AstraZeneca

Clinical Study Report

Drug Substance	Vandetanib
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An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer

Study dates: First patient enrolled: 23 November 2006
Last patient enrolled: 19 October 2007
Date of data cut-off: 31 July 2009

Phase of development: Therapeutic confirmatory (III)

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

International co-ordinating investigator

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Study centre(s)

The study was conducted at 63 study sites in Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, India, Italy, Korea, Netherlands, Mexico, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Switzerland, and the United States.

Publications

None at the time of the writing of this report.

Objectives

The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib as compared to placebo in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC).

The secondary objectives of the study were as follows:

1. To demonstrate an improvement in the objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) with vandetanib as compared to placebo

2. To demonstrate an improvement in the overall survival (OS) in patients with MTC who have been treated with vandetanib as compared to placebo

3. To demonstrate an improvement in biochemical response with vandetanib as compared to placebo, as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA)

4. To demonstrate a delay in time to worsening of pain (TWP) among patients with MTC after treatment with vandetanib as compared to placebo

5. To determine the pharmacokinetics (PK) of vandetanib in this patient population and investigate any influence of patient demography and pathophysiology on the PK

6. To assess the relationship between PK and time interval between the start of the Q wave and the end of the T wave, (corrected for heart rate) (QTc), safety, efficacy, and biomarkers

7. To determine the safety and tolerability of vandetanib treatment in MTC patients

8. To determine the mutational status of the rearranged during transfection (RET) proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumour samples

Study design

This was an international, randomised, double-blind, placebo-controlled, multicenter, Phase III study designed to assess whether vandetanib (300 mg daily) improves PFS compared with placebo in patients with unresectable, locally advanced or metastatic MTC.

Radiologic evaluation using modified Response Evaluation Criteria in Solid Tumors (RECIST) was performed every 12 weeks. Patients were evaluated until objective progression, and then followed for survival, regardless of whether they continued post-progression treatment, unless they withdrew consent. All imaging scans were assessed for progression and response by a central imaging review ("central read"), independent of AstraZeneca. Data from the central review, which was not conducted in "real time," were used in preference to data from the local site review.

Patient population and sample size

The target population was male and female patients aged ≥18 years with a previously confirmed histological diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC. Patients were to have 1 or more measurable lesions, WHO Performance status 0 to 2, and life expectancy of ≥12 weeks.

Assuming a 2:1 randomisation (vandetanib: placebo), at least 90 progression events were required to detect a doubling of PFS at the 2-sided alpha=0.05 level with 80% power. Based on an assumed median PFS of 12 months in the control group, a non-linear recruitment period of 22 months, and a minimum follow-up of 6.7 months, at least 232 patients were to be recruited for the study. The total length of the study was estimated to be 28.7 months to observe 90 progression events.

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

Table S1 provides details on vandetanib and placebo treatments.

Table S1 Details of investigational product and other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch numbers
Vandetanib	300-mg tablet (blinded and open label), once daily, oral administration	AstraZeneca	F013383	P/4099/14, P/4099/27, P/4136/46, P/4156/25, P/4156/26, P/5318/08, P/5318/11, TS27097, TS27102, TX27099
Placebo to match vandetanib	300-mg tablet (blinded), once daily, oral administration	AstraZeneca	F013385[a]	EX157X, P/4099/14, P/4099/27, P/4099/44, P/4136/47
Vandetanib	100-mg tablet (blinded and open label), once daily, oral administration[b]	AstraZeneca	F013025[a]	P/4136/41, P/4156/19, P/4156/22, P/4156/23, P/5142/9, P/5142/09 P/5142/10, P/5142/38, TS27092, TS26078
Placebo to match vandetanib	100-mg tablet (blinded), once daily, oral administration[b]	AstraZeneca	F013044	P/4099/14, P/4136/46

[a] Because of a packaging error, a very small quantity of vandetanib 100 mg (F13025) tablets were added in error into a single bulk batch of 300 mg placebo to match tablets (F013385). As a result, 1 or more patients received a small number of vandetanib 100 mg tablets in place of the intended placebo. However, all potentially affected bottles of tablets were recalled for the current study. The potential impact on patient safety or the efficacy results of the current study was considered minimal, and no patient was unblinded or excluded from any analyses.

[b] For dose reduction purposes (ie, patients who had toxicity related to vandetanib/placebo). For patients who required dose reduction to 200 mg, 2 x 100 mg tablets were to be taken.

Duration of treatment

Patients could receive randomised treatment with vandetanib or placebo until objective disease progression was documented, provided they did not meet any other withdrawal criteria. Upon disease progression, patients were discontinued from blinded study treatment and then unblinded and given the option to begin open label treatment with vandetanib 300 mg (or receive a permanently reduced dose, if applicable), or enter follow-up for survival status. With the approval of protocol Amendment 6 (made as a consequence of the analysis results, rather than before the data were analysed), investigators had the option to unblind any subjects remaining on randomised therapy, whether or not disease progression had occurred. Any patient who was unblinded had to either enter the open-label phase of the study or discontinue blinded therapy and be followed for survival. Once unblinding occurred, patients could not stay on blinded therapy. Survival follow-up will continue until ≥50% of patients are

dead. Patients who are receiving open label vandetanib can continue for as long as the investigator believes the patients are receiving clinical benefit.

Statistical methods

The primary comparison of interest was vandetanib 300 mg compared with placebo for PFS. A nominal 2-sided significance level of 5% was used for all analyses, with the exception of OS where the significance level was adjusted to account for an initial analysis at the time of the PFS analysis, and a final analysis once 50% of the patients have died.

PFS, OS and TWP were analysed using the log rank test. ORR, DCR and biochemical response rates were analysed using logistic regression. DOR was summarised using a KM plot. PFS, ORR, DCR and DOR derived from the central read data were considered primary. If a patient had not progressed according to the central read when the patient started to receive open label treatment, the open label assessments were included in the derivation of these endpoints. The site read RECIST assessments were considered supportive only. Biochemical response and TWP were derived from data collected whilst the patient was receiving randomised treatment. The primary analysis population for efficacy was the Full Analysis Set of all randomised patients.

Safety and tolerability were assessed based on AEs, laboratory data, ECG data, vital signs, and weight. The Safety Analysis Set included all randomised patients who received at least 1 dose of randomised treatment; safety data were summarized by treatment received.

Subject population

A total of 331 patients were randomised to receive treatment in this study (231 in the vandetanib arm and 100 in the placebo arm) and were included in the Full Analysis Set. One patient randomised to receive placebo never received any study treatment, therefore, the safety analysis set included 330 patients.

Of 331 patients, 287 (86.7%) had sporadic MTC, 33 (10.0%) patients had hereditary MTC, and 11 (3.3%) patients had unknown status. There was no substantial imbalance between treatment arms with respect to demographic and baseline characteristics. The patients who participated in this study were generally representative of a population of patients with unresectable locally advanced or metastatic MTC population, and their demographic and baseline characteristics generally resembled those in the target population.

RET mutation status was determined to be positive in 187 (56.5%) patients, negative in 8 patients (2.4%), and unknown in 136 (41.1%) patients. Thus, while all but 2 patients provided an archived tumour sample for RET mutation analysis, the complete mutation analysis comprising the ARMS assay for M918T and the 6-exon sequencing was not successful for all patients, suggesting that the quality of the archived samples may have been inadequate for the comprehensive sequencing analyses.

Summary of efficacy results

The primary PFS analysis was based on the number of RECIST progression events as assessed by the central independent readers. Because the central reads were not being done in "real time," the timing for when at least 90 objective progressions would have been assessed by the central readers had to be estimated based on progressions observed at the study sites, and at the time that had been estimated for this to occur (the data cut-off date of 31 July 2009), 124 progression events had occurred (14 deaths counted as progressions and 110 patients assessed with objective progression by the central readers).

There was a statistically significant improvement in PFS for the vandetanib treatment arm compared with the placebo arm (Table S2). The hazard ratio is equivalent to a 54% reduction in the rate of progression in the vandetanib arm relative to the placebo arm. The predicted median PFS in the vandetanib arm is 30.5 months, which is approximately an 11-month delay compared to the median PFS of 19.3 months observed in the placebo arm

In terms of secondary variables, there was a statistically significant improvement for vandetanib over placebo for ORR, DCR, biochemical response (both CTN and CEA), and TWP. There was no statistically significant difference in OS for the vandetanib arm compared to the placebo arm. However, the OS data are not mature, and the inclusion of an option for patients in both treatment arms to receive open label vandetanib has the potential to reduce any observed treatment effect for OS. A second survival analysis will be conducted when 50% of patients have died.

Table S2 Summary of key efficacy findings (Full Analysis set)

PROGRESSION-FREE SURVIVAL	**N**	**Median PFS**	**HR[a]**	**95% CI**	**p-value**
Vandetanib 300 mg	73/231 (32%)	Not reached (30.5 months predicted)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			
OVERALL RESPONSE RATE[b]	**N**	**Response rate**	**OR[c]**	**95% CI**	**p-value**
Vandetanib 300 mg	104/231	45.0%	5.48	2.99, 10.79	<0.0001
Placebo	13/100	13.0%			
DISEASE CONTROL RATE[b]	**N**	**Response rate**	**OR[c]**	**95% CI**	**p-value**
Vandetanib 300 mg	200/231	86.6%	2.64	1.48, 4.69	0.0010
Placebo	71/100	71.0%			
CTN RESPONSE	**N**	**Response rate**	**OR[c]**	**95% CI**	**p-value**
Vandetanib 300 mg	160/231	69.3%	72.86	26.22, 303.2	<0.0001
Placebo	3/100	3.0%			
CEA RESPONSE	**N**	**Response rate**	**OR[c]**	**95% CI**	**p-value**
Vandetanib 300 mg	119/231	51.5%	52.03	15.95, 320.3	<0.0001
Placebo	2/100	2.0%			

Table S2 Summary of key efficacy findings (Full Analysis set)

OVERALL SURVIVAL	N	Median OS	HR[a]	99.98% CI	p-value
Vandetanib 300 mg	32/231 (14%)	Not reached	0.89	0.28, 2.85	0.7115
Placebo	16/100 (16%)	Not reached			

TIME TO WORSENING OF PAIN[d]	N	Median TD in worsening of pain	HR[a]	95% CI	p-value
Vandetanib 300 mg	114/231 (49%)	7.85 months	0.61	0.43, 0.87	0.0062
Placebo	57/100 (57%)	3.25 months			

[a] A value <1 favours vandetanib. The analysis was performed using a log rank test with treatment as the only factor.
[b] Overall response rate = complete + partial responses. Disease control rate = response rate + stable disease at 24 weeks. ITT analysis includes patients who received open-label vandetanib before progression according to the central read.
[c] A value >1 favours vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.
[d] TWP (Time to worsening of pain) was a composite endpoint, derived from opioid analgesic use and the worst pain item of the BPI.

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Summary of pharmacokinetic results and pharmacokinetic/pharmacodynamic relationships

There was no clear relationship between the pharmacokinetics of vandetanib and PFS or OS or between the pharmacokinetics of vandetanib and AEs

Summary of safety results

Summaries of AEs in any category while on randomised treatment and most common AEs (≥10%) are presented in Table S3 and Table S4, respectively. A discussion of overall safety is presented following the tables.

Table S3 Summary of patients who had at least 1 AE in any category whilst on randomised treatment (Safety analysis set)

	--Vandetanib 300mg (N=231)--		--Placebo (N=99)--		
AE category	**Number (%) of patients[a]**	**Event rate (per 1000 pt years)**	**Number (%) of patients[a]**	**Event rate (per 1000 pt years)**	**Total number (%) of patients (N=330)**
Any AEs	230 (99.6)	21729.8	90 (90.9)	4374.3	320 (97.0)
Any vandetanib causally[b] related AE	222 (96.1)	9136.4	59 (59.6)	1154.7	281 (85.2)
Any AEs of CTCAE grade 3 and higher	128 (55.4)	663.9	24 (24.2)	270.7	152 (46.1)
Any SAEs (including events with outcome = death)	71 (30.7)	258.5	13 (13.1)	133.9	84 (25.5)
Any SAEs with outcome = death	5 (2.2)	15.1	2 (2.0)	19.6	7 (2.1)
Any AEs leading to discontinuation of vandetanib	28 (12.1)	85.6	3 (3.0)	29.5	31 (9.4)
Any other significant AEs[c]	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As assessed by the Investigator.
[c] Any AE deemed by the sponsor to be significant.
Event rate = (number of patients with AEs / total duration of follow-up across all patients in a given group) x 1000.

Table S4 Summary of patients who had ≥1 AE by PT and SOC whilst on randomised treatment, freq >10% (Safety analysis set)

	__Vandetanib 300mg (N=231)__		__Placebo (N=99)__		
SOC Name Preferred Term	**Number (%) of patients[a]**	**Event rate (per 1000 pt years)**	**Number (%) of patients[a]**	**Event rate (per 1000 pt years)**	**Total number (%) of patients (N=330)**
Patients with any AE	230 (99.6)	21729.8	90 (90.9)	4374.3	320 (97.0)
Skin And Subcutaneous Tissue Disorders	208 (90.0)	4240.7	30 (30.3)	427.6	238 (72.1)

SOC Name Preferred Term	__Vandetanib 300mg (N=231)__		__Placebo (N=99)__		
	Number (%) of patients[a]	Event rate (per 1000 pt years)	Number (%) of patients[a]	Event rate (per 1000 pt years)	Total number (%) of patients (N=330)
Rash	104 (45.0)	536.7	11 (11.1)	117.6	115 (34.8)
Acne	46 (19.9)	178.9	5 (5.1)	51.5	51 (15.5)
Dry Skin	35 (15.2)	121.7	5 (5.1)	52.4	40 (12.1)
Dermatitis Acneiform	35 (15.2)	125.4	2 (2.0)	19.7	37 (11.2)
Photosensitivity Reaction	31 (13.4)	104.0	0 (0.0)	0.0	31 (9.4)
Pruritus	25 (10.8)	83.9	4 (4.0)	41.5	29 (8.8)
Gastrointestinal Disorders	186 (80.5)	2142.1	56 (56.6)	984.8	242 (73.3)
Diarrhoea	130 (56.3)	838.5	26 (26.3)	317.7	156 (47.3)
Nausea	77 (33.3)	326.9	16 (16.2)	175.4	93 (28.2)
Vomiting	34 (14.7)	116.2	7 (7.1)	70.4	41 (12.4)
Abdominal Pain	33 (14.3)	111.7	5 (5.1)	51.0	38 (11.5)
Dyspepsia	25 (10.8)	82.9	4 (4.0)	40.7	29 (8.8)
Infections And Infestations	115 (49.8)	563.8	36 (36.4)	447.4	151 (45.8)
Nasopharyngitis	26 (11.3)	84.8	9 (9.1)	92.8	35 (10.6)
General Disorders And Administration Site Conditions	113 (48.9)	554.4	41 (41.4)	604.9	154 (46.7)
Fatigue	55 (23.8)	206.8	23 (23.2)	291.0	78 (23.6)
Asthenia	34 (14.7)	114.0	11 (11.1)	115.9	45 (13.6)
Nervous System Disorders	112 (48.5)	546.5	32 (32.3)	427.3	144 (43.6)
Headache	59 (25.5)	229.6	9 (9.1)	98.5	68 (20.6)
Musculoskeletal And Connective Tissue Disorders	94 (40.7)	411.3	47 (47.5)	774.8	141 (42.7)
Back Pain	21 (9.1)	68.0	20 (20.2)	228.6	41 (12.4)
Arthralgia	18 (7.8)	57.7	10 (10.1)	103.4	28 (8.5)
Pain In Extremity	16 (6.9)	50.5	13 (13.1)	139.9	29 (8.8)
Investigations	92 (39.8)	391.3	16 (16.2)	176.2	108 (32.7)
Electrocardiogram Qt	33 (14.3)	113.1	1 (1.0)	9.8	34 (10.3)

SOC Name Preferred Term	__Vandetanib 300mg (N=231)__		__Placebo (N=99)__		
	Number (%) of patients[a]	Event rate (per 1000 pt years)	Number (%) of patients[a]	Event rate (per 1000 pt years)	Total number (%) of patients (N=330)
Prolonged					
Weight Decreased	24 (10.4)	77.1	9 (9.1)	93.6	33 (10.0)
Vascular Disorders	90 (39.0)	406.9	11 (11.1)	117.3	101 (30.6)
Hypertension	73 (31.6)	300.1	5 (5.1)	50.7	78 (23.6)
Respiratory, Thoracic And Mediastinal Disorders	89 (38.5)	369.8	33 (33.3)	410.4	122 (37.0)
Cough	25 (10.8)	82.1	10 (10.1)	107.0	35 (10.6)
Metabolism And Nutrition Disorders	81 (35.1)	324.5	20 (20.2)	222.0	101 (30.6)
Decreased Appetite	49 (21.2)	170.9	12 (12.1)	125.7	61 (18.5)
Hypocalcaemia	25 (10.8)	82.0	3 (3.0)	30.1	28 (8.5)
Psychiatric Disorders	70 (30.3)	280.4	21 (21.2)	234.6	91 (27.6)
Insomnia	30 (13.0)	102.4	10 (10.1)	102.8	40 (12.1)

[a] Number (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency in the vandetanib arm.
A patient could have had 1 or more PT reported under a given SOC.
The 10% is relevant to either vandetanib or placebo actual treatment group.
Event rate = (No. of pats. with event / total duration of follow-up until 1st event for all pats. in group) x 1000

Exposure

The mean duration of exposure was longer for vandetanib 300 mg (75.0 weeks for total exposure and 73.6 weeks for actual exposure) than for placebo (53.9 weeks for total exposure and 53.7 weeks for actual exposure). Of 231 patients who started treatment with vandetanib, 70 (30.3%) patients remained on the starting dose of 300 mg daily until the date of data cut-off.

Adverse Events

As shown in Table S3, a higher percentage of patients in the vandetanib arm than the placebo arm experienced adverse events (AE) (99.6% vs 90.9%), AEs of CTCAE grade 3 or higher (55.4% vs 24.2%), SAEs (30.7% vs 13.1%), or AEs leading to discontinuation of randomised treatment (12.1% vs 3.0%. The proportion of patients with a fatal SAE was similar in the vandetanib and placebo arms (2.2% vs 2.0%). One patient in the vandetanib arm died due to a SAE of "cardiac failure acute" that was considered by the investigator to be related to study therapy.

As shown in Table S4, the 5 most frequently reported AEs in the vandetanib arm were diarrhoea, rash, nausea, hypertension, and headache. Each of these occurred with a >5% higher frequency for patients in the vandetanib arm compared with the placebo arm: diarrhoea (56.3% vs 26.3%), rash (45.0% vs 11.1%), nausea (33.3% vs 16.2%), hypertension (31.6% vs 5.1%), and headache (25.5% vs 9.1). These events are consistent with the known safety profile of vandetanib and the mechanism of action of VEGFR and EGFR inhibition. AEs of back pain (9.1% vs 20.2%), arthralgia (7.8% vs 10.1%), and pain in extremity (6.9% vs 13.1%) were reported less frequently with vandetanib than with placebo. AEs could be managed through the use of standard medical care, dose reduction, dose interruption, or by permanently discontinuing treatment.

Clinically significant laboratory abnormalities

Mean haemoglobin levels increased in vandetanib treated patients in both males and females. Mean levels of alanine aminotransferase (ALT), creatinine, and thyroid stimulating hormone (TSH) were higher in the vandetanib arm than in the placebo arm. The elevation of mean ALT levels reverted to baseline level while mean creatinine levels declined only slightly. Mean TSH levels were highest at Week 12 and declined thereafter. Vandetanib was associated with an increased frequency of new onset proteinurea or deterioration of existing proteinuria or haematuria compared with placebo; however, proteinuria and haematuria were not shown to predict subsequent development of hypertension.

Clinically significant vital sign abnormalities

There were increases in both systolic and diastolic blood pressure in patients in the vandetanib arm compared with those in the placebo arm.

QT Prolongation

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 8.2% of patients in the vandetanib arm had protocol-defined QTc prolongation during randomised treatment or the 60-day safety follow-up period compared with none of the patients in the placebo arm.

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