at data cut-off[b]	12 (85.7)
Patients who discontinued study treatment[b]	2 (14.3)
Adverse event	1 (7.1)
Subject decision	1 (7.1)
Patients ongoing study	12 (85.7)
Patients who were prematurely withdrawn from the study	2 (14.3)
Subject decision	1 (7.1)
Other	1 (7.1)

[a] Informed consent received.
[b] Percentages were calculated from number of patients who received treatment.
Patient was considered to have completed study if: (a) Patient with measurable disease at baseline had been followed until 56 weeks or until PD occurred, whichever came first, or (b) Patient had received vandetanib for ≥24 weeks.
Patients could continue on vandetanib until objective disease progression or at the discretion of the investigator.
PD Progressive disease

Summary of efficacy results: Secondary variables

Objective response rate (ORR)

Of the 13 patients in the efficacy analysis set (1 patient with no post-baseline efficacy assessment was excluded from the efficacy analysis set), 5 (38.5%) patients demonstrated an objective response. The 95% exact CI for ORR was 13.86% to 68.42%. All the patients demonstrating objective response had partial response (PR). A total of 8 (61.5%) patients had stable disease (SD) at least for 12 weeks. All patients had reduction from baseline in target lesion size at 1 or more post-baseline visit.

Progression-free survival (PFS)

None of the patients demonstrated RECIST progression, ie, the 24-week PFS rate was 100%.

Summary of pharmacokinetic results

Plasma concentrations of vandetanib at Day 57 were fairly flat, consistent with the long half-life of the drug. One patient had moderate renal impairment and his starting dose was 200 mg/day, while 1 patient had dose reduction to 200 mg before Day 57. These 2 patients were excluded from the means to characterize exposure for 300 mg. The geometric mean (Gmean) for $C_{ss\,max}$ was 1302 ng/mL and Gmean for AUC_{ss} was 28223.7 ng.h/mL with Gmean for CL_{ss}/F of 10.63 L. The median $T_{ss\,max}$ was 5.9 hours.

A 2-compartment PK model with fixed first order absorption and first order elimination characterized well the PK in Japanese patients.

Summary of pharmacokinetic/pharmacodynamic relationships

The PK-QTc relationship in Japanese patients was similar to that observed in Western patients.

Summary of safety results: Primary variables

The median total vandetanib exposure was 31.50 weeks while the median actual vandetanib exposure was 28.64 weeks. The median duration of therapy for all patients at the starting dose was 19.07 weeks. The mean relative dose intensity was 80.41 and the mean percentage intended dose was 71.72.

All 14 patients experienced at least 1 AE which was causally related to vandetanib as assessed by the investigator. Seven (50.0%) patients experienced AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher and had at least 1 AE that was

considered causally related to vandetanib by the investigator. Two (14.3%) patients experienced serious adverse event (Ascites and interstitial lung disease) and 1 (7.1%) patient discontinued vandetanib due to an SAE (interstitial lung disease).

The most commonly reported AEs by preferred term were diarrhea (12 [85.7 %] patients), hypertension (9 [64.3%] patients), nausea (5 [35.7%] patients), rash (5 [35.7%] patients), and rash maculo-papular (5 [35.7%] patients).

No trend of mean change over time or specific trend related to the treatment was observed in hematology and clinical chemistry results. QTc prolongation events observed in this study did not meet the criteria for QTc prolongation as defined by the CSP and there was no clinically significant difference in overall QTc profile compared to already reported QTc profile in other studies of vandetanib. There were no clinically relevant changes observed in vital signs and SpO_2 during the study.

The AEs reported in this study were generally consistent with the known safety profile of vandetanib and related to its pharmacological action as an inhibitor of vascular epidermal growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR).