Drug Substance Vandetanib Study Code D4200C00079 Date 17 September 2010	**SYNOPSIS**	

A Randomized, Double Blind, placebo-controlled Phase II, Multi-Centre Study to Assess the Efficacy and Safety of Zactima™ in Patients with locally advanced or metastatic papillary or follicular Thyroid Carcinoma failing or unsuitable for Radioiodine therapy

Study dates: First patient enrolled: 28 September 2007
Last patient enrolled: 16 October 2008
Date of data cut-off: 02 December 2009

Phase of development: Therapeutic exploratory (II)

Objectives and criteria for evaluation

The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib 300 mg as compared to placebo in patients with locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy.

The secondary objectives of the study were:

1. To demonstrate an improvement in Disease Control Rate (DCR) [Complete Response (CR) + Partial Response (PR) + Stable disease (SD) at 6 months] with vandetanib 300 mg as compared to placebo according to RECIST criteria.

2. To quantify the improvement in Objective Response Rate (ORR) (CR+PR) with vandetanib 300 mg as compared to placebo according to RECIST criteria.

3. To demonstrate an improvement in Overall Survival (OS) with vandetanib as compared to placebo.

4. To determine the safety and tolerability of vandetanib 300 mg in patients with locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy.

The exploratory objectives of the study were as follows:

1. To investigate the biochemical response of serum thyroglobulin (Tg) during treatment with vandetanib.

2. To investigate the association between gene signature profile in tumor tissue, and specific predictive biological markers and objective tumor response. The specific markers are RET/PTC 1, 2, 3, bRAF, RAS, PPAR γ -PAX8, VEGFR, EGFR, ERK, AKT.

3. To assess the early tumor response using PET scan: PET scan performed within 28 days before beginning the treatment and 1 week after beginning the treatment. To explore the correlation between PET scan response and tumor response. To assess the predictive value of the PET scan.

Data from the exploratory objectives were not available at the time of writing this report.

Study Design

This was an international, randomized, double-blind, placebo-controlled, multicenter, Phase II study.

Target subject population and sample size

Patients had unresectable locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy.

A randomized Phase II screening design was applied to allow a preliminary randomized comparison adjusting for false-positive and false-negative error rates while the sample size remains restricted. The randomization was 1:1 (vandetanib:placebo) and centralized. The sizing of the study was based on a median PFS of 6 months in the placebo-treated arm and improvement of PFS in the vandetanib-treated group corresponding to a hazard ratio of 0.71, with a power of 80% (β=20%) and 1-sided α = 20%. Therefore, 100 events were required. Assuming a recruitment period of 12 months and a follow-up for a minimum of 12 months, 124 evaluable subjects were to be recruited. With approximately 10% of screen failures and non evaluable subjects, a minimum of 135 subjects were to be enrolled in the study.

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

Table S1 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Vandetanib	300 mg tablet (randomised period), once daily, oral administration	AstraZeneca	F013383	2000107110 2000111260
Vandetanib	300 mg tablet (open label period), once daily, oral administration	AstraZeneca	F013383	2000107110 2000111260 09-000126AZ 09-000254AZ
Placebo to match vandetanib	300 mg tablet (randomised period), once daily, oral administration	AstraZeneca	F013385	2000109107

Duration of treatment

Subjects continued on randomized study treatment until they reached objective disease progression, as defined by RECIST guidelines, or until 12 months of stable disease, or until the end of the trial (whichever event occurred first). At disease progression or after 12 months of stable disease, all subjects (both active and placebo) discontinued blinded study treatment and entered follow up and survival, or were given the option to begin open-label vandetanib 300 mg treatment. Patients who began open label treatment were unblinded. Overall survival data were not mature at the time of the primary analysis of PFS. All subjects are followed to collect survival data until ≥50% of subjects died. Subjects who are taking vandetanib at the time of study closure and wish to remain on vandetanib treatment will be allowed to continue for as long as the Investigator feels that they are obtaining clinical benefit.

Statistical methods

The primary objective of the trial was to estimate whether vandetanib 300 mg is more promising than placebo with respect to PFS in subjects with papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy.

The analysis for PFS was performed using the log-rank test in the ITT population. The comparison of treatments was estimated using the hazard ratio (HR) together with the corresponding confidence interval (CI) and p-value. Point estimates of the median PFS were presented for each treatment group and PFS was displayed graphically using Kaplan-Meier plots. Three sensitivity analyses were performed. The primary analysis of ORR and DCR was performed using logistic regression including treatment factor only. A secondary analysis was also performed where the logistic regression model allowed for the effect of treatment and also included terms for known prognostic factors. The RECIST endpoints were all derived from site read assessments. The analyses of OS used the same method of analysis as described for PFS.

Safety was analysed descriptively, based on AEs, laboratory data and ECG data, all locally assessed.

Subject population

Among the 164 enrolled patients, 145 patients (88.4%) were randomised to receive vandetanib 300 mg once daily oral dose (n=72) or matched placebo (n=73). The main reason for non-randomisation was non-respect of eligibility criteria.

Half of the randomised patients (52.4%) were recruited in France, 12.4% in Switzerland and 11.7% in Sweden. Denmark, Spain, Belgium and Norway patients then accounted for 6.9%, 6.9%, 6.2% and 3.4% of the randomised patients, respectively. At the date of data cut-off (2 December 2009), all patients had discontinued the randomized period mainly due to disease progression, 12 months of stable disease or adverse events.

Eighty-seven patients (60.0%) chose to enter open-label vandetanib 300 mg period, i.e. 28 patients (38.9%) from the initial vandetanib 300 mg group and 59 (80.8%) from the initial placebo group. At the date of DCO, 36 patients (24.8%) were still under open-label treatment period and overall 101 patients (69.7%) were still followed for progression or survival.

The two treatment arms were generally balanced at baseline regarding demographic and baseline characteristics. All patients, except one in each arm, had metastatic disease and 94.5% had previous radioiodine treatment.

Summary of efficacy results

The total number of objective disease progressions (113) was lower for patients randomised to vandetanib 300 mg (52 patients, 72.2%) than for patients in the placebo group (61 patients, 83.6%). There was a statistically significant difference in PFS in favour of vandetanib 300 mg group (HR= 0.63, 95% CI 0.43 to 0.92). Statistical significance was obtained both with a one-sided test at 20% alpha level and with a more conservative two-sided test at 5% alpha level (p-values of 0.008 and 0.017, respectively).

Table S2 Summary of hazard ratio from primary analysis of progression free survival between vandetanib 300 mg and placebo - Investigator reading (ITT Analysis Set)

			-- Difference versus placebo --				
Randomised treatment	**N**	**Number (%) of events**	**Hazard ratio**	**60% CI**	**1-sided p-value**	**95% CI**	**2-sided p-value**
PFS - Log Rank Test							
Vandetanib 300 mg	72	52 (72.22%)	0.63	0.54, 0.74	0.008	0.43, 0.92	0.017
Placebo	73	61 (83.56%)					

Hazard Ratio less than 1 favoured vandetanib
The analysis was performed using the Log Rank Test with treatment as the only factor

Median PFS was largely improved with vandetanib 300 mg (334 days; 95% CI, 232-421 days) as compared to placebo patients (176 days; 95% CI, 119-267 days). All planned analyses of sensitivity gave similar results with statistically significant hazard ratios.

In term of secondary variables, there was no statistically significant improvement for vandetanib over placebo for ORR and DCR.

Table S3 Summary of Odds Ratio from analysis of Objective Response Rate and Disease control Rate between vandetanib 300 mg and placebo (ITT Analysis Set)

Objective Response Rate

			-- Difference versus placebo --		
Randomised treatment	**N**	**Number (%) of events**	**Odds Ratio**	**95% CI**	**2-sided p-value**
Vandetanib 300 mg	72	6 (8.3%)	1.57	0.42 , 5.81	0.5007
Placebo	73	4 (5.5%)			

Disease Control Rate

			Odds Ratio	**95% CI**	**p-value**
Vandetanib 300 mg	72	41 (56.9%)	1.79	0.93 , 3.46	0.0823
Placebo	73	31 (42.5%)			

Odds Ratio greater than 1 favoured Vandetanib
The analysis was performed using a logistic regression model with treatment as the only factor.
Best objective tumour response was derived from all available investigator read RECIST assessments collected prior to the first progression.
Objective response rate is the proportion of patients with a best objective response of complete or partial response.
Disease control is a best objective response of complete response, partial response or stable disease at 24 weeks.

At data cut-off, 40 of the 145 randomized patients died; there was no statistical improvement in overall survival in this interim analysis; final survival analysis will be conducted when ≥ 50% of patients have died.

Table S4 Summary of hazard ratio from analysis of OS between vandetanib 300 mg and placebo (ITT Analysis Set)

			-- Difference versus placebo --		
Randomised treatment	**N**	**Number (%) of events**	**Hazard ratio**	**99.24% CI [a]**	**2-sided p-value**
OS - Log Rank Test					
Vandetanib 300 mg	72	19 (26.39%)	0.92	0.40, 2.15	0.800
Placebo	73	21 (28.77%)			

Hazard Ratio less than 1 will favour Vandetanib
[a] Significance level adjusted according to Lan and DeMets methodology: alpha = 0.76%

Summary of pharmacodynamic results

The results will be delivered later in a separate report

Summary of safety results

The median duration of exposure was longer for vandetanib 300 mg (192 days) than for placebo (175.5 days). 41% of patients in the vandetanib group had to temporary interrupted or dose reduced to 300 mg every other day during the randomized period mainly due to AE, patient decision or intercurrent surgery.

Overall, more patients in the vandetanib group than the placebo group reported AEs, AEs of CTCAE grade 3 or higher, SAEs, AEs leading to discontinuation of study treatment and percentage of patients with a fatal SAE. The 6 most frequent AEs (PT) occurring during the randomised treatment period were diarrhoea, asthenia, fatigue, nausea, decrease appetite and hypertension.

Few significant laboratory abnormalities were found and they were balanced across treatment groups.

QTc values above preset thresholds of 500 and 550 msec (or changes from baseline of 60 and 100 msec) were defined as protocol-defined QT prolongation and required intervention. A total of 16.4% of patients in the vandetanib arm had protocol-defined QTc prolongation during randomised treatment compared with none of the patients in the placebo arm.

Table S5 below presents summaries of adverse events and Table S6 presents most common AEs (≥ 10%). Both are whilst on randomised treatment.

Table S5 Summary of number of AEs and of number (%) of patients who had at least 1 AE in any category whilst on randomised treatment (Safety Analysis Set)

	Treatment received Number (%) of patients [a]			Treatment received Number of AEs		
AE category	Vandetanib 300 mg N=73	Placebo N=72	Total N=145	Vandetanib 300 mg N=664	Placebo N=377	Total N=1041
Any AE	72 (98.6%)	69 (95.8%)	141 (97.2%)	664	377	1041
Any vandetanib/placebo causally [b] related AE	71 (97.3%)	40 (55.6%)	111 (76.6%)	467	113	580
Any AE of CTCAE grade 3 and higher	39 (53.4%)	14 (19.4%)	53 (36.6%)	70	27	97
Any SAE	19 (26.0%)	12 (16.7%)	31 (21.4%)	27	14	41
Any SAE with outcome = death	2 (2.7%)	1 (1.4%)	3 (2.1%)	2	1	3
Any AE leading to permanent discontinuation of vandetanib/placebo	24 (32.9%)	4 (5.6%)	28 (19.3%)	39	4	43
Any AE leading to temporary discontinuation of vandetanib/placebo	23 (31.5%)	6 (8.3%)	29 (20.0%)	37	9	46

[a] Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than one category are counted once in each of those categories.
Adverse events that occurred in the 30-day follow-up period after the last dose are included.
[b] As assessed by the investigator

Table S6 Summary of number (%) of patients who had at least 1 AE whilst on randomised treatment by preferred term arranged by system organ class with a frequency greater than 10% (Safety Analysis Set)

AE with frequency > 10% [a]	Treatment received Number (%) of patients [b]		
System Organ Class / Preferred Term	Vandetanib 300 mg N=73	Placebo N=72	Total N=145
Gastrointestinal disorders	**65 (89.0%)**	**37 (51.4%)**	**102 (70.3%)**
Diarrhoea	54 (74.0%)	12 (16.7%)	66 (45.5%)
Nausea	18 (24.7%)	11 (15.3%)	29 (20.0%)
Abdominal pain	9 (12.3%)	5 (6.9%)	14 (9.7%)
Skin and subcutaneous tissue disorders	**63 (86.3%)**	**23 (31.9%)**	**86 (59.3%)**
Acne	20 (27.4%)	6 (8.3%)	26 (17.9%)
Rash	18 (24.7%)	3 (4.2%)	21 (14.5%)
Dry skin	12 (16.4%)	4 (5.6%)	16 (11.0%)
Photosensitivity reaction	14 (19.2%)	2 (2.8%)	16 (11.0%)
General disorders and administration site conditions	**40 (54.8%)**	**35 (48.6%)**	**75 (51.7%)**
Asthenia	19 (26.0%)	16 (22.2%)	35 (24.1%)
Fatigue	17 (23.3%)	13 (18.1%)	30 (20.7%)
Nervous system disorders	**26 (35.6%)**	**26 (36.1%)**	**52 (35.9%)**
Headache	12 (16.4%)	14 (19.4%)	26 (17.9%)
Metabolism and nutrition disorders	**30 (41.1%)**	**19 (26.4%)**	**49 (33.8%)**
Decreased appetite	19 (26.0%)	10 (13.9%)	29 (20.0%)
Hypokalaemia	9 (12.3%)	3 (4.2%)	12 (8.3%)
Respiratory, thoracic and mediastinal disorders	**21 (28.8%)**	**21 (29.2%)**	**42 (29.0%)**
Dyspnoea	7 (9.6%)	9 (12.5%)	16 (11.0%)
Cough	4 (5.5%)	9 (12.5%)	13 (9.0%)
Investigations	**30 (41.1%)**	**8 (11.1%)**	**38 (26.2%)**
Weight decreased	13 (17.8%)	5 (6.9%)	18 (12.4%)
Electrocardiogram QT prolonged	17 (23.3%)		17 (11.7%)
Vascular disorders	**27 (37.0%)**	**7 (9.7%)**	**34 (23.4%)**
Hypertension	25 (34.2%)	4 (5.6%)	29 (20.0%)
Psychiatric disorders	**20 (27.4%)**	**10 (13.9%)**	**30 (20.7%)**
Insomnia	8 (11.0%)	3 (4.2%)	11 (7.6%)
Depression	8 (11.0%)		8 (5.5%)
Ear and labyrinth disorders	**12 (16.4%)**	**8 (11.1%)**	**20 (13.8%)**
Vertigo	9 (12.3%)	7 (9.7%)	16 (11.0%)

[a] Frequency per treatment group.
[b] A patient could have one or more preferred term (PT) reported under a given system organ class (SOC).