AstraZeneca

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EXECUTIVE SUMMARY

There is currently no effective or approved therapy for patients with medullary thyroid carcinoma (MTC) who present with either surgically unresectable locally advanced disease or distant metastasis, and there has been little change to the poor clinical outcome of these patients in the last 20 years. The prognosis of MTC is generally favorable if the disease can be treated surgically at an early stage, but patients with unresectable locally advanced or metastatic MTC will almost certainly die of their disease, over the course of ongoing progressive disease that can be protracted for many years. There have been few natural history studies of the outcome for patients with advanced MTC, and there have been no studies utilizing a placebo comparator. In a review of the SEER database, the 5-year survival was approximately 40% (Roman et al 2006) and in a European review the median overall survival was 2-3 years in patients with distant metastatic disease (Modigliani et al 1998). Responses to chemotherapy in these patients are infrequent and of short duration, and therefore chemotherapy is not recommended as a 1st-line treatment for patients with MTC (Kloos et al 2009). In the absence of any effective treatment for these patients, and because of the constant knowledge they have of their progressive disease over the years and the likelihood of tumor-related or calcitonin-related symptoms, a once daily oral treatment that induces frequent tumor responses of prolonged duration, delays disease progression, and is amenable to long-term chronic dosing, offers an unique clinical benefit.

Vandetinib provides a new treatment option for patients with locally advanced or metastatic MTC. The molecular pathogenesis of MTC is characterized by activation of the rearranged-during-transfection (RET) proto-oncogene, in many cases through activating point mutations, and increased expression of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) have been seen in patients with metastatic disease. Vandetanib (ZD6474) is an orally available tyrosine kinase inhibitor (TKI) with selective activity against RET, VEGFR-2, and EGFR. The basis for the studies conducted in MTC was the activity of vandetanib in which the 3 signaling pathways (VEGFR, EGFR, and RET) were biologically relevant, and where activation of RET is the primary driver that stimulates growth of the malignant cells. The dose of vandetanib in the pivotal study was 300mg, which is the maximum tolerated dose in patients, allowing for maximum inhibition of the molecular targets, and therefore the greatest potential anti-tumor activity, and preclinical models predict that this dose will inhibit RET, VEGR2, and EGFR in vivo. Dose reduction to 200mg (and then to 100mg, if necessary) was provided to patients who were unable to tolerate chronic dosing.

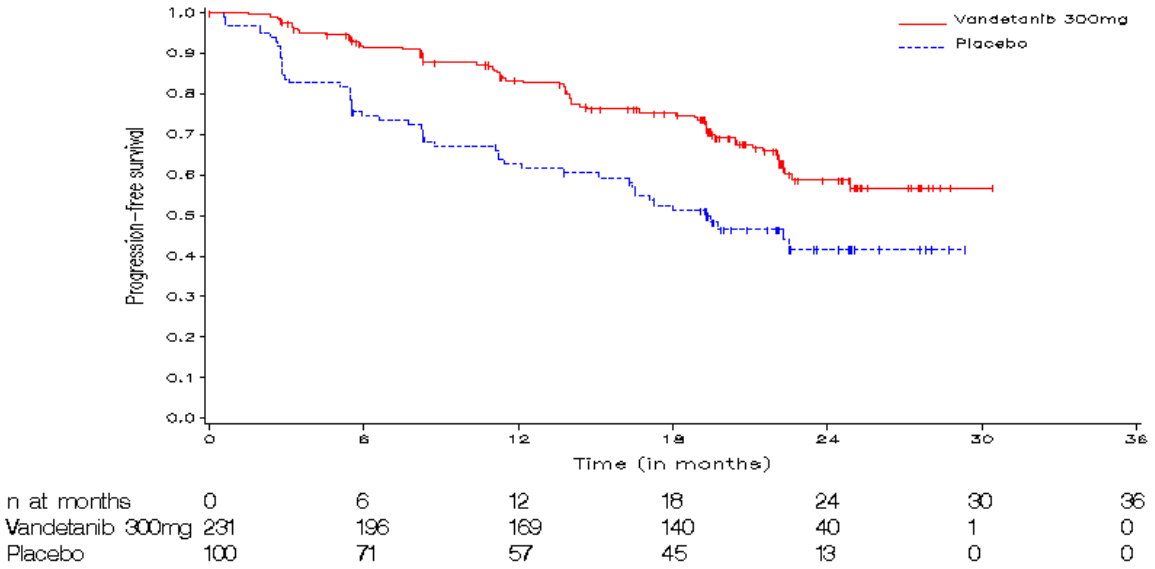
Medullary thyroid cancer is a rare disease, with approximately 2000 new cases per year in the USA. Vandetanib has been granted Orphan Drug Designation (ODD) in this indication. AstraZeneca consulted with FDA throughout the vandetanib development program for MTC, including End of Phase II and Special Protocol Assessment meetings.The results of the Phase III Study D4200C00058 (Study 58, in 331 patients with advanced unresectable or metastatic MTC) form the basis of the proposed indication and are supported by efficacy and safety data from 2 single-arm Phase II studies (D4200C00008 and D4200C00068) in MTC.

The pivotal Phase III Study D4200C00058 (Study 58) was a randomized (2:1 randomization) double-blind, placebo-controlled study that demonstrated a clinically significant benefit for vandetanib in prolonging progression-free survival (PFS). Upon disease progression (as assessed by the investigator), patients in both treatment groups were given the option to continue on open-label vandetanib, and all patients were followed for overall survival. The study, which is the largest ever conducted in MTC (331 patients, with a median tumor size of 11.3 cm as measured by the sum of the longest dimension in target lesions), ensured a reliable assessment of the primary endpoint (PFS), with independent blinded review of radiographic images (ie, a 'central read' based on RECIST) supported by sensitivity analyses. Subgroup analyses were also performed to assess consistency across pre-specified subgroups of clinical relevance.

In Study 58, the primary endpoint of PFS showed a benefit for vandetanib that is compelling ($p = 0.0001$, HR = 0.46), based on an independent, blinded central review including all randomized patients. The pre-specified sensitivity analyses were all consistent with the primary analysis of PFS. The benefit represents an approximately 11 month delay to the median PFS for patients receiving vandetanib (not reached in the vandetanib arm with median follow-up of 24 months, but estimated at 30 months, compared to 19 months for placebo). The data also shows consistent benefits in tumor response. A total of 45% of patients randomized to vandetanib had an objective tumor response in Study 58. The responses were durable, with a median duration not reached at median follow-up of 24 months. Twelve of the 13 responses observed in placebo patients happened after they had switched over to open-label vandetanib. Figure 1 below presents a Kaplan-Meier plot of the primary PFS analysis. Table ES 1 below presents an overview of the efficacy results from Study 58. Sensitivity analyses were performed to confirm the robustness of the results and are presented in more detail in Section 4.2.2 of this document.

Other secondary endpoints were consistent and supportive of the primary endpoint; these included increases in the disease control rate; delays in the time to worsening of pain; and significant decreases in calcitonin (CTN) and carcinoembyonic antigen (CEA) levels. At the time of the primary analysis of PFS, only 14% of patients on the vandetanib arm and 16% of patients on the placebo arm had died, and there was no significant difference in overall survival (OS; HR = 0.89; 99.98% CI = 0.28 – 2.85). As per the protocol, a final analysis of survival will be conducted once at least 50% of patients have died (projected for 2012 or beyond). The survival comparison between vandetanib and placebo will likely be affected by the cross-over design of the study. Furthermore, following review of the PFS analysis results, the study was unblinded on 06 January 2010 with FDA's agreement and understanding of the potential for further confounding the planned survival update. At the time of data cutoff (31 July 2009), a total of 58 of 100 patients who had been randomized to the placebo arm had entered the open-label phase of the study and had received vandetanib. As of 31 July 2009, a total of 59 patients were still participating in the on-going open-label phase of Study 58; 17 who were previously on vandetanib and 42 who were previously on placebo.

Figure 1 Kaplan-Meier plot of PFS (Full analysis set)



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

Note: "Full Analysis Set" includes all randomized patients.
PFS was derived from all available central read RECIST assessments.

Table ES 1 Summary of key efficacy findings: Study 58 (Full analysis set)

PROGRESSION-FREE SURVIVAL	N	Median PFS	HR[a]	95% CI	p-value
Vandetanib 300 mg	73/231 (32%)	Not reached (estimated 30.5 months)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			
OBJECTIVE 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%[d]			

a HR= Hazard Ratio. A value <1 favors vandetanib. The analysis was performed using a log rank test with treatment as the only factor.
b Objective response rate = complete + partial responses. ITT analysis includes patients who received open-label vandetanib before progression according to the central read.
c OR=Odds Ratio. A value >1 favors vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.
d The response rate was 13% in patients who were randomized to placebo. However, it is important to note that 12 of the 13 responses in the placebo group were only seen after patients received open-label vandetanib following disease progression. The actual response rate in the placebo group during randomized treatment was 1%.
N, Number of events/number of randomized patients; OS, overall survival; PFS, progression-free survival; CI, confidence interval.

Note: "Full Analysis Set" includes all randomized patients.

The median duration of randomized treatment in Study 58 was 1 year 9 months for patients randomized to vandetanib vs. 9 months for patients randomized to placebo. At data cutoff (31 July 2009) nearly half the patients randomized to vandetanib (48%) continued to receive randomized vandetanib, while 28% of patients continued to receive placebo. A total of 23% of patients randomized to vandetanib required a single dose reduction while 13% required two dose reductions. Only 13% of patients discontinued vandetanib for an adverse event, which is similar to the proportion of patients who discontinued vandetanib for an AE in the 2 Phase III NSCLC studies with vandetanib 300 mg monotherapy, even though the median duration of treatment was 10 times longer on Study 58 than on the NSCLC studies.

Patients who received vandetanib experienced more AEs than those receiving placebo, but AEs due to vandetanib could be controlled through dose reduction or medical management, Most of the AEs initially occur in the first 3-6 months of dosing, suggesting the effectiveness of dosing to tolerance – ie, the idea of starting patients at the maximum tolerated dose (MTD) of 300 mg daily, but understanding that some patients may require dose reductions at some point in their therapy.

The side effects of vandetanib are generally consistent with the non-clinical safety findings and related to its pharmacological action as an inhibitor of VEGFR and EGFR. Common AEs, defined as those with a frequency of ≥20% in any treatment arm, as well as the number of NCI CTCAE Grade ≥3 events, are presented by system organ class (SOC) and preferred term (PT) in Table ES 2 below. Overall, the 5 most frequently reported AEs in this study were diarrhea, rash, nausea, hypertension, and fatigue. The most common AEs that occurred with a >5% higher frequency for patients in the vandetanib arm compared with the placebo arm included diarrhea, rash, nausea, hypertension, and headache. The 5 most frequently reported events that were CTCAE Grade ≥3 in the vandetanib arm were diarrhea, electrocardiogram QT prolonged, hypertension, fatigue, and decreased appetite; all were reported more frequently in the vandetanib arm than the placebo arm. However, AEs such as diarrhea and fatigue were also commonly reported in the placebo arm. Most adverse events of CTCAE Grade ≥3 were Grade 3 events and were observed early in the course of the treatment.

Table ES 2 Study 58: Adverse events in >20% of patients in either arm (randomized phase only)

	Vandetanib 300mg (n=231)		**Placebo (n=99)**	
	All AEs	**AEs CTCAE Grade ≥3**	**All AEs**	**AEs CTCAE Grade ≥3**
Diarrhea	56.3%	10.8%	26.3%	2.0%
Rash	45.0%	3.5%	11.1%	1.0%
Nausea	33.3%	0.9%	16.2%	1.0%

	Vandetanib 300mg (n=231)		Placebo (n=99)	
	All AEs	**AEs CTCAE Grade ≥3**	**All AEs**	**AEs CTCAE Grade ≥3**
Hypertension	31.6%	6.9%	5.1%	1.0%
Fatigue	23.8%	5.6%	23.2%	1.0%
Headache	25.5%	0.9%	9.1%	0
Decreased Appetite	21.2%	3.9%	12.1%	0

AEs listed as MedDRA preferred terms. Severity was graded using NCI CTCAE v.3

Patients who receive vandetanib will need to have ECGs obtained periodically to assess QT prolongation, but otherwise will require only standard monitoring that is used for patients on systemic oncologic therapies, such as assessments of blood pressure, electrolytes, and renal and hepatic function. Routine anti-diarrheal agents are recommended for the treatment of diarrhea, and serum electrolytes should be monitored if diarrhea develops. Hypertension should be monitored and controlled as appropriate. Patients may have had exacerbation of rash in patterns on the body consistent with exposure to sunlight, and therefore care should be taken with sun exposure by wearing protective clothing and/or sunscreen.

The data from the pivotal study 58 are supported by the results from 2 single-arm phase II studies in patients with hereditary MTC. Results of Study 08 showed that vandetanib 300 mg monotherapy had an acceptable side-effect profile and demonstrated clinical activity (20% objective response). Study 8 (N = 30) provided the rationale for conducting the pivotal Study 58.

Study 68 (N = 19)was conducted in parallel with Study 58 to assess the efficacy and tolerability of vandetanib 100 mg monotherapy. Results showed that the vandetanib 100 mg dose also had an acceptable side-effect profile and showed activity (16% objective response). The 300mg dose was chosen as the starting dose for patients on study 58, as this dose would be predicted to provide the maximum inhibition against the molecular targets.

In conclusion, MTC is a rare disease with no effective or approved therapy for patients with unresectable locally advanced metastatic disease. Vandetanib has shown a compelling benefit in PFS, with HR=0.46 and an estimated 11 month improvement in median PFS. Almost half of all patients treated with vandetanib experienced durable objective tumor responses, and there were significant delays in the time to worsening of pain. The pivotal study to support the indication clearly demonstrates the benefit of vandetanib in patients with unresectable locally advanced or metastatic MTC. All prespecified subgroups of patients derived benefit from vandetanib. By dosing to tolerance, the starting dose of 300 mg can be reduced as necessary to manage side effects and to avoid discontinuing the drug in most patients to maintain the maximum possible derived clinical benefit and engagement with molecular targets over many

months to years. Vandetanib meets the unmet need in patients with unresectable locally advanced or metastatic MTC for a treatment with clear and consistent benefits and a safety profile that allows for chronic dosing. Data from the vandetanib clinical program demonstrate a positive benefit:risk profile and support the following proposed indication:

> **Proposed indication:** Vandetanib is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.
>
> **Proposed dose:** 300 mg vandetanib, oral tablet, once daily.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this document.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ARMS	Amplification refractory mutation system
BFGF	Basic fibroblast growth factor
BPI	Brief pain inventory
CDRH	Center for Devices and Radiological Health
CEA	Carcinoembryonic antigen
CI	Confidence Interval
C_{max}	Maximum concentration of drug
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
CTN	Calcitonin
CYP3A4	Cytochrome P450 3A4 isoform
DCR	Disease control rate
DLT	Dose limiting toxicity
DODP	Division of Oncology Drug Products
DOR	Duration of response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
FMO	Flavin-containing monooxygenase
FMTC	Familial medullary thyroid carcinoma
HR	Hazard ratio
ICH	International conference on harmonisation
ILD	Interstitial lung disease
ITT	Intention to treat
MEN	Multiple endocrine neoplasia
MTC	Medullary thyroid carcinoma

Abbreviation or special term	Explanation
MTD	Maximum tolerated dose
NDA	New Drug Application
NSCLC	Non-small cell lung cancer
OCT2	Organic cation transporter 2
OR	Odds ratio
ORR	Objective response rate
PD	Pharmacodynamic
PFS	Progression-free survival
PI	Prescribing information
PK	Pharmacokinetics
PRO	Patient reported outcomes
PT	Preferred term
QoL	Quality of Life
QTc	QT interval on electrocardiogram, Bazett's correction
RECIST	Response evaluation criteria for solid tumors
RET	Rearranged during transfection
RPLS	Reversible posterior leucoencephalopathy syndrome
RR	Response rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SPA	Special protocol assessment
T4	Thyroxine, or 3,5,3',5'-tetraiodothyronine
TDP	Torsade de pointes
TKI	Tyrosine kinase inhibitor
TWP	Time to worsening of pain
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WHO PS	World Health Organization Performance Status

1. PRODUCT DEVELOPMENT RATIONALE

Vandetanib 300 mg has demonstrated a positive benefit:risk profile for the treatment of patients with medullary thyroid carcinoma (MTC). AstraZeneca is now requesting approval for this marketing application for the following indication:

> **Proposed indication:** Vandetanib is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.
>
> **Proposed dose:** 300 mg vandetanib, oral tablet, once daily.

This briefing document supports the ODAC meeting for the vandetanib NDA for the treatment of patients with MTC. It critically presents and evaluates the benefits and risks of the product in its intended use, based on all relevant clinical as well as non-clinical data with clinical implications.

1.1 Clinical background and treatment of medullary thyroid cancer

1.1.1 Background

Medullary thyroid carcinoma is a rare disease that represents about 5% of thyroid cancers, and occurs in about 2000 new patients per year in the US. MTC is a distinct subtype of thyroid cancer, arising from the parafollicular cells (C-cells) of the thyroid, that has particular prognostic and genetic features, including activation of the RET proto-oncogene in the majority of cases.

MTC presents either as a sporadic cancer or as part of a hereditary syndrome. The sporadic form accounts for 75% of cases; in the remainder, MTC occurs as part of 1 of 3 hereditary syndromes: Multiple Endocrine Neoplasia (MEN) type 2a, MEN type 2b, or Familial Medullary Thyroid Carcinoma (FMTC). Each of these syndromes is inherited as an autosomal dominant trait, and each is characterized by a distinct genotype and clinical phenotype. The prognosis of MTC is generally favorable if the disease can be treated surgically at an early stage. There have been few natural history studies of the outcome for patients with advanced MTC. In a review of the SEER database, the 5-year survival was approximately 40% (Roman et al 2006) and in a European review the median overall survival was 2-3 years in patients with distant metastatic disease (Modigliani et al 1998). Approximately 35% of patients present with tumor extending beyond the thyroid with regional lymph node involvement, and 13% have metastatic disease at initial diagnosis (Roman et al 2006). Approximately 90% of patients with metastatic disease die of progressive cancer (Cohen et al 1996, Modigliani et al 1998).

Metastatic MTC most often spreads to regional lymph nodes and to liver, lung, and bone, and patients may experience a variety of symptoms related either to humoral factors produced by the tumor or to the location of the tumor. Local symptoms related to regional disease include difficulty swallowing, neck pain, hoarseness, and dyspnea. Bone metastases may cause pain, which can be severe enough to require opiates. Diarrhea and flushing are common symptoms

related to humoral factors. Metastases may also cause liver dysfunction or spinal cord compression.

MTC is primarily characterized by the activation of the rearranged during transfection (RET) oncogene, most commonly due to specific point mutations. In the early 1990s it was demonstrated that the RET proto-oncogene was the susceptibility gene for the inherited cancer syndrome MEN2a, MEN2b, and FMTC (Donis-Keller et al 1993, Mulligan et al 1993, Hofstra 1994), and hereditary MTC is characterized by germline mutations in RET in up to 100% of patients. In up to 80% of sporadic cases, there is a somatic mutation in RET (Eng et al 1996), while in cases where a RET mutation is not detected, activation of RET through other pathways may be important to the pathogenesis (Cerrato et al 2009). A range of single point mutations in the RET gene has been described, and common mutations include codon 634, found in 85% of MEN 2a cases, and codon 918, found in 95% of MEN 2b cases and 80% of the mutations in sporadic MTC (Eng 1999; Castellone and Santoro 2008). Patients with RET mutations, especially the common M918T mutation, are more likely to have regional lymph node involvement or distant metastases and a worse outcome (Elisei et al 2008). The incidence of RET mutations in sporadic MTC has been reported to be as high as 80%, although there can be inter-tumoral heterogeneity and differences in the molecular characteristics between the primary tumor and metastases (Eng et al 1996, Eng 1999, Marsh et al 1996).

MTC cells secrete calcitonin (CTN), carcinoembryonic antigen (CEA), and several biogenic amines. High levels of calcitonin are associated with diarrhea and flushing, common symptoms in patients with metastatic MTC. The diarrhea can be particularly severe in patients with plasma CTN levels above 30,000 pg/mL, requiring frequent intervention. Measurement of CTN is routinely used in clinical practice to monitor the progression of disease, as CTN levels are associated with tumor burden. CEA is also associated with tumor burden, and elevated levels are associated with disease progression and metastases (Barbet et al 2005, Giraudet et al 2008).

1.1.2 Limitations of current treatments and novel approaches

There is currently no effective or approved therapy for patients with MTC who present with either surgically unresectable locally advanced disease or distant metastasis, and there has been little change to the poor clinical outcome of patients with MTC in the last 20 years. Medullary thyroid carcinoma (MTC) is relatively unresponsive to conventional doses of radiation therapy and to all tested chemotherapeutic regimens. There have been several case reports and small case series investigating the use of chemotherapy for patients with MTC (Orlandi et al 2001). The findings from these studies are of limited value for patients with MTC as they frequently include other types of thyroid cancer in addition to MTC, and there have been no placebo-controlled studies until now. Partial responses have been reported in 10-20% of patients and are generally short-lived. The duration over which chemotherapy can be given may also be limited by cytotoxic side effects. The most commonly used agents are dacarbazine, 5-fluorouracil, and doxorubicin (Kloos et al 2009, Orlandi et al 2001). Radioiodine therapy is of limited use. Some tyrosine kinase inhibitors (TKIs), such as sorafenib, have been used in patients with MTC, but the objective tumor response rate is also

less than 20% (Lam et al 2010). Because of the limitations of current treatments, the latest guidance from the American Thyroid Association recommends that "the use of standard chemotherapy agents should not be considered as first-line therapy for patients with persistent or recurrent MTC", stating that patients should be enrolled on an appropriate clinical study (Kloos et al 2009).

Patients with unresectable locally advanced or metastatic MTC will almost certainly die of their disease, over the course of ongoing progressive disease that can be protracted for many years. In the absence of any effective treatment for these patients, and because of the likelihood of tumor-related or calcitonin-related symptoms, the medical need is clear for a treatment that delays disease progression, induces tumor responses, and is amenable to long-term chronic dosing.

1.2 Rationale for the development of vandetanib in MTC

1.2.1 Vandetanib

Vandetanib (ZD6474) is an orally available tyrosine kinase inhibitor (TKI) with selective activity against:

- The RET proto-oncogene
- The cell surface receptor for VEGF ([VEGFR] primarily VEGFR-2 with less potency for VEGFR-1 and VEGFR-3) and
- EGFR.

As noted above, mutations in the RET proto-oncogene are the key pathogenic events in the majority of patients with MTC, However, even in tumors that do not carry a RET mutation, recent data suggest that activation of the wild-type RET pathway is relevant, and other signaling pathways, including EGFR, play a role in the pathogenesis (Cerrato et al 2009, Croyle et al 2008, Gorla et al 2009). As with all solid tumors, angiogenesis due to activity of the VEGF signaling pathway is necessary to sustain tumor growth, and over-expression of both EGFR and VEGFR is seen in metastases from patients with MTC (Rodriguez-Antona et al 2010). Therefore, there is a strong scientific rationale for targeting MTC with vandetanib, which inhibits RET (both wild-type and mutated; Carlomagno et al 2002, Knowles et al 2006), EGFR, and VEGFR.

Preclinical data suggest that vandetanib inhibits the 3 signaling pathways (VEGFR, EGFR, and RET) at the doses used in the clinic (100mg to 300mg), and that the maximum anti-tumor effect will be achieved at the highest tolerated dose (300mg). The initial Phase II signal-searching study using the 300 mg dose in 30 patients assessed tumor responses with progression-free survival (PFS) as a secondary endpoint, and in the Phase III study progression-free survival was the primary endpoint. A second, smaller signal-searching Phase II study using the 100 mg dose was conducted in 19 patients in parallel with the pivotal Phase III study. Descriptions of these studies can be found in Section 1.2.4.

1.2.2 Objectives of the clinical development program

In the early development program, 2 Phase I studies, conducted in 77 patients in the US and Australia and in 18 patients in Japan with various solid tumors, demonstrated a maximum tolerated vandetanib dose of 300 mg. Higher doses were limited by diarrhea, rash, and prolongation of the electrocardiogram QT interval. Subsequently, 5 studies have been conducted to evaluate vandetanib in the treatment of patients with MTC, and 1 study has been completed in patients with differentiated thyroid cancer and results are available (Table 1).

Table 1 Vandetanib studies in thyroid cancer

Study number	Phase	Disease setting	Vandetanib dose	Number of patients	Status
AstraZeneca sponsored studies					
D4200C00008 (Study 08) uncontrolled, single arm	II	Hereditary MTC	300 mg	30	Complete
D4200C00068 (Study 68) uncontrolled, single arm	II	Hereditary MTC	100mg	19	Complete
D4200C00058 (Study 58) placebo-controlled, randomized	III	MTC (hereditary and sporadic)	300 mg	331 (231 randomized to vandetanib)	Complete
D4200C00079 (Study 79) Randomized, placebo-controlled	II	Differentiated thyroid cancer	300 mg	146 (72 on vandetanib)	Complete
Investigator sponsored studies					
IRUSZACT0113	I/II	MTC; combination with bortezomib	Dose seeking	117 projected	Ongoing
IRUSZACT0098 Uncontrolled, single-arm	I/II	Pediatric hereditary MTC	Dose escalation	19 projected	Ongoing

The results of studies 8, 68, and 58 are discussed in this briefing document and form the basis for the proposed indication. Study 79 was recently completed and the results are also presented here.

The pivotal Study 58 was designed as a randomized, double-blind, placebo-controlled study to demonstrate a clinically significant and consistent benefit for vandetanib in prolonging progression-free survival, with a planned long-term follow-up for overall survival. The study ensured a reliable assessment of the primary endpoint (PFS), with independent review of radiographic images supported by sensitivity analyses. Subgroup analyses were also performed to assess consistency across pre-specified subgroups of clinical relevance.

The use of PFS to investigate clinical benefit was supported by a series of relevant secondary endpoints, which included:

- Overall survival (OS).
- Overall response rate, duration of response, and disease control rate.
- Time to worsening of pain
- Side effect profile over long-term dosing and role of dose adjustment for tolerability

1.2.3 Vandetanib in lung cancer

In addition to the Phase III study in MTC, 4 other Phase III studies have been conducted with vandetanib. These Phase III studies investigated the efficacy of vandetanib in patients with refractory NSCLC: 2 at a dose of 100 mg daily in combination with chemotherapy and 2 at a dose of 300 mg daily as monotherapy. The primary objective of prolongation of PFS was met for vandetanib in combination with docetaxel (vs. docetaxel) (HR 0.79, $p<0.0001$), but was not met for vandetanib in combination with pemetrexed (vs. pemetrexed) (HR 0.86, $p=0.1075$), although there was a significant improvement in response rate in both studies, 17.3% vs. 10.2% and 19.1% vs. 7.9% for vandetanib + chemotherapy vs. chemotherapy alone in the studies with docetaxel and pemetrexed, respectively. The primary objective of prolongation of PFS was also not met for vandetanib vs. erlotinib (HR=0.98, $p=0.7214$), although PFS, OS, and RR were similar in the 2 arms. In the 4th study, there was an improvement in PFS compared to placebo in patients following treatment with an EGFR inhibitor (HR 0.63, $p<0.0001$), although the primary objective of improvement in OS was not met (HR 0.95, $p=0.5273$). While vandetanib was shown to have efficacy similar to erlotinib as monotherapy, and improved response rates when combined with chemotherapy, AstraZeneca is not pursuing an indication for patients with NSCLC at this time. The studies in NSCLC provide an extensive safety database for vandetanib, although the median duration of treatment in NSCLC of 8-9 weeks for 300 mg monotherapy was considerably shorter than in MTC, where the median duration of treatment was 1 year 9 months in the Phase III study (as of the data cutoff of 31 July 2009).

1.2.4 Studies pertinent to the MTC indication

Primary clinical efficacy and safety data for vandetanib 300 mg in support of the proposed indication are provided by study D4200C00058 (referred to as Study 58): An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 (Vandetanib) versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer. This study was conducted with 331 patients and demonstrated a clinically and statistically significant advantage for vandetanib in PFS (HR 0.46) determined by a blinded central review, and a side effect profile that allowed for long-term dosing. The median duration of treatment was 1 year 9 months at the data cut-off, with median follow-up of 2 years and 48% of patients remaining on active randomized treatment. By design, patients had the option to switch to open-label treatment with vandetanib at disease progression as determined by the site investigator. Long-term follow-up is ongoing, with a planned update to the secondary endpoint of overall survival when at least 50% of patients have died, which is projected to occur in 2012 or later. As this is the only randomized and controlled study of vandetanib in MTC, it provides the majority of the data to support the proposed indication. A single pivotal study, with a large, robust, persuasive and significant benefit supported by relevant secondary endpoints (see Section 1.2.2), appears sufficient to support approval in this rare disease for which Orphan Drug Designation has been granted.

Two single-arm Phase II studies were conducted in patients with hereditary MTC, and provide supportive efficacy and safety data. The first of these studies in MTC, Study D4200C00008 (Study 08), was an open-label, monotherapy, Phase 2 study in 30 patients, conducted to evaluate the efficacy and tolerability of vandetanib at a daily dose of 300 mg in patients with hereditary MTC. Results of the study showed that vandetanib 300 mg was well tolerated and demonstrated clinical activity (objective response) in patients with metastatic hereditary MTC, and provided the rationale for conducting the pivotal Study 58.

Although pre-clinical data indicate that the best anti-tumor effect can be achieved at the highest tolerated dose of vandetanib (300 mg), there may be some activity of vandetanib at lower doses. To assess this, Study D4200C000068 (Study 68), a Phase 2, open-label study in 19 patients, was conducted in parallel with Study 58 to assess the efficacy and tolerability of vandetanib 100 mg monotherapy in patients with locally advanced or metastatic hereditary MTC. Results showed that the vandetanib 100 mg dose was also well-tolerated and showed activity (objective responses) in patients with locally advanced or metastatic hereditary MTC.

Efficacy and safety information for the supportive studies can be found in Sections 4.1.6, 4.2.7, and 5 of this document.

1.3 Previous regulatory consultations relevant to this submission

Vandetanib has been granted orphan drug designation and fast-track status for MTC. AstraZeneca has held several discussions with FDA relevant to the development of vandetanib as a treatment for patients with MTC. The key FDA interactions and advice are summarized below.

Special Protocol Assessment (SPA) for Study 58 protocol.

It should be noted that although a formal SPA agreement was not reached with FDA, the SPA review and subsequent SPA related discussions with FDA provided clarification on several key areas which are summarized below. AstraZeneca took the decison to initiate Study 58 after taking into consideration the Division's advice provided at this point, understanding that further additional cycles of review and discussions with FDA would potentially be required to reach a formal written agreement on the protocol and that this would impact on the timeframe for start of this study.

Study 58 design and endpoints

- Based on FDA advice at the End of Phase II meeting, a randomized, placebo controlled study was incorporated

- Progression-free survival (PFS) was considered by FDA to be an appropriate primary endpoint, recognizing that a study to assess overall survival as a primary endpoint in this disease setting is difficult to conduct

- It was appropriate for patients originally randomized to a placebo arm to be offered optional treatment with vandetanib after disease progression

- FDA considered that the magnitude of the PFS advantage should be clinically relevant with and acceptable risk/benefit ratio; this would be considered during the NDA review

- End of Phase II advice from FDA was that secondary endpoints could include improvement in response rate and analgesic use. Quality of Life (QOL) tools, such as FACT-G, would not be considered by FDA as a valid basis for any labeling claims. However, AstraZeneca could choose one symptom that is the hallmark of the disease to gain scientific information to be considered during the NDA review.

- Thus, for the SPA, the proposed patient reported outcomes (PRO) endpoints focused on the symptom of pain. FDA recommended that timing of the measurement of patients'experience of pain should be on a daily, as opposed to a weekly, basis. The schedule was of less concern to FDA if the intent of this measure is not to support a proposed claim. Following the discussion, AstraZeneca did not modify the protocol from weekly to daily measurement.

- Patients and physicians did not need not to be blinded to the results of carcinoembryonic antigen (CEA) and calcitonin (CTN) assessments despite the potential that knowing these results could lead to unblinding.

Identification of patients with RET mutation status as a determinating factor for eligibility for treatment – co-primary analysis populations

- The original hypothesis for the study was that while vandetanib may have benefit in the overall population of patients with MTC, there may be a greater benefit in patients with RET mutation. Therefore, two co-primary analysis populations were initially included in the study 58 protocol: for all subjects and for all subjects with RET mutation. FDA advised that with regard to subjects with RET mutation, clearance or approval of a test or test(s) to identify this subpopulation would be required at the time of drug registration.

- In a follow-up discussion, AstraZeneca presented preliminary, blinded data on the RET mutation status of patients in Study 58, which showed that a proportion of patients would have unknown RET mutation status because of assay and sample limitations. With regard to the co-primary analysis population, CDRH advised that if drug registration is to be based on a patient population defined on RET mutation, the analysis population must be pre-specified

- Based on the limitations of the RET mutation assay, CDRH considered that for Study 58, a statistically significant and clinically relevant benefit in the co-primary analysis of the overall population would be needed to support registration.

- The co-primary analysis population of patients with a known RET mutation initially planned in the protocol was subsequently removed from the study in a protocol amendment because the assays used to identify tumor RET mutations were unable to establish the mutation status in a high proportion of the patients. The planned number of PFS events in the study was not modified, thus slightly increasing the power of the study.

Statistical Analysis Plan (SAP)

- FDA requested that the SAP, as it related to the primary endpoint, should be submitted as part of the special protocol assessment, before initiation of study 58

- It should be noted that AstraZeneca submitted a draft SAP in December 2006 together with the study 58 protocol submission to start recruitment into the study in the US. The SAP was finalized in October 2009, prior to data base lock of study 58 and subsequent unblinding of the data, which occurred in November 2009, and which was then included in the NDA submission.

Dosing Strategy

- A 300 mg oral, once daily starting dose, allowing for dose reduction based on protocol-defined toxicity, was considered appropriate. AstraZeneca raised the possibility of changing the starting dose during the study if any emerging data from study 68 strongly supported a different dose. The FDA view was that a

change of starting dose, based on further results from another study in MTC patients exploring a 100mg dose, would be problematic.

Imaging

- The FDA considered that the independent, central radiology review of the data should be blinded

- Study 58 included modifications of the RECIST criteria, based on specific patterns of disease in MTC. These were considered appropriate although the FDA recommended that AstraZeneca conduct a sensitivity analysis of PFS, without the RECIST modifications.

January 2010: Study 58 protocol amendment

With the agreement of FDA, the protocol was amended to provide investigators with the option to unblind patients remaining on blinded, randomized therapy to allow patients on the placebo arm to receive open-label vandetanib. If a subject was unblinded, the subject must either enter the open-label portion of the study or discontinue blinded therapy. All patients would continue to be followed for survival. This amendment was based on the results of the primary analysis for the study, which showed a significant benefit for patients in the vandetanib arm compared with the placebo arm.

2. OVERVIEW OF BIOPHARMACEUTICS

Vandetanib is provided as tablets containing 300 mg or 100 mg of vandetanib.

Intravenous dosing of vandetanib has not been attempted in humans. During early development an oral solution was evaluated along with vandetanib tablet variants and all were found to have similar performance. The FDA agreed that the relative bioavailability study (D4200C00030) fulfilled the requirements for an absolute bioavailability study and no formal waiver would be required.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1 Overview of clinical pharmacokinetics

The PK of healthy volunteers and patients with MTC are similar. Therefore the results from studies conducted in healthy volunteers or non-cancer patients, can be extrapolated to patients with MTC.

3.1.1 Pharmacokinetics

The PK properties are linear in volunteers. C_{max} occurs approximately 6 hours (range 4 – 10 hours) after the dose. Clearance is 10-14 L/h in volunteers. The volume of distribution is very

large at approximately 3000 L, the terminal half-life is long at 10-12 days and steady state is reached by 2 months.

In Study 58, the pivotal study in MTC, clearance was 13 L/h, volume of distribution was 7450L, and half-life was 19 days. There was high inter-individual variability (up to 100%). Vandetanib binds to human serum albumin and α1-acid-glycoprotein with approximately 90% protein-bound. It is excreted via kidney and liver and there are 2 major metabolites. N-desmethyl-vandetanib is produced by CYP3A4, has similar potency to vandetanib, and is present at 14% of the plasma concentration of vandetanib. Vandetanib-N-oxide is produced by flavin-containing monooxygenase-1 (FMO1) and FMO3, is essentially inactive, and is present at 2% of the plasma concentration of vandetanib. There is no effect of food on the PK of vandetanib.

3.1.2 Drug interactions

Because of the role of CYP3A4 in the metabolism of vandetanib, studies investigated the potential interactions with inducers or inhibitors of CYP3A4. There was no clinically significant effect on exposure to vandetanib in the presence of the potent CYP3A4 inhibitor itraconazole in healthy volunteers. However, the potent CYP3A4 inducer rifampicin reduced exposure to vandetanib by 40%, although this may be partially compensated by the 2-3-fold increase in exposure to the active N-desmethyl metabolite. As a result, patients receiving vandetanib may receive concomitant CYP3A4 inhibitors, but should avoid the use of potent inducers of CYP3A4, as these may reduce the efficacy of vandetanib. It is unlikely that vandetanib will affect the cytochrome-P450 metabolism of other medications, and in clinical studies vandetanib had no clinically relevant effect on the exposure to docetaxel or irinotecan, which are substrates for CYP3A4.

Vandetanib is an inhibitor of the organic cation transporter OCT2, which could lead to reduced renal clearance of substrates of OCT2 and increases in serum creatinine. However, to date there is no evidence from the clinical development program for an adverse clinical consequence of this effect.

3.1.3 Hepatic and renal impairment

Two studies in non-cancer subjects (n = 62) evaluated the effect of hepatic or renal impairment on vandetanib exposure. Subjects with severe renal impairment (creatinine clearance [CrCL] ≤30 mL/minute) had an approximate 2-fold increase in exposure to vandetanib compared to those with normal renal function, while subjects with mild and moderate renal impairment had a 1.5- and 1.6-fold increase, respectively. In the 2nd study, subjects with mild, moderate, or severe hepatic impairment, based on Child-Pugh criteria, showed no significant difference in the exposure to vandetanib.

Patients with mild to moderate renal impairment have a safety profile similar to that of patients with normal renal function. The safety and efficacy of vandetanib have not been established in patients with hepatic impairment. There is limited clinical experience in patients with severe renal impairment, so safety and efficacy have not been established.

3.1.4 Pharmacokinetics in relation to efficacy and safety

The population PK-PD analysis for Study 58 investigated the effect of baseline characteristics on the PK of vandetanib and relationships between PK and efficacy and safety. There was a statistically significant effect of weight on the clearance and volume of distribution, although this is unlikely to be clinically relevant given the high inter-individual variability. There was no difference in PK between males and females. No conclusions could be reached on the effect of race on PK in patients with MTC, as 95% of the patients were Caucasians, but the Phase III studies in NSCLC, which included a significant number of Asian patients, have not shown differences in PK based on race.

There was no relationship between PK and CTCAE grade ≥3 events of rash, diarrhea, hypertension, or QT prolongation, although firm conclusions cannot be reached as the incidence of grade ≥3 events in the study was low. PK-PD modeling predicts that a maximum average change in QTc of 25-30 msec above baseline will be seen within 1 month of starting oral daily treatment with little additional increase in the QTc values in patients continuing vandetanib for more than 6 weeks. There was no relationship between PK and PFS or overall survival, but there was a greater decline in CTN values at higher concentrations of vandetanib, and a higher steady-state exposure predicted a higher chance of an objective tumor response. Despite there being a relationship between PK and CTN reduction, this was not reflected as a relationship between PK exposure and PFS or OS.

3.2 Pharmacodynamic data and clinical dose considerations

3.2.1 Non-clinical pharmacodynamic properties

The non-clinical studies demonstrate that vandetanib inhibits the VEGFR2, EGFR, and RET tyrosine kinases in vitro and in vivo, and that inhibition of these targets leads to anti-tumor effects. The concentrations of vandetanib that inhibit the molecular targets and that lead to anti-tumor effects in pre-clinical models are equivalent to the concentrations that can be achieved in patients over the dose range of 100mg to 300mg. However, the greatest benefits in the pre-clinical models are seen when the concentration of vandetanib is at the higher end of this range, consistent with greater inhibition of the targets, predicting that efficacy in the clinic will be greatest at the maximum tolerated dose (MTD).

Non-clinical toxicology studies in the rat and dog identified dose-limiting toxicities (DLT) consistent with the pharmacology of vandetanib, including gastrointestinal effects (vomiting and diarrhea) and skin lesions (folliculitis and abscesses). Effects on cardiac repolarization and blood pressure were also seen.

3.2.2 Dose considerations for the clinical studies

There was no formal dose-ranging study during Phase II. For Study 58 (pivotal) and Study 08 (supportive) in MTC, the highest tolerated dose was used to maximize inhibition against the molecular targets. The Phase I studies investigated a range of doses from 50-600 mg and established the MTD as 300 mg per day in Western and Japanese patients. Dose-limiting toxicities (DLTs) included diarrhea, skin rash and hypertension, and QTc prolongation was observed at all doses (particularly at doses above 400 mg per day). Based on the pre-clinical

data which predict that the greatest anti-tumor effect will come when vandetanib is used at the MTD, the 300 mg dose was selected as the monotherapy dose for the initial study of vandetanib in patients with MTC and for the pivotal Phase III study with the intent to dose to tolerance – ie, the idea of starting patients at the maximum tolerated dose (MTD) of 300 mg daily, but understanding that some patients may require dose reductions for chronic dosing because they are not able to tolerate dosing at the 300mg dose over a chronic dosing period.

3.2.3 Dosing frequency, duration and adjustment for toxicity

The suppression of tumor growth in mouse xenograft models is maintained only with continuous dosing with vandetanib. When the drug is withdrawn, tumor growth resumes at a rate similar to that seen in untreated controls. Therefore, the dosing interval for vandetanib was chosen to ensure that the plasma concentration at steady state allows for a constant effect against the molecular targets. Given the long half-life, dosing more frequently than once daily is not necessary. With daily dosing, the plasma concentrations are fairly constant at steady-state, with little fluctuation between peak and trough levels. All of the pivotal clinical efficacy and safety data were obtained using the once-daily dosing frequency.

Given the long half-life of vandetanib, if a patient misses a dose, the next dose can be taken on the following day. The impact on long-term exposure would be minimal. This was done in the MTC trials.

Patients in the studies in MTC received vandetanib (or placebo) until disease progression, toxicity, death, or withdrawal of consent. In the Phase III study, patients who had disease progression on either arm were permitted to receive open-label vandetanib as long as they were receiving benefit. For patients starting at 300 mg daily dosing, dose reduction to 200mg daily, and then to 100mg daily is the recommended option for management of toxicity, in addition to medical management of specific side effects. This allows patients to have the potential for maximum benefit by starting at the highest dose of vandetanib, and for those patients who do not tolerate 300 mg to continue to receive treatment at an acceptable toxicity level, ie, dosing to tolerance. Although the half-life of vandetanib is long, this dose reduction plan was effective in the clinical studies as a method for managing side effects with only 13% discontinuing treatment due to AEs and 48% of patients who were randomized to vandetanib still on active treatment at the time of data cutoff (31 July 2009), with a median follow-up of 2 years. Please see Section 5.2.3 for more information.

4. OVERVIEW OF EFFICACY

4.1 Design

4.1.1 Study population

Study 58 enrolled patients with both hereditary and sporadic MTC. Patients were required to have unresectable locally advanced or metastatic disease at study entry. Furthermore, patients were required to have measurable tumor at baseline and a CTN level of at least 500 pg/mL to ensure that patients had objective evidence of advanced disease at study entry. As

chemotherapy is not widely used in patients with MTC, there was no requirement for patients to have received prior chemotherapy, and concurrent chemotherapy was not allowed on the study so that the benefit of vandetanib alone could be clearly defined. Patients with World Health Organization (WHO) performance status >2 were excluded.

4.1.1.1 RET mutation status

Patients were required to provide an archived tumor sample prior to randomization for RET mutation analysis, although no sample was required for patients with hereditary disease who had a documented germline mutation in RET. The results of the RET analysis were not required before randomization of patients in Study 58. Patients who did not have an archived sample or a documented germline mutation in RET were required to provide a fresh tumor sample before randomization.

Tumors were assessed for the presence of a RET mutation in 2 ways. First, an amplification-refractory mutation system (ARMS) analysis (an assay based on a polymerase chain reaction [PCR] test) was used to detect the M918T mutation, expected to be the most common mutation in this patient population. Second, the 6 most commonly mutated exons of RET in MTC, exons 10, 11,13,14,15 and 16, were sequenced. The blinded analysis of RET mutation status was conducted during the study, and the RET co-primary analysis population was removed in a protocol amendment in May 2009 when it was found that a complete analysis of RET mutation status could not be conducted on a substantial number of samples because of insufficient quality or quantity of DNA. Results of the subgroup analysis by RET mutation status are presented in Section 4.2.2.3.

When a mutation was found by any of the assay methods (ARMS for M918T or sequencing of exons 10, 11, 13, 14, 15, and 16), the patient was considered RET mutation status positive. If all of the assays were completed successfully and all showed wild-type sequence, then the patient was considered RET mutation negative. Patients were classified with unknown RET mutation status if any of the assays technically failed and no mutation was demonstrated by any assay that was technically successful. For example, if 5 of the 6 sequencing assays showed no mutation, but 1 sequencing assay failed, this patient would be considered RET mutation status unknown. This was a very rigorous definition for being defined as RET mutation negative, and this was done to minimize the possibility of falsely labeling patients RET mutation negative. It is understood that setting such a high bar to define the RET mutation negative population could enrich the RET mutation unknown population with RET mutation negative patients. According to the definitions for each of these populations, 57% of patients were RET mutation positive, 41% were RET unknown, and 2% RET mutation negative.

4.1.2 Study design

Study 58 was a randomized, double-blind, placebo-controlled Phase III study, and the primary endpoint was progression-free survival. Randomization and a placebo control group were critical in order to define clearly the benefit of vandetanib in PFS in this disease in which patients can have prolonged stable disease without treatment. Furthermore, the placebo control allowed for a clear interpretation of the safety of vandetanib on the background of the signs

and symptoms experienced by patients with advanced MTC. Placebo was considered to be an appropriate comparator because there are no standard or approved therapies available for patients with MTC.

Study 58 was initiated after encouraging data from the single-arm Study 08 showed a 20% objective response rate in patients with hereditary MTC. Because of the results of Study 08, and because of the unmet need for effective therapies in MTC, patients were permitted to receive open-label vandetanib following objective disease progression on blinded therapy. Patients remained on blinded, randomized therapy until the investigator determined that objective disease progression by RECIST had occurred. At the time of progression, patients were provided the option to receive open-label vandetanib. Because the central review of radiographic images was not performed in real-time, some patients received open-label therapy before progression was confirmed by the central read. This is discussed further in Section 4.2.2.

4.1.3 Dose

The dose of vandetanib in Study 58 was 300 mg based on the results of Study 08, which showed efficacy and tolerability of vandetanib 300 mg in patients with MTC. Phase I studies had previously demonstrated that the maximum tolerated dose of vandetanib is 300 mg daily. Pre-clinical data demonstrate that increasing the dose of vandetanib over the range of concentrations, equivalent to those tolerated by patients with daily dosing, leads to increasing inhibition of the key targets RET, VEGFR2, and EGFR. Similarly, increasing the dose of vandetanib over the same range leads to greater anti-tumor effect in xenograft models. In MTC all 3 targets are relevant (see Section 1.2.1); therefore, the 300 mg dose maximizes the potential for patients to gain an efficacy benefit. Study 08 demonstrated that the 300 mg dose has efficacy in MTC, and also that it is tolerable over long-term dosing. Adjusting the dose for tolerance allows each patient to receive a dose that maximizes the chance for efficacy while managing the side effects.

The Phase II Study 68 was conducted in parallel with the Phase III Study 58 to assess whether there was efficacy of a lower 100 mg dose of vandetanib in patients with MTC. Study 68 had a similar design to Study 08, with no control group and enrolling patients with only the hereditary form of MTC. No formal comparison of data from Studies 08 and 68 was conducted, but Table 4 in Section 4.2.7 provides a side-by-side presentation of major efficacy variables, confirming the rationale to start dosing at 300 mg/day.

4.1.4 Endpoints

There is no effective treatment for patients with locally advanced or metastatic MTC, and patients typically experience a protracted period of disease progression over many years. A compelling improvement in progression-free survival that is reliably assessed and that is consistent with improvement in other efficacy endpoints represents a clear clinical benefit for these patients. Therefore, PFS was selected as the primary endpoint for Study 58, and this was advised by the FDA at the end of phase II meeting and during the SPA discussions as an appropriate endpoint to support approval. Durable responses also represent meaningful outcomes for patients with MTC, and therefore objective response rate and duration of

response were secondary endpoints. This is also supported by evidence of activity (response rate) upon unblinding and open label treatment. The time to worsening of pain endpoint, although limited by incomplete compliance, provides an opportunity to assess outcomes based on self-reported measures during the blinded placebo-controlled treatment period.

Progression and response in Study 58 were assessed using RECIST criteria, with radiographic assessments every 3 months. These criteria were prospectively modified in the study protocol from standard RECIST criteria to account for 2 particular patterns of disease seen in patients with MTC. First, guidance was provided for the measurement of calcified lesions, where tumor measurements were modified if the calcified component of a lesion represented >80% of a lesion's longest diameter. Second, specific guidance was provided for the interpretation of hypodense lesions that appear during treatment. These lesions were noted in Study 08, where patients had the appearance of new hypodense lesions that actually reflected changes to pre-existing tumor rather than new lesions. The primary analysis of PFS used these 2 modifications of the RECIST criteria, but following a request from the FDA, sensitivity analyses were performed to assess PFS in the absence of these 2 modifications. Death in the absence of progression was considered a PFS event if death occurred within 3 months of the last evaluable RECIST assessment, but not if it occurred later, to avoid over-estimating the time to progression in these patients. In this latter case, PFS was censored at the last RECIST assessment.

Because the central read was not conducted in real-time, the initial determination of progression, and thus the decision to proceed to open-label vandetanib, was based on the site read. This allowed some patients to receive open-label vandetanib before progression had occurred according to the central read. As the primary analysis of PFS was based on an intention-to-treat (ITT) analysis, these open-label events were included in the analysis of PFS. Therefore, additional sensitivity analyses for PFS were conducted to look at the outcome based both on the central and site read, excluding scans performed while patients were receiving open label treatment. ITT analysis was also used to assess the radiographic secondary endpoints (response rate and disease control rate), and therefore included any patients who received open-label vandetanib before progression.

Overall survival was also assessed as a secondary endpoint in Study 58, although the data may be affected by patients on the placebo arm receiving open-label vandetanib following progression. A planned initial analysis for OS was conducted at the time of the primary analysis of PFS with a significance level of 0.02% based on the number of events that had occurred. The final analysis for overall survival is not expected before 2012.

Objective disease progression can be associated with a number of different signs and tumor-related symptoms for patients, including pain due to the tumor location, diarrhea due to secretion of calcitonin and other factors by the tumor cells, difficulty in swallowing, impingement of nerves & blood vessels, and progression of liver disease. With the availability of a validated scale, the Brief Pain Inventory (BPI; Cleeland and Ryan 1994), to assess pain, an evaluation of the effect of vandetanib on pain was assessed as a secondary endpoint. The endpoint was amended in the protocol before the study was unblinded to account for the

potential impact of opiate analgesics on the assessment of pain. Worsening of pain was defined as an increase of 2 in the worst pain score on the BPI scale of 0 to 10. Worsening of opiate analgesic use was defined as an increase from baseline of ≥10 mg/day of morphine sulfate equivalent. The endpoint was measured in all patients, not just in those patients with pain at baseline. Patients were asked to record their pain and opiate use weekly. TWP was assessed every 3 months. Exploratory PRO endpoints included quality of life using the FACT-G scale, changes in opiate analgesic use, changes in diarrhea, and changes in weight.

Finally, changes in the tumor biomarkers of calcitonin (CTN) and carcinoembryonic antigen (CEA) were assessed as secondary endpoints, both because these markers are commonly used in the clinic to track the response of progression of the tumor, and also because CTN and other factors produced by the tumor can contribute to the symptoms experienced by patients.

4.1.5 Statistical Considerations

The Phase III study was designed with 2:1 randomization to vandetanib:placebo. The study had >80% power to detect an HR of 0.5 for PFS. The assumed median in the comparator arm was 12 months. PFS was calculated from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression), provided that the death was within 3 months from the last evaluable RECIST assessment and analyzed using a log-rank test.

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 0.02% to account for an initial analysis at the time of the PFS analysis. The final OS analysis will occur once at least 50% of the patients have died.

4.1.6 Supporting studies 8 and 68

Study 08 was the initial pilot Phase II study to assess the efficacy and safety of vandetanib in patients with hereditary MTC. The study enrolled 30 patients to receive vandetanib 300 mg, and the primary endpoint was response rate.

In parallel with the pivotal Study 58, a second single-arm Phase II study was started in patients with hereditary MTC. Study 68 enrolled 19 patients to receive vandetanib 100mg to determine the efficacy and safety of a lower dose in this disease. As with Study 08, the primary endpoint was response rate.

4.2 Efficacy results in MTC

The pivotal Study 58 demonstrated statistically significant and clinically meaningful benefits in PFS, response rate, duration of response, disease control rate, biochemical response (ie, reductions in CTN or CEA levels), and time to worsening of pain. The efficacy results are described in this section, and summarized in Table 4.

4.2.1 Patient population

A total of 331 patients were randomized at 60 sites in 23 countries with 199 (60%) patients randomized in the European Union and 73 (22%) patients randomized in the US. Only 5% of patients were non-Caucasian. Out of 331 patients, 231 were randomized to vandetanib and 100 to placebo. This exceeded the expected ratio of 2:1 due to random chance, since numerous sites randomized a total number of patients which was not an exact multiple of the block size of 3.

Table 2 summarizes the baseline demographics for patients randomized to study 58. Overall, the minor differences in the baseline characteristics between the 2 study arms did not appear to affect the outcome of the study.

Table 2 Summary of demographic characteristics – Study 58

Baseline characteristics		**Vandetanib 300mg (N=231)**	**Placebo (N=100)**	**Total (N=331)**
Age (years)	Mean	50.7	53.4	51.5
	<65	182 (78.8)	80 (80.0)	262 (79.2)
	>=65	49 (21.2)	20 (20.0)	59 (17.8)
Sex n (%)	Male	134 (58.0)	56 (56.0)	190 (57.4)
	Female	97 (42.0)	44 (44.0)	141 (42.6)
Race n (%)	Caucasian	218 (94.4)	97 (97.0)	315 (95.2)
	Other	13 (5.6)	3 (3.0)	16 (6.9)
WHO Performance Status n (%)	(0) Normal Activity	154 (67.0)	58 (58.0)	212 (64.0)
	(1) Restricted Activity	67 (29.0)	38 (38.0)	105 (32.0)
	(2) In Bed <= 50% of the Time	10 (4.0)	4 (4.0)	14 (4.0)
Genetic basis of MTC	Hereditary disease	28 (12%)	5 (5%)	33 (10%)
	Sporadic disease	203 (88%)	95 (95%)	298 (90%)

Baseline characteristics		Vandetanib 300mg (N=231)	Placebo (N=100)	Total (N=331)
Extent of disease	Locally advanced disease	14 (6%)	3 (3%)	17 (5%)
	Metastatic disease	217 (94%)	97 (97%)	314 (95%)
Number of organs involved	0-1	29 (13%)	8 (8%)	37 (11%)
	≥2	202 (87%)	92 (92%)	294 (89%)
Prior systemic therapy for MTC	None	141 (61%)	58 (58%)	199 (60%)
	≥1	90 (39%)	42 (42%)	132 (40%)
CTN doubling time	≤24 months	124 (54%)	46 (46%)	170 (51%)
	>24 months	83 (36%)	43 (43%)	126 (38%)
	Unknown	24 (10%)	11 (11%)	35 (11%)
CEA doubling time	≤24 months	69 (30%)	33 (33%)	102 (31%)
	>24 months	119 (52%)	48 (48%)	167 (50%)
	Unknown	43 (19%)	19 (19%)	62 (19%)
RET mutation	Positive	137 (59%)	50 (50%)	187 (56%)
	Negative	2 (1%)	6 (6%)	8 (2%)
	Unknown	92 (40%)	44 (44%)	136 (41%)

Only 21% of patients had received prior chemotherapy. Ninety five percent of patients had metastatic disease, although the protocol also allowed patients who had only locally advanced disease. Possible reasons for the predominance of patients with metastatic disease include (i) aggressive surgical techniques so that fewer locally advanced tumors are unresectable, (ii) eligibility criteria for the study requiring a CTN level ≥500 pg/mL and clearly measurable tumor, which could favor patients with metastatic disease, and (iii) investigator choice to select predominately patients with metastatic disease for the study.

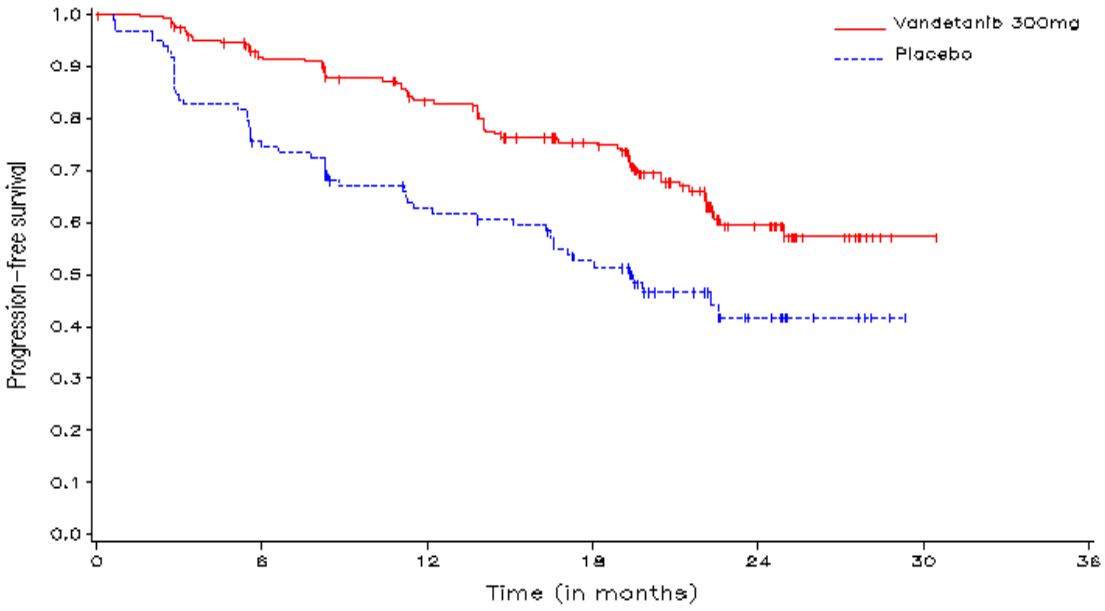
Most patients had extensive disease with at least 2 organs involved (89%). The most common sites of metastatic disease were hepatic (including gall bladder) (66%), lymph node (61%), lung (56%), and bone (36%). Overall, the median volume of disease at baseline was 11.3 cm. Volume of metastasis at the most common sites (in cm) by treatment group (vandetanib vs placebo) at baseline was liver (6.1), mediastinum (6.2), neck (3.3), lung (2.5). A short CTN or CEA doubling time <24 months can be a marker of poor prognosis and more aggressive disease (Barbet et al 2005); this was seen in 51% of patients for CTN and 31% for CEA. The majority of patients, 96%, had WHO Performance Status (PS) 0 or 1 at study entry with the remaining patients all having WHO PS of 2.

4.2.2 Progression-Free Survival

The primary endpoint of PFS was based on an intention-to-treat (ITT) analysis of all randomized patients, with the PFS variable assessed by an independent central radiographic assessment. The study had been intended to randomize a minimum of 232 patients, with the primary analysis of PFS to occur once a minimum of 90 events (39%) had occurred. Due to a late and unexpected increase in the rate of screening and consenting patients for the study, the final number of randomized patients was 331. The data cut-off date of 31 July 2009 was set based on a date when it was expected that at least 90 events would have occurred. The central read was not conducted in real time and once the central read results were available, it was found there were 124 PFS events that had occurred as of this data cut-off date. The total number of 124 PFS events at the final analysis represents a similar proportion of events (37%) to the proportion that was originally anticipated in the protocol (39%).

The median duration of follow-up was 1.96 years on the vandetanib arm and 2.04 years on the placebo arm. The primary analysis for PFS was performed using the log-rank test (unadjusted model with treatment factor only). There was a statistically significant improvement in PFS for patients randomized to vandetanib compared to placebo (Hazard Ratio (HR) = 0.46; 95% Confidence Interval (CI) = 0.31-0.69; p=0.0001). This represents a 54% reduction in the risk of progression for patients randomized to vandetanib over the period of follow-up. The median PFS for patients randomized to placebo was 19.3 months while the median PFS for patients randomized to vandetanib has not been reached but is predicted to be approximately 30 months (Figure 2). For vandetanib, a total of 73 (32%) of patients had progressed. The remaining 158 patients (68%) were censored in the analysis of PFS. For placebo, a total of 51 (51%) of patients had progressed. The remaining 49 patients (49%) were censored in the analysis of PFS. A total of 23 patients on the vandetanib arm and 28 patients on the placebo arm received open-label vandetanib before progression according to the central read. The corresponding open-label data were included in the primary ITT analysis of PFS for these patients.

Figure 2 Kaplan-Meier Plot of PFS (Full Analysis Set)



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	231	198	171	141	42	1	0
Placebo	100	72	57	45	13	0	0

Note: "Full Analysis Set" includes all randomized patients.

4.2.2.1 Sensitivity analyses for PFS

The following pre-specified sensitivity analyses were conducted for PFS:

1. Cox-proportional hazards model, with the following prespecified covariates: RET mutation status (positive or negative/unknown); CTN doubling time (≤24 months or >24 months/unknown); CEA doubling time (≤24 months or >24 months/unknown); number of prior systemic anticancer therapies (none or ≥1); response to the most recent systemic anticancer therapy (response or no response/unknown), and MTC status (hereditary or sporadic/unknown)

2. Per-protocol analysis, which excluded patients who had a protocol violation that could have the potential to impact the efficacy result. Protocol deviations/violations included patients who were found to have failed certain entry criteria, patients who took certain disallowed concomitant medications during the course of the study, and patients who had their baseline RECIST assessment more than 4 weeks before first dose or after first dose.

3. A grouped survival method, to assess the impact of any differential frequency of assessments between treatment groups (Whitehead 1989).

4. PFS based on the central read with data excluded from the open-label phase. For patients entering the open-label phase without centrally reviewed progression, dates were imputed based on a linear regression of central review measurements taken prior to open-label.

5. PFS based on the investigator assessment of progression (site read).

6. PFS based on central read, but with no correction of calcified lesions applied.

7. PFS based on central read, but with new hypodense or hypo-intense lesions at the first 2 RECIST assessments automatically considered to represent progression.

The results of these analyses, both by analysis method and derivations of PFS, are summarized in Table 3, which indicates that all of the sensitivity analyses support the primary analysis of PFS. All point estimates of hazard ratios were either less than, or in very close range (0.27 – 0.51) to the HR observed from the primary analysis (0.46), in favor of vandetanib, establishing the robustness of the results.

A HR of 0.40 was observed for the site read, in this analysis scans obtained during the time patients received open label treatment were excluded. The extent to which site read progressions were recorded earlier than the central read was similar between arms (52% (53/101) of vandetanib and 50% (31/62) of placebo site read progressions); indicating there was no differential discordance in the site and central read between the two treatment arms. This blinded phase only analysis therefore allowed an estimate of the underlying vandetanib benefit in absence of confounding by patients taking open label vandetanib.

Table 3 Sensitivity analyses of PFS

	Vandetanib 300 mg; No. of events/patients	Placebo; No. of events/patients	Hazard ratio	95% CI	2-sided p-value
Primary analysis (log-rank)	73/231	51/100	**0.46**	0.31 - 0.69	0.0001
Cox proportional hazards model	73/231	51/100	**0.46**	0.32 - 0.68	0.0001
Per Protocol analysis	71/215	48/91	**0.45**	0.30 - 0.68	0.0002
Grouped survival analysis	73/231	51/100	**0.51**	0.35 – 0.72	0.0002

	Vandetanib 300 mg; No. of events/patients	Placebo; No. of events/patients	Hazard ratio	95% CI	2-sided p-value
Central read excluding data from open-label phase	64/231	59/100	**0.27**	0.18 - 0.41	<0.0001
Site read excluding open-label	101/231	62/100	**0.40**	0.27 - 0.58	<0.0001
Calcified lesions	74/231	51/100	**0.47**	0.31 - 0.70	0.0002
Hypodense/ hypointense lesions in liver	78/231	52/100	**0.49**	0.33 - 0.72	0.0003

4.2.2.2 Further supportive analyses for PFS

Further supportive analyses were performed after the data were unblinded. An analysis was performed to explore the possible impact of patients censored more than 3 months before the data cut-off and three additional analyses were requested by FDA.

A total of 8% (19) vandetanib and 7% (7) placebo patients had site progression and were censored for central progression more than 3 months prior to the data cut-off date. The censoring of such patients is likely to be informative (Dodd et al 2008) and therefore an additional analysis was performed by assuming an event would have occurred according to the central review at the next scheduled visit following the latest site assessment. This analysis produced a HR of 0.51; 95% CI = 0.36-0.74; p=0.0004. There were a further 10% (23) vandetanib and 5% (5) of placebo patients who were censored more than 3 months prior to the data cut-off date in the absence of either site or central progression, the majority were withdrawal from study recorded as 'voluntary discontinuation'. There was no obvious difference between these early dropouts and the overall population in terms of baseline demography or in terms of biomarkers of disease progression at the time of dropout. If these twenty-eight dropouts are conservatively retained as events in the analysis, then the treatment effect still retains significance with a HR of 0.57; 95% CI=0.40, 0.82; p=0.0024.

Three additional sensitivity analyses for PFS were conducted at the request of the FDA, all of which showed a benefit in PFS consistent with the primary endpoint:

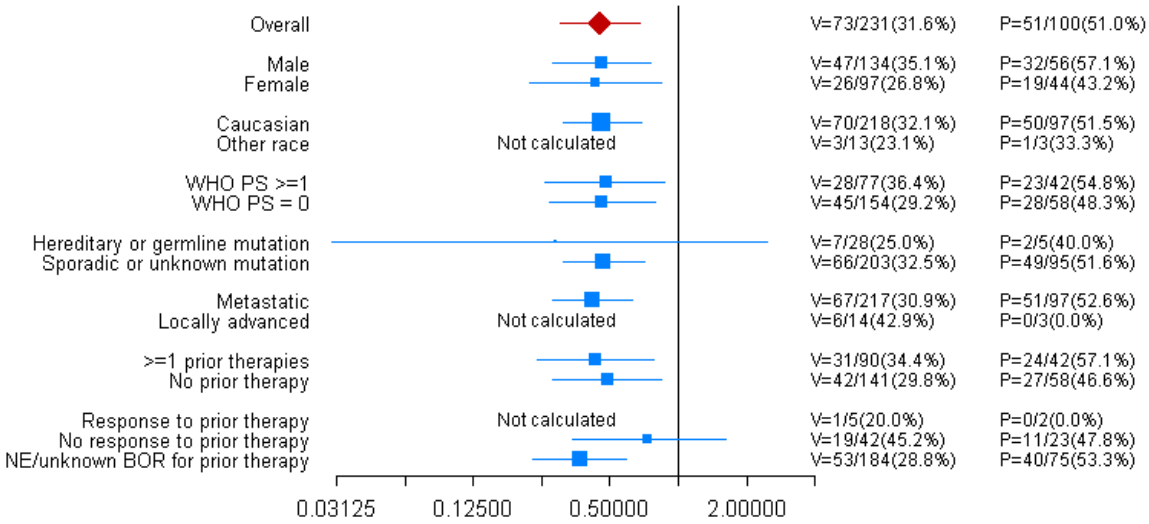
- Including all deaths, rather than just those that occurred within 3 months of the last RECIST assessment, as PFS events: HR=0.46 (95% CI = 0.31-0.68; p=0.0001)
- Removing both RECIST corrections, for calcified and for hypodense lesions: HR=0.49 (95% CI = 0.33-0.73; p=0.0004)

- PFS in US patients only: HR=0.39 (95% CI = 0.16-0.95; p=0.0384)

4.2.2.3 Subgroup analyses for PFS

The benefits in PFS were seen in all subgroups of patients, and the global interaction test was not significant (p = 0.177) (Figure 3), indicating that overall the variability in treatment effects observed is consistent with, chance given the number of subgroup analyses performed. Nevertheless, a retrospective interaction test was performed for each individual subgroup separately, excluding any patient with unknown status, to further explore specific variations in outcome. The pre-specified subgroups included gender, number of previous therapies, WHO PS at baseline, and plasma levels of VEGF, VEGFR2, and basic fibroblast growth factor (bFGF) (Figure 4). There was equal benefit observed in patients with a WHO PS of 0 vs. ≥1, and this was also true for patients with 0 or 1 or more previous systemic treatments.

Figure 3 Forest plot of subgroup analyses for PFS - Baseline characteristics and disease status (Full analysis set)



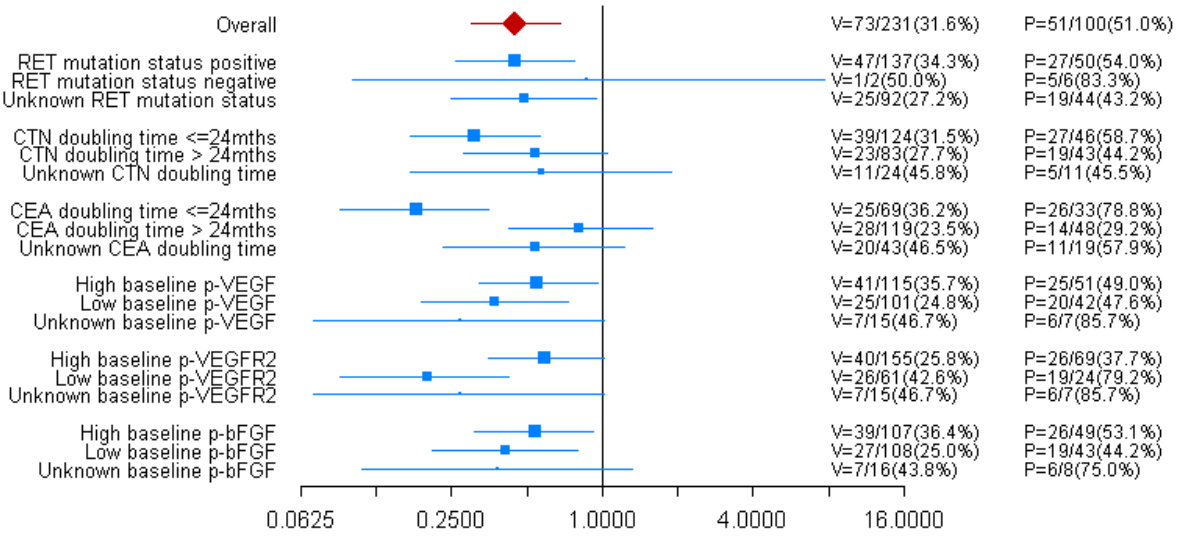
A hazard ratio < 1 favors vandetanib.
The analyses were performed using a log rank test with treatment as the only factor.
PFS was derived from all available central read RECIST assessments.
Prior therapy refers to systemic anti-cancer therapy for medullary thyroid cancer taken prior to the first dose of randomized treatment.
A response to prior therapy is defined as a best objective response of CR or PR to the most recent prior therapy.
No response to prior therapy is defined as a best objective response of SD or PD to the most recent prior therapy.
BOR = Best Objective Response.
Note: "Full Analysis Set" includes all randomized patients.

There was clear benefit in PFS for patients who were RET mutation positive (HR=0.45) (Figure 4). Patients were classified as RET mutation positive if a mutation was detected by any of the assay methods (ARMS for M918T or sequencing of exons 10, 11, 13, 14, 15, and 16). Only 8 patients on the study (and only 2 randomized to vandetanib) were RET mutation negative, defined as patients for whom all of the assays were completed successfully and all showed wild-type sequence. However, there was a clear benefit in PFS for patients whose RET mutation status was unknown (HR=0.49), defined as patients for whom at least one of the assays could not be completed successfully, but all successful assays showed wild-type sequence. The most common reason for an unsuccessful assay was failure of the one of the exon sequencing assays due to insufficient quantity or poor quality DNA; the ARMS assay for M918T was successful in 79% of cases. Of the patients with unknown RET status, 54% were known to be wild-type at M918T. Therefore because at least 50% of patients with sporadic MTC will have the M918T mutation, the majority of ARMS assay negative patients may be RET mutation negative (Eng 1999).

Although the original hypothesis was that vandetanib would have better efficacy in patients with RET mutation, the benefit seen in RET mutation unknown patients suggests that this may not be true. Recent data suggest that the RET signaling pathway may be activated even in tumors that do not have a RET mutation (Cerrato et al 2009), and wild-type RET is inhibited by vandetanib to a similar degree as mutant RET (Knowles et al 2006). Consequently, the patients in study 58 may have responded to treatment with vandetanib because the RET pathway was activated in the tumor, regardless of the RET mutation status.

Visual inspection of the Forest plots shows a greater advantage in PFS for patients with short doubling times (≤24 months) of CTN and CEA, compared to those with longer doubling times. However, for both subgroups with longer doubling times (>24 months) the point estimates of the hazard ratios are <1. The interaction test for the CEA subgroup was the only one that was significant at the 5% level (p=0.006). However, there were objective tumor responses in both of these subgroups for patients who were randomized to vandetanib (CTN doubling time >24 months: RR=40%; CEA doubling time >24 months: RR=37%).

Figure 4 **Forest plot of subgroup analyses for PFS - Biomarkers (Full analysis set)**



Note: A hazard ratio < 1 favors vandetanib.
The analyses were performed using a log rank test with treatment as the only factor.
PFS was derived from all available central read RECIST assessments.
CTN/CEA doubling time is derived by taking the natural log of each pre-dose CTN/CEA measurement, fitting a linear regression line to
these data to obtain the slope m and the CTN/CEA doubling time is m divided by ln 2. Negative doubling times are assigned to the > 24 months group.
High p-VEGF > 55.0 pg/ml at baseline. Low p-VEGF <= 55.0 pg/ml at baseline. High p-VEGFR2 > 9.88165 pg/ml at baseline.
Low p-VEGFR2 <= 9.88165 pg/ml at baseline. High p-bFGF > 2.10 pg/ml at baseline. Low p-bFGF <= 2.10 pg/ml at baseline.
Baseline is defined as the value closest to and preceding randomization.
Note: "Full Analysis Set" includes all randomized patients.

4.2.3 Response rate, duration of response, disease control rate, and biochemical response

The primary analysis of objective tumor response rate, duration of response, and disease control rate, similar to the primary analysis of PFS, was based on the ITT analysis including all randomized patients and using the blinded, independent central read. This analysis included all scans up to the time of progression according to the central read. Statistically significant advantages were seen for vandetanib for response rate and disease control rate. The objective response rate of patients randomized to vandetanib was 45% (104/231). For patients randomized to placebo, the response rate was 13% (13/100) according to the ITT analysis, but

12 of the 13 patients had a response only after receiving open-label vandetanib. When open-label assessments are excluded, the response rates are 44% (101/231) for vandetanib and 1% (1/100) for placebo.

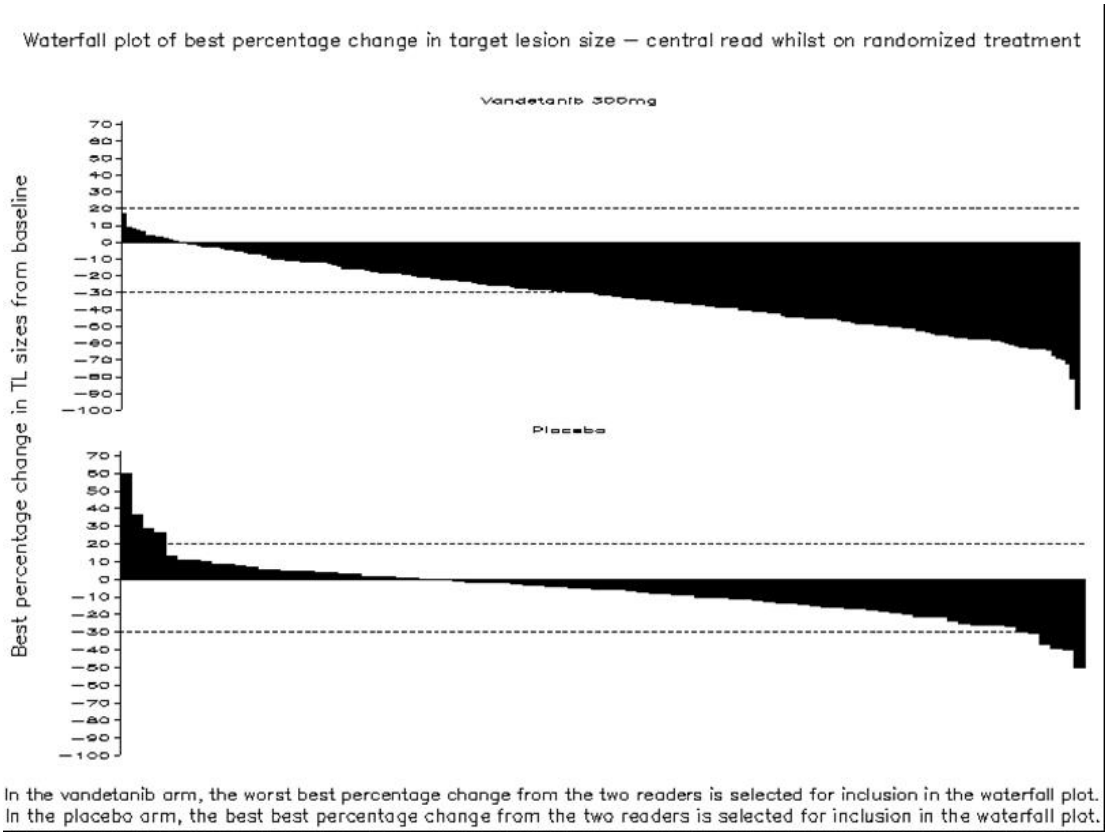
The response rate for patients randomized to placebo and who then received open-label vandetanib provides further evidence for the activity of vandetanib in MTC. Of the 100 patients randomized to placebo, 58 received vandetanib in the open-label phase; 28 of these received open-label vandetanib before central read progression, and 30 received open-label vandetanib after central read progression. Of the 28 patients who received open-label vandetanib before progression, the response rate according to the central read was 43% (12/28). For the remaining 30 patients, the response rate cannot be determined using the central read, as these patients had already progressed according to the central read and no further central read assessments were conducted. However, using the site read, the response rate in all 58 patients who received open-label vandetanib following placebo was 34% (20/58).

The median duration of response in the both groups appeared to be similar, which would be expected as all but 1 of the responses in the placebo group occurred after the patients received vandetanib. The responses were durable, and the median had not been reached at 24 months follow-up. Disease control rate (response rate + stable disease at 24 weeks) is an indicator of benefit, as many patients with MTC have prolonged slowly progressing disease. The results showed a significant improvement for vandetanib (87% vs. 71%; p=0.001).

The response rate to vandetanib does not appear to be affected by the amount of disease at baseline. An exploratory analysis of response rate according to the sum of the longest diameter of all target lesions at baseline was conducted, and showed that the response rate based on central read in patients with a sum <10cm was 39% (46 of 231 patients), and for patients with a sum ≥10cm was 48% (55 of 231 patients). The response rates for vandetanib at the most common sites of metastases were: liver 51%, mediastinum 50%, neck 35%, lung 61%.

Waterfall plots were created showing the most favorable change in tumor size according to the central read for each patient randomized to the vandetanib arm (Figure A) or the placebo arm (Figure B) in Figure 5 below. The dotted lines in the figure indicate a 20% increase or 30% decrease in target lesion size. Because some patients randomized to placebo received vandetanib before disease progression according to the central read, data are shown only for the randomized phase of the study. In cases where there was a difference between the 2 central readers on the best percentage change, the worse change was selected for the vandetanib plot, and the better change was selected for the placebo plot. Overall, more patients who received vandetanib had a decrease in the size of target lesions, and the magnitude of the decrease was larger than for patients who received placebo.

Figure 5 Waterfall plot of best percentage change in target lesion size while on randomized treatment (central read) – Study 58



4.2.4 Biochemical response

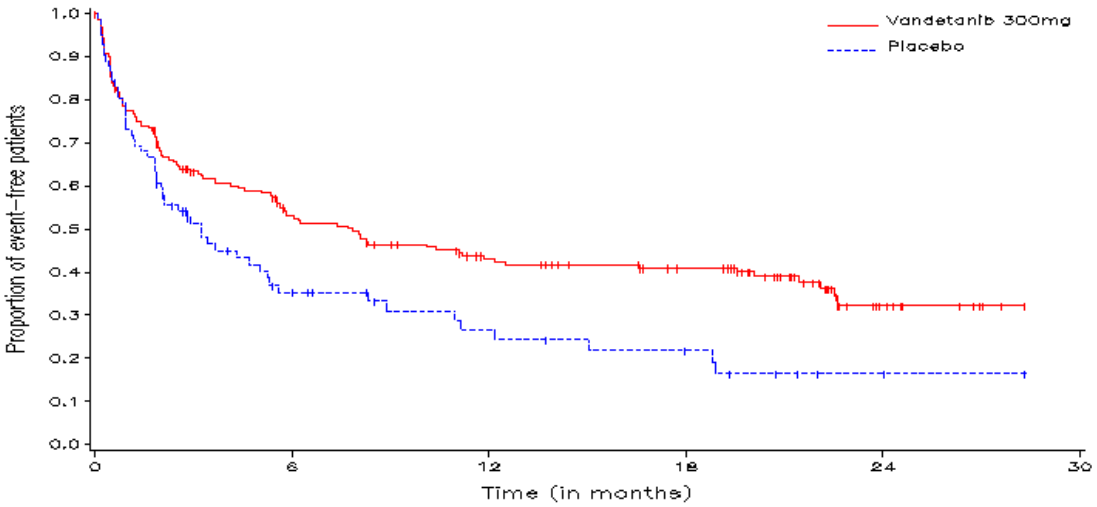
The data for CTN and CEA response are derived from the data collected during the randomized phase of the study only. These markers are routinely measured in clinical practice as they are sensitive indicators of prognosis in MTC. In the absence of therapeutic intervention, rising levels suggest tumor progression, and falling levels generally correlate with reductions in tumor burden (Giraudet et al 2008). The difference between vandetanib and placebo in the proportion of patients with reductions in these tumor markers was striking, with 69% of patients on the vandetanib arm experiencing a CTN response (decline of at least 50% from baseline), and 52% having a CEA response, compared to 3% and 2% on the placebo arm, respectively.

4.2.5 Time to worsening of pain

Time to worsening of pain (TWP) was derived from the worst pain score on the Brief Pain Inventory (BPI) and patient-reported opioid analgesic use. A significant advantage for vandetanib was seen (HR=0.61; 95% CI 0.43, 0.87; p=0.006) with a delay in the median TWP of 4.6 months over placebo (Figure 6). The median time to deterioration in worsening of pain was 7.9 months in the vandetanib arm, compared with 3.3 months in the placebo arm. The composite endpoint was used to account for any effect on the BPI of changes in opiate

analgesic use. It is difficult to make definitive conclusions based on this result because the compliance with the BPI assessments was approximately 50% over the course of the study. However, the observation is consistent with the benefit seen in the objective and blinded radiographic endpoints.

Figure 6 Kaplan-Meier plot of TWP (Full analysis set)



n at months	0	6	12	18	24	30
Vandetanib 300mg	231	88	62	48	10	0
Placebo	100	21	12	8	2	0

Worsening in pain is considered to be a worsening with no improvement in the next 14 days.
Worsening in pain is derived from the worst pain score (from BPI) and patient reported opioid analgesic use.
Note: "Full Analysis Set" includes all randomized patients.

A number of exploratory analyses are related to the TWP endpoint. The advantage in TWP was seen regardless of whether patients were taking more or less than 10mg of opiate equivalents at baseline. When the BPI was used alone to assess TWP, there was a numerical advantage in TWP that was not statistically significant (HR=0.76; p=0.140), suggesting that some of the benefit in TWP is reflected in a reduced need for higher doses of opiates.

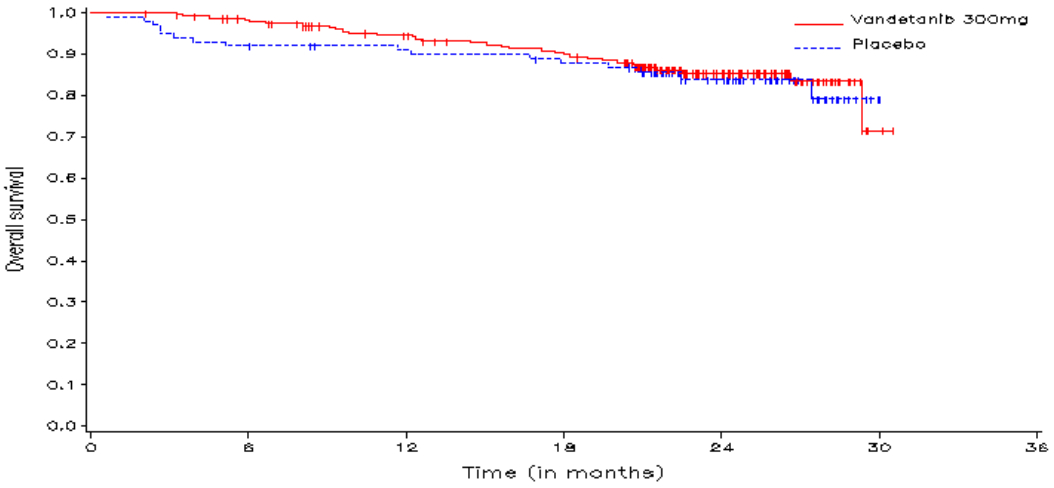
The percent of patients showing an improvement in pain, using the BPI and accounting for opiate use, was higher in patients taking vandetanib compared to placebo, but the result was not statistically significant (34% vs. 27%). A greater reduction in opiate use in patients taking

at least 10mg of opiate equivalent at baseline was seen in patients taking vandetanib: 63% of patients on vandetanib had a reduction of >50% in opiate use for at least 14 days (with no worsening of pain in that time), compared to 38% on placebo. However, definitive conclusions are difficult, as only 40 patients on the study were taking at least 10mg of opiates at baseline.

4.2.6 Overall survival

Following progression, patients had the option to receive open-label vandetanib. Of the 100 patients randomized to placebo, 58 received open-label vandetanib by the time of the data cut-off. Therefore, the overall survival result may be affected by any benefit that patients initially randomized to placebo receive from open-label vandetanib. At the time of the primary analysis of PFS (data cut-off date 31 July 2009), 15% of randomized patients had died, and there was no significant difference in overall survival between treatment groups (Hazard ratio = 0.89; 99.98% CI = 0.28 – 2.85; p=0.712) (Figure 7 and Table 5). At the time of this analysis, 32 patients (14%) on the vandetanib arm and 16 patients (16%) on the placebo arm had died. As per the protocol, a final analysis of survival will be conducted once at least 50% of patients have died. However, the survival comparison between vandetanib and placebo will likely continue to be affected by the cross-over of patients from the placebo arm to open-label vandetanib. Following the primary analysis for PFS and after consultation with the FDA, the study protocol was amended to allow patients currently receiving placebo (28 at the time of the data cut-off) to become unblinded and have the option to receive open-label vandetanib immediately.

Figure 7 Kaplan-Meier plot of OS (Full analysis set)



n at months	0	6	12	18	24	30	36
Vandetanib 300mg	231	221	202	189	81	2	0
Placebo	100	92	88	84	44	0	0

Note: "Full Analysis Set" includes all randomized patients.

4.2.7 Other exploratory endpoints

Additional exploratory endpoints looked at improvement in weight, time to deterioration of WHO performance status, quality of life, and stool frequency. Weight improvement was defined as an increase of >5% from baseline for at least 4 weeks, and there was a significant advantage in the percent of patients with weight improvement on the vandetanib arm compared to placebo (29% vs. 11%; p=0.0003). For the time to deterioration of WHO performance status, there was no statistically significant difference (HR=0.74; p=0.165). There did not appear to be any differences between vandetanib and placebo in either reported stool frequency or quality of life (assessed using the Functional Assessment of Cancer Therapy – General [FACT-G]) over the course of the study, although assessment of these endpoints is challenging given compliance issues similar to those for the other Patient-Reported Outcomes.

4.2.8 Efficacy in supporting studies in hereditary MTC

The initial pilot Phase II Study 08 enrolled 30 patients with hereditary MTC to receive vandetanib 300 mg daily. The objective response rate was 20% (95% CI 7.7-38.6), with a median duration from onset of response of 10 months. The primary analysis of response rate was based on investigator assessments using RECIST. The median PFS was 28 months and CTN reduction of at least 50% from baseline was seen in 80% of patients. The median PFS in Study 08 (28 months) was similar to the estimated median PFS in study 58 (30 months). However, the objective response rate was less in study 08 (20%) than in study 58 (45%). There is no clear explanation for this apparent difference in response rate. Two differences in the baseline characteristics of patients in the 2 studies were in the proportion of patients with hereditary disease (100% in study 08 and 10% in study 58) and in the proportion of females (70% in study 08 and 43% in study 58). However, in study 58 the efficacy in patients with hereditary disease and in females appeared similar to the efficacy in patients with sporadic disease and in males, so these differences in baseline characteristics seem unlikely to explain the difference in response rate.

In Study 68, 19 patients received the lower 100 mg dose of vandetanib. This dose was also active: the response rate (according to investigator assessments) was 16% (95% CI 3.4-39.6), with a median duration of response of 6 months. The median PFS was estimated to be 16.2 months. A CTN reduction of at least 50% was seen in only 16% of patients. Table 4 below provides a side-by-side view of common efficacy variables between Studies 8, 58 and 68.

Table 4 Summary of results for common efficacy outcome variables in Study 08, Study 68, and Study 58

Variable		Study 58		Study 08	Study 68
		Vandetanib 300 mg (N=231)[a]	**Placebo (N=100)[a]**	**Vandetanib 300 mg (N=30)[a]**	**Vandetanib 100 mg (N=19)[a]**
PFS	Median, months	30.5[b]	19.3	27.9	16.2[b]
ORR	Number of responses	104 (45.0%)	13 (13.0%)[c]	6 (20.0%)	3 (15.8%)
DCR	Number with best response of CR,PR, or SD≥24 weeks	200 (86.6%)	71 (71.0%) [c]	22 (73.3%)	13 (68.4%)
DOR[d]	Median, months	22.2[b]	16.3 [b,c]	10.9	8.3
CTN response rate	Number of responses	160 (69.3%)	3 (3.0%)	24 (80.0%)	3 (15.8%)

		Study 58		Study 08	Study 68
CEA response rate	Number of responses	119 (51.5%)	2 (2.0%)	16 (53.3%)	1 (5.3%)

CEA carcinoembryonic antigen; CTN calcitonin; DCR disease control rate; DOR duration of response; ORR objective response rate; PFS progression-free survival

Note: Results for progression and response for Study 58 are based on a central imaging review ("central read"), independent of AstraZeneca. Results for Study 08 and Study 68 are based on a site imaging review.

[a] Refers to treated patients in Study 08 and Study 68 and randomized patients in Study 58.

[b] Represents predicted median based on a Weibull model.

[c] The ITT analysis included patients who received open-label vandetanib before disease progression was documented according to the central read. A total of 12 of the 13 objective responses in the placebo arm occurred during open label treatment with vandetanib.

[d] From onset of response.

Overall, the data presented in Table 3 above are consistent with the hypothesis that vandetanib 100 mg and 300 mg are active doses in MTC, but that a greater level of activity is seen at 300 mg.

Preliminary results from an ongoing study of vandetanib in pediatric patients with hereditary MTC were reported at the American Society for Clinical Oncology meeting in 2009 (Fox et al 2009). All 6 patients with MEN2B enrolled at that time have had decreases in tumor size, with objective responses in 5 patients.

4.2.9 Efficacy in differentiated thyroid cancer

Study 79 was a randomized, placebo-controlled, Phase II study of vandetanib 300 mg in patients with locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy. The study randomized 145 subjects to receive vandetanib (72 patients) or placebo (73 patients). By design, patients continued blinded randomized treatment until objective disease progression or until 12 months of stable disease, and then had the option to receive open-label vandetanib.

There was a statistically significant advantage in the primary endpoint of PFS for vandetanib over placebo, with a hazard ratio (HR) = 0.63; 95% confidence interval (0.43, 0.92); p=0.017, based on an ITT analysis including all randomized patients. At the time of the data cut-off, 113 patients had progressed; 52 (72%) of the patients randomized to the vandetanib arm and 61 (84%) of the patients randomized to the placebo arm. There was no clear evidence of a differential benefit in the pre-specified subgroups of age (greater or less than 45 years), metastasis volume (greater or less than 7.6 cm^3), presence of metastasis in bone, lung or lymph nodes, or prior radioiodine uptake.

Among the 145 patients of the ITT population, objective tumor responses were seen in six patients randomized to vandetanib 300 mg (8.3%) and four patients in the placebo group (5.5%). These 4 responses occurred during randomized period. All but one of these responses under placebo were observed in patients with only one small target lesion at baseline.

Unadjusted logistic regression (i.e. with treatment as the only factor) led to an Odds Ratio (OR) of 1.57 in favor of vandetanib though it was not significantly different from 1 at a 5% alpha level (p-value of 0.50, 95% CI [0.42 ; 5.81]).

The number of patients that achieved disease control, 6 months after randomization, was higher in the vandetanib 300 mg group (56.9%) than in the placebo group (42.5%). Logistic regression with treatment as the only factor led to an OR of 1.79 in favor of vandetanib though it was not significantly different from 1 at a 5% alpha level (p-value of 0.08, 95% CI [0.93 ; 3.46]). However, the magnitude of the benefit appeared consistent with the magnitude of the benefit in PFS.

A total of 29% of patients in the vandetanib arm and 66% of patients in the placebo arm discontinued randomized treatment because of disease progression. Randomized treatment was stopped after 12 months, in the absence of progression, for 29% of patients in the vandetanib arm, and 22% of patients in the placebo arm. The remaining patients discontinued randomized treatment for adverse events (33% on vandetanib and 6% on placebo) or for other reasons.

There was no statistically significant difference between vandetanib and placebo in the secondary endpoints of overall response rate, disease control rate, or overall survival. The assessment of OS was potentially confounded by the use of subsequent therapy, as patients in the placebo arm who discontinued randomized treatment were unblinded and given the option to take open label vandetanib. The inclusion of this option had the potential to reduce the treatment effect observed for vandetanib in the analysis of OS. A total of 49% of patients randomized to vandetanib and 81% of patients randomized to placebo received open-label vandetanib after stopping randomized treatment. At the time of the data cut-off, 26% of patients in the vandetanib arm had died, and 29% of patients in the placebo arm had died. A final survival analysis will be conducted when at least 50% of patients have died (anticipated by 2012).

4.2.10 Efficacy conclusions in MTC

The results of the primary and secondary efficacy endpoints for the pivotal Study 58 are shown in Table 5 below.

Table 5 Summary of key efficacy findings: Study 58 (Full analysis set)

PROGRESSION-FREE SURVIVAL	N	Median PFS	HR[a]	95% CI	p-value
Vandetanib 300 mg	73/231 (32%)	Not reached[b]	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			
OVERALL RESPONSE RATE[c]	**N**	**Response rate**	**OR[e]**	**95% CI**	**p-value**
Vandetanib 300 mg	104/231	45.0%	5.48[g]	2.99, 10.79	<0.0001
Placebo	13/100	13.0%[d]			
DISEASE CONTROL RATE[c]	**N**	**Response rate**	**OR[e]**	**95% CI**	**p-value**

Vandetanib 300 mg	200/231	86.6%	2.64	1.48, 4.69	0.001
Placebo	71/100	71.0%			
CTN RESPONSE	**N**	**Response rate**	**OR[e]**	**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[e]**	**95% CI**	**p-value**
Vandetanib 300 mg	119/231	51.5%	52.03	15.95, 320.3	<0.0001
Placebo	2/100	2.0%			
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[f]	**N**	**Median time to worsening of pain**	**HR**	**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 HR= Hazard Ratio. A value <1 favors vandetanib. The analysis was performed using a log rank test with treatment as the only factor.
b Estimated to be 30.5 months using a parametric model
c 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.
d The response rate was 13% in patients who received placebo. However, it is important to note that 12 of the 13 responses in the placebo group were seen in patients receiving open-label vandetanib following disease progression. The actual response rate in the placebo group during randomized treatment was 1%.
e OR=Odds Ratio. A value >1 favors vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.
f TWP (Time to worsening of pain) was a composite endpoint, derived from opioid analgesic use and the worst pain item of the BPI.
g The OR of 5.48 refers to the comparison of 45% to 13%.
BPI, Brief Pain Inventory questionnaire; N, Number of events/number of randomized patients; OS, overall survival; PFS, progression-free survival; CI, confidence interval.
Note: "Full Analysis Set" includes all randomized patients.

In conclusion, Study 58 demonstrated a compelling and consistent improvement in PFS, supported by benefits in secondary efficacy endpoints including an objective response rate of 45% with vandetanib and a duration of response >18 months. These data therefore show clear evidence of clinical benefit in patients with locally advanced or metastatic MTC.

5. OVERVIEW OF SAFETY

This section focuses on the safety data from the pivotal Phase III Study 58 in MTC. Across all vandetanib clinical studies, approximately 5000 patients have received vandetanib. This includes patients at all doses of vandetanib, either as monotherapy or in combination with chemotherapy, across a range of tumor types. Approximately 2000 patients have received vandetanib 300 mg monotherapy, the majority in studies of NSCLC. The 231 patients who

were randomized to receive vandetanib in Study 58 represent a small proportion of the total number of patients who have received vandetanib, but they have a greater duration of exposure than patients with other tumors, with a median duration of treatment of 1 year 9 months, compared to 8-9 weeks on the Phase III NSCLC studies with vandetanib 300 mg. Conventional analyses of adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, dose reductions and/or interruptions, and deaths are presented in Section 5.2, and Section 5.3 presents further detail on particular findings relevant to vandetanib in MTC.

5.1 Exposure to vandetanib

As of the data cutoff date (31 July 2009), a total of 1851 patients received 300 mg vandetanib in the clinical studies contributing to this evaluation of safety (Study 58 in MTC and pooled 300 mg monotherapy studies). The majority of patients who have received 300 mg monotherapy had NSCLC (79%); 17% had MTC. The ICH E3 criterion for adequate exposure in support of long-term use (at least 100 patients be treated for ≥1 year) has been met by Study 58, in which the median duration of treatment on the vandetanib arm (231 patients) was 1 year 9 months and 172 patients received vandetanib on the randomized and open label phases of the study for at least 1 year. Data from the monotherapy pool provide additional insight regarding uncommon events that were not observed in Study 58 but might be experienced once larger numbers of patients received marketed drug.

Overall, the median duration of exposure on Study 58 was longer for vandetanib 300mg than for placebo (1 year 9 months vs. 9 months, respectively), and this should be considered when interpreting difference in incidence of adverse events.

5.2 Tolerability of vandetanib in MTC

Data for vandetanib monotherapy in MTC are provided primarily from the blinded, randomized phase of Study 58 at the 300 mg daily dose (n=231); the data cut-off date for Study 58 was 31 July 2009. Comparison against placebo during the blinded treatment phase enabled the isolation of the safety profile related to the drug against the background of advanced or metastatic disease. Without treatment, patients will experience substantial signs and symptoms, as evidenced by the incidence of AEs and severe and serious AEs in the placebo group during blinded treatment.

The tolerability of vandetanib 300 mg monotherapy was concordant with the non-clinical safety findings and is generally related to its pharmacological action. A summary of patients with at least 1 AE in any category is presented in Table 6 below. One patient randomized to placebo died before receiving any randomized treatment; this patient is excluded from the safety analysis set. Of the patients on the vandetanib arm, 54% of patients had AEs of Grade 3, 8% had Grade 4 events, and 2% had Grade 5 events. Of the patients on the placebo arm who had AEs marked as CTCAE Grade ≥3, 20% of patients had AEs of Grade 3, 5% had Grade 4 events, and 2% had Grade 5 events. Most AEs initially occurred in the first 3-6 months after starting vandetanib. The prevalence of CTCAE ≥2 and CTCAE≥3 events remains stable at 30% and 10%, respectively, after the first 3-6 months , and through medical

management of side effects and dose modifications of vandetanib, most patients were able to manage the side effects over a chronic dosing period.

Table 6 Summary of patients in Study 58 who had at least 1 AE in any category while on randomized treatment (Safety analysis set)

	--Vandetanib 300 mg (N=231)--	--Placebo (N=99)--
AE category	**Percent (%) of patients [a]**	**Percent (%) of patients [a]**
Any AEs	99.6	90.9
Any vandetanib/placebo causally [b] related AE	96.1	59.6
Any AEs of CTCAE grade 3 and higher	55.4	24.2
Any SAEs	30.7	13.1
Any SAEs associated with an outcome of death	2.2	2.0
Any AEs leading to discontinuation of randomized treatment	12.1	3.0

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As assessed by the Investigator.

5.2.1 Common AEs

Common AEs, defined as those with a frequency of ≥10% in any treatment arm, and the proportion of those events with CTCAE Grade ≥3 were coded using MedDRA v13.0 and are presented by system organ class (SOC) and preferred term (PT) in Table 7 and Table 8, respectively. Overall, the 5 most frequently reported AEs in this study were diarrhea, rash, nausea, hypertension, and fatigue. The most common AEs that occurred with a >5% higher frequency for patients in the vandetanib arm compared with the placebo arm included diarrhea (56.3% versus 26.3%), rash (45.0% versus 11.1%), nausea (33.3% versus 16.2%), hypertension (31.6% versus 5.1%), and headache (25.5% versus 9.1%). These events are consistent with the known safety profile of vandetanib and the mechanism of action of VEGFR and EGFR inhibition. All vandetanib studies rated the severity of AEs using Version 3 of the CTCAE grading system. Overall, 55.4% of patients in the vandetanib arm and 24.2% of patients in the placebo arm experienced AEs of CTCAE Grade ≥3. Approximately 8% of patients on the vandetanib arm and 5% on the placebo arm experienced AEs of CTCAE Grade 4. The 5 most frequently reported events that were CTCAE Grade ≥3 in the vandetanib arm were diarrhea, electrocardiogram QT prolonged, hypertension, fatigue, and decreased appetite; all were reported more frequently in the vandetanib arm than the placebo arm.

Table 7 Summary of patients who had >=1 AE by PT and SOC while on randomized treatment, frequency >10% (Safety analysis set)

SOC Name Preferred Term	__Vandetanib 300 mg (N=231)__ Percent (%) of patients [a]	__Placebo (N=99)__ Percent (%) of patients [a]
Patients with any AE	**99.6%**	**90.9%**
Skin And Subcutaneous Tissue Disorders	**90.0%**	**30.3%**
Rash	45.0%	11.1%
Acne	19.9%	5.1%
Dry Skin	15.2%	5.1%
Dermatitis Acneiform	15.2%	2.0%
Photosensitivity Reaction	13.4%	0.0%
Pruritus	10.8%	4.0%
Gastrointestinal Disorders	**80.5%**	**56.6%**
Diarrhea	56.3%	26.3%
Nausea	33.3%	16.2%
Vomiting	14.7%	7.1%
Abdominal Pain	14.3%	5.1%
Dyspepsia	10.8%	4.0%
Infections And Infestations	**49.8%**	**36.4%**
Nasopharyngitis	11.3%	9.1%
General Disorders And Administration Site Conditions	**48.9%**	**41.4%**
Fatigue	23.8%	23.2%
Asthenia	14.7%	11.1%
Nervous System Disorders	48.5%	32.3%
Headache	25.5%	9.1%
Musculoskeletal And Connective Tissue Disorders	**40.7%**	**47.5%**
Back Pain	9.1%	20.2%
Arthralgia	7.8%	10.1%
Pain In Extremity	6.9%	13.1%
Investigations	**39.8%**	**16.2%**
Electrocardiogram QT Prolonged	14.3%	1.0%

SOC Name Preferred Term	__Vandetanib 300 mg (N=231)__ Percent (%) of patients [a]	__Placebo (N=99)__ Percent (%) of patients [a]
Weight Decreased	10.4%	9.1%
Vascular Disorders	**39.0%**	**11.1%**
Hypertension	31.6%	5.1%
Respiratory, Thoracic And Mediastinal Disorders	**38.5%**	**33.3%**
Cough	10.8%	10.1%
Metabolism And Nutrition Disorders	**35.1%**	**20.2%**
Decreased Appetite	21.2%	12.1%
Hypocalcaemia	10.8%	3.0%)
Psychiatric Disorders	**30.3%**	**21.2%**
Insomnia	13.0%	10.1%

SOC = System Organ Class, PT = Preferred Term.
[a] Percent (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency in the vandetanib arm.
A patient can have one or more PT reported under a given SOC.
The 10% is relevant to either vandetanib or placebo actual treatment group.

Table 8 Summary of patients with an AE of CTCAE grade >=3 by PT and SOC while on randomized treatment - frequency > 1% (Safety analysis set)

SOC Name Preferred Term	Vandetanib 300mg [b] (N=231) Percent (%) of patients [a]	Placebo [b] (N=99) Percent (%) of patients [a]
Patients with any AE of CTCAE grade 3 and higher	**55.4**	**24.2**
Gastrointestinal Disorders	**17.7**	**3.0**
Diarrhea	10.8	2.0
Investigations	**12.6**	**1.0**
Electrocardiogram QT Prolonged	7.8	1.0
Vascular Disorders	**9.1**	**1.0**
Hypertension	6.9	0.0
General Disorders And Administration Site	**8.7**	**2.0**

SOC Name Preferred Term	Vandetanib 300mg [b] (N=231) Percent (%) of patients [a]	Placebo [b] (N=99) Percent (%) of patients [a]
Conditions		
Fatigue	5.6	1.0
Asthenia	2.6	1.0
Metabolism And Nutrition Disorders	**8.2**	**1.0**
Decreased Appetite	3.9	0.0
Skin And Subcutaneous Tissue Disorders	**7.8**	**0.0**
Rash	3.5	0.0
Respiratory, Thoracic And Mediastinal Disorders	**5.2**	**5.1**
Dyspnea	1.3	3.0
Nervous System Disorders	**5.2**	**4.0**
Syncope	0.0	2.0
Musculoskeletal And Connective Tissue Disorders	**3.5**	**4.0**
Back Pain	0.4	3.0

SOC = System Organ Class, PT = Preferred Term.
[a] Percent (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency in the vandetanib arm.
Event rate = (No. of pats. with event / total duration of follow-up until 1st event for all pats. in group)x 1000

The safety profile of vandetanib in the open-label phase was similar to the randomized treatment phase. A total of 102 patients opted to receive open-label treatment; 44 (19 %) patients who had been randomized to vandetanib in the blinded phase, and 58 (58%) patients who had been randomized to placebo in the blinded phase. A total of 92 (90.2%) patients had at least 1 AE; 50 (49.0%) patients had AEs of CTCAE grade ≥3; 28 (27.5%) patients had SAEs, including 1 patient who died due to an SAE. The only SAEs reported in more than 1 patient were diarrhea, vomiting, renal failure acute, back pain, and pneumonia aspiration, each of which occurred in 2 (2.0%) patients.

5.2.2 Serious adverse events

A total of 84 (25.5%) patients had at least 1 SAE during the randomized phase of Study 58. This included 71 (30.7%) patients in the vandetanib group and 13 (13.1%) in the placebo group.

SAEs that were reported by more than 1 patient in the vandetanib arm were diarrhea (5 [2.2%] patients), pneumonia (5 [2.2%] patients), decreased appetite (4 [1.7%] patients), hypertensive

crisis (4 [1.7%] patients), urinary tract infection (3 [1.3%] patients), abdominal pain (3 [1.3%] patients), hypercalcemia (3 [1.3%] patients), hypertension (3 [1.3%] patients), nephrolithiasis (3 [1.3%] patients), depression (3 [1.3%] patients), and bronchitis (2 [0.9%] patients). SAEs occurring in the placebo arm were reported by no more than 1 patient each.

5.2.3 Dose interruptions, reductions, and discontinuations

A summary of dose reductions and interruptions in Study 58 is presented below. Overall 23% of patients on the vandetanib arm required a single dose reduction and 13% required 2 dose reductions. Of the 231 patients who started treatment with 300 mg vandetanib, 70 (30.3%) continued on the starting dose of 300 mg daily at the time of data cutoff; 51 (22.0%) stopped 300 mg vandetanib because of disease progression; and 27 (11.7%) stopped 300 mg vandetanib for AEs or other reasons. A total of 83 (35.9%) patients were dose reduced from 300 mg vandetanib. Of these, 81 (35.1%) had their dose reduced to 200 mg daily, and 2 (0.9%) were reduced directly to 100 mg daily. Of the 81 patients who received the 200 mg dose, 24 (10.4%) continued on the 200 mg dose at the time of data cutoff; 15 (6.5 %) stopped because of disease progression; and 12 (5.2%) stopped for AEs or other reasons. A total of 30 (13.0%) patients required further dose reduction, 29 (12.6%)patients were reduced directly to 100 mg daily, and 1 (0.4%) patient was reduced to 200 mg every other day before receiving 100 mg daily. Patients who had dose reduction remained on the reduced dose of 200 mg for a median 23 weeks, and on 100 mg for a median of 29 weeks.

The most common events that led to dose reduction were diarrhea, QT prolongation, and rash. Adverse events of CTCAE grade ≥3 leading to dose reduction for vandetanib from 300 to 200 mg per day were recorded for 19 (8.2%) patients in the vandetanib arm and 1 (1.0%) patient in the placebo arm. QTc prolongation led to dose reduction to 200mg for 16 (6.9%) patients and to 100mg in 8 (3.5%) patients.

The mean total exposure to vandetanib 300 mg in the randomized phase of Study 58 was 75 weeks, which includes time when patients interrupted daily dosing for at least 1 day. The mean actual exposure, excluding dose interruptions, was 73.6 weeks, or 98% of the total exposure. A total of 47% of patients had dose interruptions, however, the impact on dose intensity was low, ie, less than 2% of planned exposure. Twenty-eight of the 231 patients (12.1%) in the vandetanib arm and 3 (3.0%) in the placebo arm discontinued randomized treatment because of an adverse event. Fourteen of the 28 patients (50%) who stopped vandetanib for an AE discontinued without a dose reduction. As of the date of data cutoff of 31 July 2009, 139 patients (111 vandetanib, 28 placebo) were still receiving randomized treatment. In addition, 59 patients were continuing to receive open label treatment at data cut off;17 who were previously on vandetanib and 42 who were previously on placebo.

5.2.4 Deaths

The proportion of patients who had adverse events leading to death on Study 58 was similar between the arms of the study. A total of 5 (2.2%) patients on the vandetanib arm had an adverse event leading to death, compared to 2 (2.0%) on the placebo arm. The 5 deaths on the vandetanib arm were due to staphylococcal sepsis, aspiration pneumonia, respiratory arrest,

pneumonia, and one patient of acute cardiac failure and arrhythmia. For patients in the placebo arm, the deaths were due to gastrointestinal hemorrhage and gastroenteritis.

5.3 Key safety findings with vandetanib in MTC

This section includes both the more common events that patients are likely to experience when receiving vandetanib as treatment for MTC, and the uncommon to rare events that are clinically significant events. These include those identified from the non-clinical findings, the early clinical setting, and class effects of EGFR or VEGFR signaling inhibitors. There are no known class effects of RET-specific inhibitors, as all RET inhibitors that have been tested in the clinic also have other molecular targets. The prevalence of adverse events was defined as the probability of a patient experiencing the event of interest at a particular time after randomization, by treatment arm. Unlike incidence, this takes both duration of events and multiple occurrences of events into account.

5.3.1 Rash and other skin reactions

Rash and other skin reactions (including photosensitivity reactions and palmar-plantar erythrodysaesthesia syndrome) have been observed in patients who have received vandetanib. In Study 58, 88.7% of patients who received vandetanib experienced an AE under the collective term “skin reaction,” compared to 23.3% on the placebo arm. Photosensitivity reaction was observed in 13.4% of patients who received vandetanib and in no patients who received placebo. The majority of skin reactions were CTCAE Grade 1 or 2; skin reactions that were CTCAE Grade 3 or greater were reported for 17 (7.35%) patients in the vandetanib arm. One CTCAE grade 4 rash was reported in a patient treated with vandetanib. Vandetanib was discontinued and the patient was treated with oral methylprednisolone and the rash resolved, although a photosensitivity reaction was still present. Mild to moderate skin reactions can usually be managed by symptomatic treatment, or by dose reduction. More severe skin reactions may require systemic glucocorticoids and permanent discontinuation of vandetanib. Care should be taken with sun exposure by wearing additional clothing and /or sunscreen.

The median time to onset of the first incidence of a CTCAE Grade ≥3 skin reaction for vandetanib (n=17) was 2.5 months (range 0.3 to 10.4). Overall, the prevalence of skin reactions reaches approximately 70% for all grades, 20% for CTCAE grade ≥2 in the first 3 months, and then remained at these levels over time, indicating that there is no cumulative toxicity. Only 4 (1.7%) patients in the vandetanib arm discontinued randomized treatment due to skin reactions (rash in 3 (1.3%) patients, eczema in 1 (0.4%), and photosensitivity reaction in 1 (0.4%)). There were no reports of toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, or toxic skin eruption, although these events have occurred in other vandetanib studies.

5.3.2 Diarrhea

Diarrhea is a common symptom for patients with MTC, but was reported more often in patients who received vandetanib compared with placebo in Study 58 (56.3% versus 26.3%, respectively). Diarrhea was treated through standard symptomatic treatment, such as the use

of loperamide. Diarrhea was the most common AE with CTCAE grade ≥3, seen in 10.8% of patients who received vandetanib in the randomized phase of Study 58. CTCAE Grade 4 diarrhea was seen in 1 patient (0.4%) in the vandetanib treatment arm.

The mean time to onset of the first incidence of CTCAE ≥3 diarrhea (n = 25) was 5.0 months (range 0.3 to 13.6) in patients who received vandetanib in the randomized phase of Study 58. Forty-six (19.9%) patients treated with vandetanib and 9 (9.1%) of patients treated with placebo developed CTCAE Grade 2 diarrhea. Overall, the prevalence of diarrhea reaches approximately 40% at 3 months for all grades, and 15% for CTCAE grade ≥2, and does not increase after the first 3 months, indicating that there is no cumulative toxicity. Only 2 (0.9%) patients in the vandetanib arm discontinued randomized treatment due to diarrhea.

Routine anti-diarrheal agents (including loperamide) and fluid and electrolyte correction, as needed, are recommended for the treatment of diarrhea. Serum electrolytes should be monitored if persistent or severe diarrhea develops. If severe diarrhea (CTCAE grade 3-4) develops, vandetanib should be stopped until diarrhea improves. Upon improvement, treatment with vandetanib may be resumed at a reduced dose.

5.3.3 Hypertension

Hypertension is a class side effect of VEGF pathway inhibitors, and was reported more frequently in the vandetanib arm of Study 58 than the placebo arm (31.6% versus 5.1%). CTCAE Grade ≥3 events of hypertension were reported in 16 (6.9%) patients in the vandetanib arm and 1 (1.0%) patient in the placebo arm. Four patients (1.7%) had hypertensive crisis, as reported by the investigator, and 1 patient (0.4%) had an AE of accelerated hypertension, both occurring in patients in the vandetanib arm. Two (0.9%) patients in the vandetanib arm discontinued due to AEs of hypertension. No placebo patients discontinued due to hypertension. Elevations in blood pressure were generally seen within the first 3 months of treatment, and the prevalence of hypertension of any grade was approximately 20% and showed a very gradual increase over time to nearly 25%.

Hypertension was readily treated with antihypertensive agents, mostly calcium channel blockers. The occurrence of hypertension in patients who received vandetanib did not increase the incidence of ischemic events or death compared to all patients who received vandetanib. Patients with elevated blood pressure at baseline (as judged by the use of antihypertensives) were not more likely to develop worsening hypertension when treated with vandetanib.

Patients should be monitored for hypertension and controlled as appropriate, and vandetanib must not be restarted until the blood pressure is controlled medically. Reduction in vandetanib dose may be necessary.

5.3.4 QTc-related events and QTc interval prolongation

QTc prolongation with vandetanib was initially seen in Phase I and pre-clinical studies, and over the course of the clinical development the vandetanib protocols have included a management plan including ECG schedules, criteria to define QTc prolongation, and guidance

for dose reduction. This management plan has been amended, in consultation with cardiology experts and FDA, as data became available over the course of the clinical studies. The Phase III QT management plan was agreed at the end of Phase II with FDA. In the Phase III protocols, QTc prolongation using Bazett's correction was defined as a single value of ≥ 550msec or ≥100msec increase over baseline, or a confirmed prolongation of the QTc interval to value of ≥500 msec, or an increase from baseline of ≥60 msec to a level ≥480 msec. Any one of these criteria mandated a dose interruption until resolution and restarting treatment at a reduced dose. All ECGs were assessed by an independent, central cardiologist.

Adverse events with a preferred term of "electrocardiogram QT prolonged" were seen in 33 (14.3%) patients in the vandetanib arm of Study 58, and 1 (1.0%) patient in the placebo arm. However, QTc prolongation according to the protocol criteria was seen in 8.2% of patients in the vandetanib arm, and none in the placebo arm, during randomized treatment. One patient in the vandetanib arm had a Grade 2 event of exercise-induced ventricular tachycardia and had a reported AE of electrocardiogram QT prolonged a year later, although the protocol defined criteria for QT prolongation were not met. Two patients in the vandetanib arm had loss of consciousness, and 1 additional patient had syncope, but no protocol-defined QT prolongation. QTc prolongation led to discontinuation of vandetanib in 2 (0.6%) patients. The PK-PD modelling shows that a maximum average rise in QTc of 25-30 msec from baseline will occur in the first month, and that further increases are unlikely in patients continuing on vandetanib beyond 6 weeks, but sporadic reports of QTc prolongation may occur after several months on therapy.

In Study 58, there were no adverse events reported as "death" or "sudden death", and no reports of Torsade de pointes. However, out of approximately 5000 patients who have received vandetanib, 2 reports of Torsade de pointes, documented by ECG, have occurred. Both cases occurred in patients who were receiving vandetanib 300 mg monotherapy, 1 in a patient with differentiated thyroid cancer after 5 weeks of therapy, and 1 in a patient with NSCLC after 12 weeks of therapy, and in both cases there were other factors that may have contributed to the development of the arrhythmia: prior bradycardia and atrioventricular block in the first case, and myocardial ischemia, electrolyte imbalances, and concomitant levofloxacin in the second case. Both patients recovered, and vandetanib was not restarted.

Vandetanib treatment should not be started in patients whose corrected electrocardiogram QT interval is confirmed to be greater than 480 msec. Vandetanib should not be given to patients who have a history of Torsade de pointes unless all risk factors that contributed to Torsade have been corrected. Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

An electrocardiogram, and levels of serum potassium, calcium and magnesium and TSH should be obtained at baseline, at 2-4 and 8-12 weeks after starting treatment with vandetanib and every 3 months for at least a year after. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. The serum potassium level should be maintained at 4 mEq/L or higher and serum magnesium and serum calcium should be kept within normal range to reduce the risk of electrocardiogram QT prolongation. Vandetanib

may be administered with drugs known to prolong the electrocardiogram QT interval if there is no appropriate alternative therapy. If such drugs are given to patients already receiving vandetanib, ECG monitoring of the QT interval as appropriate to the pharmacokinetics of the added drug should be performed. Patients who develop a single value of corrected electrocardiogram QT interval of at least 550 msec or a repeated value of at least 500 msec should stop taking vandetanib and be monitored according to the specifics and severity of the situation. Dosing of vandetanib can be resumed at a reduced dose after return of the electrocardiogram QTc interval to baseline status has been confirmed.

5.3.5 Visual findings

After initial reports of changes in color vision in patients treated on the phase II study 08, ophthalmologic examinations were included in Study 58 to assess whether vandetanib is associated with any change in visual pathology, and an external consultant ophthalmologist reviewed the exam findings.

In Study 58, visual adverse events were more common in patients receiving vandetanib than placebo (35.9% versus 12.1%). Unlike rash, diarrhea, and hypertension, these generally occurred after several months on therapy. Most events were CTCAE Grade 1 or 2. The most common visual adverse event reported with vandetanib was blurred vision (8.7%). Of the 159 patients randomized to vandetanib who had an ophthalmology exam, 31% were found to have vortex keratopathy (corneal opacity). None of the 52 patients on the placebo arm who had an ophthalmology exam were found to have vortex keratopathy by the ophthalmology consultant.

Vortex keratopathy, also called corneal verticillata, is commonly reported with other drugs such as amiodarone, chloroquine, meperadine, indomethacin, and tamoxifen, and is recognized at slit lamp examination of the eye by the appearance of fine grayish or brown linear opacities in the epithelial layer of the cornea (Hollander and Aldave 2004). The linear opacities typically branch repeatedly to form a distinctive whorl-like pattern. This finding is typically not associated with significant symptoms and rarely requires discontinuation of the drug. Routine ophthalmologic examinations are not necessary, but patients experiencing visual events should consult with their physician.

5.3.6 Hypothyroidism

Most patients with MTC undergo thyroidectomy to remove the primary tumor, and subsequently receive thyroid hormone replacement therapy. On Study 58, elevations in TSH in association with declines in T4 were commonly seen within the first 3 months after starting vandetanib, and 49% of patients required increases in their T4 replacement.

5.3.7 Cardiac failure

In Study 58, 1 (0.4%) patient in the vandetanib arm had a CTCAE Grade 1 adverse event of cardiac failure (following a CTCAE grade 3 event of abnormal left ventricular function) and 1 (0.4%) patient had a CTCAE Grade 5 SAE of cardiac failure acute during the randomized treatment period; no patients in the placebo arm reported these events. In other studies with

300 mg monotherapy, 0.5% of patients have reported adverse events of cardiac failure or related terms.

5.3.8 Interstitial lung disease (ILD)

ILD has been observed in patients receiving vandetanib. It was reported most commonly in study 32, which investigated the combination of vandetanib 100mg and docetaxel in patients with NSCLC. In that study, ILD was reported more frequently in patients treated with vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9%), and more frequently in patients from Japan (16.7% vandetanib + docetaxel vs. 7.4% docetaxel alone) than outside Japan (0.8% vandetanib + docetaxel vs 0.2% docetaxel alone). The incidence of ILD was <1% in the other 3 NSCLC Phase III studies, including 2 studies with vandetanib 300 mg monotherapy; however those studies, like Study 58, did not recruit in Japan. The increase in the reported frequency of ILD from Study 32 appears to be a consequence of having Japanese patients in Study 32.

In Study 58, there were 2 (0.6%) reports of pneumonitis reported in patients taking vandetanib in the randomized phase and 1 case of ILD in the open label phase, but none of these were considered by the investigator to be related to vandetanib. If a patient presents with respiratory symptoms such as dyspnea, cough and fever, vandetanib should be interrupted and prompt investigation initiated. If ILD is confirmed, vandetanib should be permanently discontinued and the patient treated appropriately.

5.3.9 Reversible posterior leucoencephalopathy syndrome (RPLS)

There have been no reports of RPLS in patients with MTC receiving vandetanib. However, 4 reports of RPLS have occurred in the vandetanib program. Two cases occurred in patients receiving vandetanib in combination with chemotherapy (for NSCLC and for transitional cell cancer), and 2 occurred in pediatric patients with brain tumors receiving concomitant radiotherapy. This syndrome should be considered in any patient presenting with seizures, headache, confusion or altered mental function.

5.3.10 Fatigue

In Study 58, the overall incidence of fatigue was similar between the arms of the study, but there was a higher incidence of CTCAE grade ≥2 and ≥3 fatigue in the vandetanib arm (grade ≥2: 14.4% vs. 10.1%; grade ≥3: 5% vs. 1.0%). The imbalance in CTCAE ≥3 fatigue between the arms was due to events that occurred after 12 months on randomized therapy. The incidence of fatigue and asthenia are similar in the 2 arms (23.8% vs 23.2% fatigue and 14.7% and 11.1% asthenia in the vandetanib and placebo arms, respectively), but the incidence appears to be higher in patients treated with vandetanib beyond 1 year.

5.3.11 Hepatic findings

Adverse events related to abnormal hepatic chemistries were reported more frequently in the vandetanib arm than the placebo arm. These included ALT increased (3.9% vs.1.0%), AST increased (4.3% vs.1.0%), transaminases increased (1.7% vs. 0), and liver function test abnormal (0.4% vs.0.0%). The incidence of adverse events of blood bilirubin increased was

similar (0.4% vs. 1.0%). No patients in Study 58 had both an elevation of ALT of 3 x ULN and an elevation of bilirubin of 2 x ULN.

A laboratory finding for ALT of CTCAE Grade 3 was seen in 1.7% of patients on the vandetanib arm. An increase in ALT of CTCAE grade ≥2 was seen 12% of patients on vandetanib; 75% of those improved without any change in vandetanib dose. No patient in Study 58 discontinued vandetanib because of an ALT elevation. Periodic monitoring of ALT is recommended in patients receiving vandetanib. Patients were not required to stop vandetanib for ALT elevations unless CTCAE Grade ≥3.

5.3.12 Renal findings

In Study 58, 42 patients in the vandetanib arm and 14 patients in the placebo arm experienced a CTCAE grade 1 or 2 increase in creatinine within the first few months of dosing. This may be due in part to blockade of the renal OCT-2 channel, which is responsible for creatinine excretion. No patients had CTCAE Grade ≥3 elevations in creatinine. The increase in creatinine does not appear to be due to intrinsic renal pathology. The increases in creatinine that were reported as events of renal failure or renal insufficiency all had other possible causes such as dehydration, electrolyte imbalance, or nephrolithiasis. There is no evidence of a direct toxic effect of vandetanib on the kidney, other than proteinurea.

Proteinuria has been seen with other VEGF pathway inhibitors, and was an adverse event in 10% of patients in vandetanib in Study 58. However, it was not associated with a higher risk of hypertension, or with other renal pathology.

5.4 Safety in special populations

5.4.1 Gender

In Study 58, the overall safety profile of vandetanib was similar for males and females, although females had a higher incidence of rash (51.5% vs. 40.3%), diarrhea (60.8% vs. 53.0%), hypertension (37.1% vs. 27.6%), and fatigue (29.9% vs. 19.4%). Males receiving vandetanib had a higher incidence of asthenia (17.2% vs. 11.3%). Similar differences were not seen for patients receiving placebo.

5.4.2 Age

In Study 58, there was no major difference in the safety profile for patients aged ≥65 to <75 years compared to those <65 years. A total of 17.8% of patients were ≥65 years of age at baseline, and only 3.0% of patients were at least 75 years old. The incidence of adverse events of asthenia, fatigue, and pneumonia was higher in patients ≥75 years compared to younger patients; however, the small numbers in this age group make firm conclusions difficult.

5.4.3 Race

In Study 58, 95% of patients were Caucasians so no conclusions can be made about safety differences in other races. In other vandetanib studies, there was no evidence of differences in the safety profile between Caucasians and Asians, although there was a higher incidence of

ILD reported in patients with NSCLC in Japan compared to other Asian countries or to the West. There were not enough other minorities enrolled in vandetanib studies to draw any conclusions about differences in the safety profile compared to Asians or Caucasians.

5.4.4 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women using vandetanib. Based on preclinical data, the risk that vandetanib is associated with developmental abnormalities is predicted to be high. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats.

If vandetanib is used during pregnancy or if a patient becomes pregnant while receiving vandetanib, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. Women of childbearing potential must use effective contraception during therapy and for at least three months following the last dose of vandetanib.

There are no data on the use of vandetanib in breast feeding women. Breast feeding mothers are advised to discontinue nursing while receiving vandetanib therapy. Vandetanib was excreted into milk in rat and found in plasma of pups following dosing to lactating rats.

5.4.5 Renal and hepatic impairment

5.4.5.1 Hepatic impairment

Pharmacokinetic data from volunteers suggest that no change in starting dose is required in patients with mild or moderate or severe hepatic impairment. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 x ULN, which is standard for oncology trials and used in this program as a definition of liver impairment). Vandetanib should not be indicated for use in patients with hepatic impairment, as safety and efficacy have not been established.

5.4.5.2 Renal impairment

Clinical data, together with pharmacokinetic data from volunteers suggests that no change in starting dose is required in patients with mild or moderate renal impairment at baseline. A pharmacokinetic study suggests that in volunteers with severe renal impairment, exposure to vandetanib may be increased up to 2-fold. There is limited clinical experience in patients with severe renal impairment, so safety and efficacy have not been established. Patients with mild to moderate renal impairment have a safety profile similar to that of patients with normal renal function.

5.5 Safety in differentiated thyroid cancer

Study 79 was a randomized, placebo-controlled, Phase II study of vandetanib 300 mg in patients with locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy. The study randomized 145 subjects to receive vandetanib

(72 subjects) or placebo (73 subjects). Subjects continued blinded randomized treatment until objective disease progression or until 12 months of stable disease, and then had the option to receive open-label vandetanib.

The median total exposure to vandetanib was 27 weeks, compared to 25 weeks on placebo. At the time of the data cut-off, no patients remained on randomized treatment, and 36 patients were receiving open-label vandetanib.

Adverse Events

Overall, more patients in the vandetanib arm than the placebo arm reported any AE, AEs of CTCAE grade 3 or higher, SAEs, AEs leading to discontinuation of randomized treatment, and SAEs leading to death. The 5 most common adverse events for patients receiving vandetanib were diarrhea (74% vs. 17% on placebo), hypertension (34% vs. 6%), acne (27% vs. 8%), asthenia (26% vs. 22%), and decreased appetite (26% vs. 14%), and each of these events occurred more frequently than in patients receiving placebo. The most common AEs of CTCAE grade 3 or higher on vandetanib were electrocardiogram QT prolonged (14% vs. 0), diarrhea (10% vs. 0), asthenia (7% vs. 4%), and fatigue (6% vs. 0). The most common adverse events leading to discontinuation were electrocardiogram QT prolonged and diarrhea.

Dose reduction to 300 mg/placebo every other day occurred in 21.9% of patients on vandetanib, and 28% on placebo. Discontinuation because of AEs was reported in 32.9% of patients on the vandetanib arm and 5.6% of patients on the placebo arm.

A total of 16.4% of patients in the vandetanib arm had protocol-defined QTc prolongation during randomized treatment. There was one reported case of Torsade de pointes occurring in a patient receiving vandetanib (refer to Section 5.3.4).

The AEs that led to death during the randomized phase were skin hemorrhage (1 report on vandetanib) and pneumonia (1 report each in each arm). Three AEs leading to death were reported during the open-label phase: pancreatitis, pneumonia, and tumor lysis syndrome.

Qualitatively, the side effect profile was similar to that seen in other studies with vandetanib 300 mg monotherapy, although the incidences of diarrhea and of discontinuation due to adverse events were higher than seen in MTC.

5.6 Overall safety conclusions

The side effects of vandetanib are generally consistent with the non-clinical safety findings and related to its pharmacological action as an inhibitor of VEGFR and EGFR. Patients with MTC will require chronic dosing with vandetanib for the treatment of their disease, and hence have longer exposure to the drug than other previously studied patient populations. For example, the median duration of treatment in Study 58 was 1 year 9 months for patients randomized to vandetanib. Most of the adverse events seen with vandetanib initially occur within the first 3-6 months of dosing, with the exception of visual findings and CTCAE grade ≥3 fatigue which generally occur after several months of dosing. However, the higher incidence of grade ≥3 fatigue may be partly related to greater time at risk for events for

patients on vandetanib compared to placebo. There is no evidence of cumulative toxicity in patients treated for more than 1 year. Only 13% of patients discontinued vandetanib for an adverse event, which is similar to the proportion of patients who discontinued vandetanib for an AE on the 2 Phase III NSCLC studies with vandetanib 300 mg monotherapy, even though the median duration of treatment was 10 times longer on Study 58 than on the NSCLC studies. The safety profile on the open-label phase of Study 58 was similar to that seen in the randomized phase.

The safety profile indicates that patients who receive vandetanib will need to have ECGs obtained periodically to assess QT prolongation, and otherwise require standard monitoring that is used for patients on systemic therapies, such as assessments of blood pressure, electrolytes, and renal and hepatic function. The most common AEs in patients receiving vandetanib are diarrhea and rash. Routine anti-diarrheal agents are recommended for the treatment of diarrhea, and serum electrolytes should be monitored if diarrhea develops. Patients with hypertension should be monitored and controlled as appropriate. The exacerbation of rash has been observed in patterns on the body that are commensurate with exposure to sunlight. Care should be taken with sun exposure by wearing protective clothing and /or sunscreen. Where necessary, AEs can be managed symptomatically with standard procedures or by reducing, or stopping the vandetanib dose.

An updated summary of safety with a data cutoff date of 01 June 2010 was prepared in accordance with FDA requirements. This update provides an additional 10 months of follow-up on the patients from Study 58, with an increase in exposure on the randomized phase of the study of 24% for vandetanib and 19% for placebo, compared to the original data cut-off date. There were no changes to the overall safety profile for vandetanib based on the safety update. Table 9 below summarizes the AEs seen in at least 20% of patients in either arm of the study. Despite the longer follow-up period, there is little difference in the incidence of AEs, consistent with the finding that most AEs initially occur in the first 3-6 months of dosing.

Table 9 **Summary of patients who had >=1 AE by PT while on randomized treatment, freq >20%, at the original data cut-off date and at the safety update (Safety analysis set)**

Preferred Term	Vandetanib 300 mg (N=231)		Placebo (N=99)	
	Percent (%) of patients [a]		Percent (%) of patients [a]	
	Original 31 July 2009	Update 1 June 2010	Original 31 July 2009	Update 1 June 2010
Diarrhea	56%	56%	26%	27%
Rash	45%	46%	11%	11%
Nausea	33%	33%	16%	16%
Hypertension	32%	33%	5%	6%
Headache	26%	27%	9%	9%
Fatigue	24%	24%	23%	24%

Preferred Term	Vandetanib 300 mg (N=231)		Placebo (N=99)	
	Percent (%) of patients [a]		Percent (%) of patients [a]	
	Original 31 July 2009	Update 1 June 2010	Original 31 July 2009	Update 1 June 2010
Decreased Appetite	21%	21%	12%	13%

PT = Preferred Term.
The 20% is relevant to either vandetanib or placebo actual treatment group.

6. BENEFITS AND RISK CONCLUSIONS

There is a strong scientific rationale for using vandetanib for the targeted treatment of patients with MTC. Vandetanib is a selective inhibitor of the tyrosine kinases VEGFR2, EGFR, and RET. Activation of RET is the main pathogenic factor in MTC, and VEGF and EGF signalling also play key roles in the pathogenesis of MTC, particularly in patients with advanced disease. The benefit of targeting advanced MTC has been demonstrated by the results of the pivotal Study 58, the largest study ever conducted in MTC. This study demonstrates significant clinical benefit in the primary endpoint of progression-free survival. Importantly for patients with locally advanced or metastatic MTC, who can live quite long with progressive disease, vandetanib has a tolerability profile that allows for dosing of several months to years. Overall, the data presented in this briefing document show a favorable benefit: risk profile for vandetanib in this rare disease with no standard treatment option after failing or being ineligible for surgery.

6.1 Benefits of vandetanib in the treatment of MTC

Vandetanib successfully meets the unmet need for patients with locally advanced or metastatic MTC. MTC can only be cured by surgery. Responses to chemotherapy in patients with unresectable disease are infrequent and of short duration, and therefore chemotherapy is not recommended as a 1st-line treatment for patients with advanced MTC (Kloos et al 2009). There is a need for a convenient therapy that can be given over several months to provide a sustained efficacy benefit. Up to 90% of patients with unresectable tumor will ultimately die of progressive disease. Therefore, a high response rate (assessed independently), durable response, reduction in the rate of progression, and increase in median PFS by approximately 11 months represent clinical benefit for patients with MTC. The objective responses observed with open label treatment in subjects initially treated with placebo further demonstrates the activity and benefit of vandetanib in patients with advanced MTC. This further validates generalizability of results to the population intended to be treated, ie unresectable locally advanced or metastatic MTC.

In Study 58, the primary endpoint of PFS showed a benefit that is compelling and robust, based on an independent, blinded central review in patients with advanced or metastatic disease. The study demonstrated a large, clinically meaningful and statistically robust

advantage for vandetanib over placebo in PFS (HR=0.46), using an ITT analysis including all randomized patients, and using the central read to assess progression. This represents an approximately 11 month delay to the median PFS (predicted to be approximately 30 months for vandetanib). The pre-specified sensitivity analyses were all consistent with the primary analysis of PFS. While it is expected that there will be differences between the site and central reads for individual patients, there was no difference in the rate at which investigators called progression early compared to the central reviewers. Therefore, the PFS benefit according to the investigator's review (HR=0.40) that excluded scans from the open-label phase is likely to be reflective of the underlying benefit of vandetanib. There were some differences noted in the number of patients censored early, however further analyses that explored their potential impact were supportive of the primary analysis.

Patients selected for inclusion in the phase III study were required to have at least 2 cm measurable disease and a CTN level of at least 500pg/ml. These criteria were selected to identify the patients with more advanced disease that would require therapy. Within this study population, the protocol defined pre-specified subgroup analyses, all of which demonstrated a consistent benefit in each of the subgroups of clinical relevance. The data show that both patients with aggressive disease and those with more indolent disease have a benefit in PFS. For example, PFS was prolonged in patients who had more aggressive disease based on a CTN or CEA doubling time <24 months (HR=0.31 and 0.19, respectively), and also in patients with longer CTN and CEA doubling times (HR=0.56 and 0.81, respectively). Objective tumor response rates of at least 37% were also seen in each of these doubling time subgroups. Patients also had benefit regardless of whether they had prior therapy for MTC (HR=0.49 for patients with no prior therapy; HR=0.43 for patients with ≥1 prior therapy), indicating that vandetanib is appropriate as a first-line therapy. Males and females had similar benefit (HR=0.46 and 0.44, respectively). There were insufficient numbers of patients with locally advanced (non-metastatic) disease to draw any conclusions, but the low numbers may be because most patients with unresectable disease that would be considered for systemic therapy have metastases. However, there are no biologic reasons to expect that the activity of vandetanib would be different in patients with locally advanced disease, compared to those with metastatic disease. There were also very few patients that were not Caucasian, but there are no known genetic differences in MTC between different races that would predict a differential benefit.

Vandetanib inhibits 3 key targets that are relevant in MTC: RET, EGFR, and VEFGR2, but the relative contribution of each of these targets cannot be determined from the current data. It is likely that RET inhibition plays the most important role, given the importance of RET activation in the pathogenesis of MTC, and this may explain why the efficacy benefit of vandetanib in MTC is so striking compared to the more modest activity seen in other tumors such as NSCLC. Mutation in RET, as assessed in this study, does not appear to be necessary for patients to benefit from vandetanib. The ARMS assay and the additional 6 sequencing assays were not successful for all patients, and therefore 41% of samples were classified as being RET mutation unknown. The protocol criteria to classify a patient as being RET mutation negative were quite stringent, as failure of any one of the assays would classify a patients as RET mutation unknown, even if all of the other assays showed wild-type sequence.

There is clear benefit in the patients who are known to have a RET mutation (HR=0.45), but no definitive conclusions can be reached for patients who do not have a RET mutation, according to the methodology used in study 58, as there were only 2 patients in the vandetanib arm who were RET mutation negative, and only one of those progressed. One RET-negative patient had an objective response on open-label vandetanib after having been randomized to placebo. Patients whose mutation status is unknown have clear benefit (HR=0.49); 53% of patients with sporadic disease who had unknown mutation status were known to have wild-type sequence at codon 918, the most common site of mutations in sporadic MTC. Patients without a mutation may have activation of wild-type RET, which is also inhibited by vandetanib, or may have a stronger dependence on other signaling pathways such as EGFR. The current standard of care does not require testing for somatic RET mutations in patients with MTC (Kloos et al 2009), and the current data, which demonstrate clear benefit even if mutation status is unknown, and the potential limitations of the assay indicate that vandetanib should be used regardless of RET mutation status.

The data from Study 58 shows consistent benefits across other efficacy endpoints. A total of 45% of patients randomized to vandetanib had an objective tumor response in Study 58. This is particularly remarkable when considering that MTC has typically been refractory to most chemotherapy agents, which only give response rates up to 20% in small, uncontrolled studies (Kloos et al 2009). The responses to vandetanib are durable, and the median duration of response is at least 18 months in Study 58. The side effects of vandetanib can be managed by dosing to tolerance for most patients to allow for a long duration of response. Subjects were on oral, self-administered treatment for prolonged period of time, and the rate of discontinuation of treatment for adverse events was low (13%) and not different than that observed in studies with shorter treatment duration for subjects with NSCLC. There was no difference in overall survival at the time of the primary analysis for the study. The survival data are immature, as only 15% of patients had died, and there is a planned final analysis for survival once at least 50% of patients have died. It is anticipated that this will not occur before 2012, and the outcome will continue to be confounded by patients receiving open-label vandetanib after having been randomized to the placebo arm.

Improvements in PFS, response rate, and biochemical markers would be expected to result in an improvement in the signs and symptoms associated with MTC. One of the important symptoms for patients with MTC is pain. The time to worsening of pain (TWP) was the pre-defined endpoint to assess symptomatic benefits and was a composite endpoint to account for changes in opioid analgesic use. Vandetanib shows a significant improvement in TWP over placebo (HR=0.61), with a delay in the median TWP of 4.6 months. The benefit was seen regardless of whether patients were taking more or less than 10 mg of opiate equivalents at baseline. Definitive conclusions based on these data is difficult given the compliance rates for the pain assessments of approximately 50% over the course of the study, but the observations are consistent with the benefits seen in the objective, blinded, and independent radiographic assessments.

The 300 mg dose was chosen for Study 58 based on favorable efficacy and safety data from the Phase II study 08, which showed that vandetanib 300 mg causes tumor responses and has

acceptable tolerability over chronic dosing in patients with advanced hereditary MTC. Pre-clinical and Phase I data indicate that 300 mg is the optimal dose for vandetanib, as the greatest anti-tumor effect is obtained by maximizing inhibition of the molecular targets of vandetanib, and the highest dose that can be given with daily dosing in patients is 300 mg. Dose reductions may be required to maintain tolerability, but starting at 300 mg allows for the greatest potential efficacy benefit. Adjusting the dose for tolerance should be encouraged, as it allows those patients who do not develop significant side effects to stay on the highest dose of vandetanib and thereby derive the maximum potential benefit, and permits patients who develop toxicity to control it by changing to a lower dose. The data from Study 58 show that patients who dose reduced to 200mg or 100mg were able to stay on the lower dose for a median of 5.3 months or 6.7 months, respectively. This strategy is effective in allowing patients to stay on the drug even with chronic dosing, as the discontinuation rate for adverse events was 13% in Study 58, with a median duration of therapy of 1 year 9 months, which is similar to the discontinuation rate in the Phase III monotherapy studies in NSCLC, where the median duration of treatment was only 8-9 weeks.

The Phase II Study 68 was conducted in parallel with the Phase III Study 58 to assess whether there is any efficacy of a lower 100 mg dose of vandetanib in patients with MTC. Study 68 had a similar design to Study 08, with no control group and enrolling patients with only the hereditary form of MTC. No formal comparison of data from Studies 08 and 68 was conducted, but the response rates were similar, 20% in Study 08 and 16% in Study 68. The duration of response was 10.2 months in Study 08 and 5.5 months in study 68. A greater proportion of patients in Study 08 had declines in CTN or CEA: 80% for CTN and 53% for CEA in Study 08, and only 16% for CTN and 3% for CEA in study 68. Overall, these data are consistent with the hypothesis that vandetanib 100 mg and 300 mg are active doses in MTC, but that a greater level of activity is seen at 300 mg, and the data from Study 58 show clearly that the 300 mg dose provides significant benefit and allows for dosing to tolerance.

6.2 Risks of vandetanib in MTC

There are a number of side effects that may occur with vandetanib, and patients and their physicians need to be aware of these and the means that can be taken to avoid or manage them. The median duration of treatment on vandetanib was 1 year and 9 months at the time of the data cut-off, and there is little evidence of cumulative toxicity over time, as the prevalence of CTCAE $\geq$2 and CTCAE$\geq$3 events remains stable at 30% and 10%, respectively, after the first 3-6 months, and the safety update 10 months after the original data cut-off showed minimal increases in the incidence of common adverse events. Almost half of the patients randomized to vandetanib who had disease progression and who were eligible to receive open-label vandetanib after progression elected to do so, suggesting that they were tolerating the side effects at that time. Dose reductions were also uncommon after 10 months on treatment, and the rate of discontinuation for adverse events (13%) was similar to that seen in Phase III studies of vandetanib 300 mg in NSCLC, even though the median duration of treatment was 10 times longer in patients with MTC.

Almost 90% of patients may be expected to develop a skin reaction of some sort while on vandetanib, although the prevalence of skin reactions in the treated population reaches a

maximum at approximately 70% for all grades and 20% for grade ≥2 in the first 3 months of dosing and then declines over time. In many cases, this rash is similar to the rash seen with other EGFR inhibitors, and there have been several publications providing guidance on the management of these rashes (Shah et al 2005, Robert et al 2005). One type of rash that is idiosyncratic for vandetanib is a photosensitivity reaction, with some patients developing a rash only in sun-exposed areas. Patients who are taking vandetanib should be cautioned to avoid sun exposure, and to use protective clothing and/or sunscreen when outside. Although the overall incidence of rash is high, only 6.9% of patients developed a grade 3 or 4 rash (including all types of rash), and skin reactions do not become more common with chronic dosing.

Another of the common side effects that patients with MTC may experience on vandetanib is diarrhea, reported in 56% of patients at all grades, and in 30% at grade ≥2. As with rash, the prevalence of diarrhea is lower than the incidence, and remains stable at 40% for all grades and 15% for grade ≥2 after the first month of dosing. Diarrhea is one of the frequent symptoms of MTC, especially in patients with high CTN levels, and was the most common CTCAE grade 3-4 event reported in patients receiving vandetanib in Study 58 (11% of patients). However, only 1% of patients discontinued vandetanib because of diarrhea. Diarrhea can be controlled with the use of loperamide, or with dose reduction if necessary. Patients who experience severe diarrhea should have electrolytes monitored to avoid abnormalities that could increase the risk of QTc prolongation.

The definition and management of QTc prolongation was defined in consulation with internal and external cardiologists as well as with the FDA. Prolongation of the QT interval using Bazett's correction was defined as a single value of ≥ 550msec or > 100msec increase over baseline , or a confirmed prolongation of the QTc interval to ≥500 msec, or an increase from baseline of ≥60 msec to a level ≥480 msec. QTc prolongation occurred in 8% of patients receiving vandetanib on Study 58. This was consistent with the frequency seen in other studies with vandetanib 300 mg. There have been approximately 5000 patients treated with vandetanib in clinical studies, and at least 2000 at the 300 mg dose. Of those, there have been 2 reports of documented Torsade de pointes, both of which occurred in patients taking vandetanib 300 mg. These 2 patients had other concomitant factors that also increased the risk of QTc prolongation, and in both cases the patients recovered. The risk of Torsade de pointes can be managed by ensuring a QTc value <480msec before starting the drug, periodic ECG and electrolyte monitoring, and avoiding concomitant medications that also have a risk of QTc prolongation where possible. The PK-PD modelling predicts that QTc prolongation is unlikely after the first 6 weeks on treatment, but this event may occur at any time, particularly in patients with significant electrolyte abnormalities.

Other than ECGs, monitoring for patients is similar to the assessments required for patients on other systemic therapies. Blood pressure should be followed regularly and anti-hypertensives used to manage hypertension. Electrolytes and renal and hepatic function can be assessed using routine blood tests; abnormalities in these findings rarely require intervention. Patients with MTC generally require routine monitoring of TSH to manage their thyroid hormone replacement, and investigators should be aware that some patients on vandetanib will require

adjustment of the thyroxine dose while on vandetanib. Mild visual findings may occur in patients on vandetanib after several months on therapy, but these are not associated with significant corneal pathology; ophthalmology examinations can be considered for any serious visual problems. Finally, physicians should be aware of some less common, but potentially severe adverse events that have been seen on patients taking vandetanib. ILD has occurred primarily in studies of vandetanib in NSCLC (with most reports in Japan), RPLS has occurred rarely, and heart failure has also been reported infrequently, including in one patient who died in Study 58. There is no specific monitoring required for these, but physicians should be aware of the signs and symptoms that may warrant further investigation.

6.3 Overall benefit-risk assessment

MTC is a rare disease with no effective or approved therapy for patients with unresectable locally advanced metastatic disease. Vandetanib has shown a compelling benefit in PFS across all subgroups examined, with HR=0.46 and an approximately 11 month improvement in median PFS. Almost half of all patients treated with vandetanib experienced durable objective tumor responses, and there were significant delays in the time to worsening of pain. Subgroup analysis demonstrated a consistent PFS benefit across all patient subgroups, which supports the use of vandetanib in all patients in this population. The pivotal study to support the indication is the largest study ever conducted in this rare disease, and clearly identifies the benefit of vandetanib and supports the rational targeting of unresectable locally advanced or metastatic MTC with this drug. By dosing to tolerance, the starting dose of 300 mg can be reduced as necessary to manage side effects and to avoid discontinuing the drug to maintain the maximum possible efficacy benefit over many months to years. Thus, vandetanib meets the unmet need of patients with unresectable locally advanced or metastatic MTC for a treatment with clear and consistent benefits, a manageable safety profile that allows for chronic dosing, and a favorable benefit-risk profile.

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