17 November 2011

EMA/128076/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Caprelsa

vandetanib

Procedure No.: EMEA/H/C/002315//0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Invented name of the medicinal product:	Caprelsa
Applicant:	AstraZeneca AB AstraZeneca European Regulatory Affairs (ERA) Building 411A Floor 4 S-151 85 Södertälje Sweden
Active substance:	vandetanib
International Nonproprietary Name/Common Name:	vandetanib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE12)
Therapeutic indication:	Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. 'For patients in whom rearranged during transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1)).
Pharmaceutical form:	Film-coated tablet
Strengths:	100 mg, 300 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PVDC/alu)
Package size:	30 tablets

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List of abbreviations

AEs	Adverse Events
ALT	ALanine AminoTransferase
AST	ASpartate aminoTransferase
ATP	Adenosine TriPhosphate
AUC	Area under the plasma concentration time curve
bFGF	basic Fibroblast Growth Factor
BOR	Best Objective Response
BPI	Brief Pain Inventory
BRK	Breast Tumour Kinase
CEA	CarcinoEmbryonic Antigen
Cmax	Maximum observed plasma concentration
CNS	Central Nervous System
CR / PR	Complete response / partial response
CTN	Calcitonin Levels
CYP	Cytochrome P450
DCR	Disease Control Rate
DOR	Duration of response
EGFR	Epidermal Growth Factor Receptor
ECOG PS	Eastern Cooperative Oncology Group performance status
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy General Scale
FGF	Fibroblast Growth Factor (bFGF is basic fibroblast growth factor)
FGFR	Fibroblast Growth Factor Receptor (family members include FGFR-1, -2, -3, -4)
FMO	Flavine containing Mono-Oxygenase
GCP	Good clinical practices
GLP	Good Laboratory Practice
HR	Hazard ratio
HEK	Human Embryonic Kidney
hERG	human Ether-a-go-go-Related Gene
HPAEC	Human Pulmonary Artery Endothelial Cells
HPLC-MS/MS	High Performance Liquid Chromatography tandem Mass Spectrometry
HPMC	HydroxyPropylMethylCellulose
HUVEC	Human Umbilical Vein Endothelia Cell
IC50	Concentration that reduces the effect by 50%
LC-MS/MS	Liquid Chromatography tandem Mass Spectrometry
LSC	Liquid Scintillation Counting
ITT	Intent to treat
MAA	Marketing Authorisation Application
MDR1	Multi Drug Resistance 1 transporter
MEN	Multiple Endocrine Neoplasia
MLEC	Mouse Lung Endothelial Cells
MTC	Medullary Thyroid Cancer
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NE	Not evaluable
NRTK	Non-Receptor Tyrosine Kinase
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic

PP	Per protocol
PR	Partial response
PRO	Patient reported outcome
PPI	Patient's pain intensity
PTC	Papillary Thyroid Cancer
QoL	Quality of Life
QTcV	Heart rate corrected QT interval (Van der Waters correction)
QWBA	Quantitative Whole Body Autoradiography
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during Transfection receptor (proto-oncogene)
RTK	Receptor Tyrosine Kinase
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable disease
T1/2	Half life
TK	Tyrosine Kinase
TKIs	Tyrosine Kinase Inhibitors
TDPS	Time to Decline in WHO Performance Status
Tmax	Time of maximum observed plasma concentration
TTC	Threshold of Toxicological Concern
TTOU	Time To Opioid analgesic Use
TWP	Time to Worsening in Pain
ULRR	upper limit of reference range
VDss	Volume of Distribution at steady state
VEGF	Vascular Endothelial Growth Factor(4 family members: -A, -B, -C and –D)
VEGFR	Vascular Endothelial Growth Factor Receptor (3 family members: -1, -2 and -3)
VEGFR-2	Vascular Endothelial Growth Factor Receptor-2
TTP	Time to tumour progression
WHO PS	World Health Organization Performance Status
ZD6474	vandetanib

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 1 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Caprelsa, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was initially agreed upon by the EMA/CHMP on 23 March 2010 and subsequently on 20 September 2010.

The applicant applied for the following indication: Vandetanib is indicated for the treatment of adult patients with unresectable locally advanced or metastatic medullary thyroid cancer

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/94/2008 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000052-PIP01-07 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Derogation(s) of market exclusivity

Not applicable.

Conditional marketing authorisation

In accordance with Article 3 (2) of Regulation EC No 507/2006, the CHMP proposed the application to be considered for a Conditional Marketing Authorisation based on the following claim(s):

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

Based on the randomized, double-blind, placebo-controlled study presented in patients with unresectable locally advanced or metastatic MTC, the superiority of vandetanib was demonstrated compared to placebo, with a 11.2 months increase (19.3 vs 30.5 months) of median PFS (HR=0.46,

95% CI, 0.31 to 0.69, p=0.0001). The benefit risk balance of vandetanib in patients with unresectable locally advanced or metastatic MTC is therefore considered to be positive.

From a quantitative point, of view, the specific benefit in patients with RET - tumours might be less as compared with what was observed in RET+ tumours. There is a need to further confirm such differences in terms of efficacy in RET negative patients with vandetanib,

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

The applicant claimed that it is likely to be in a position to provide the comprehensive clinical data from an open label study with vandetanib in patients with sporadic medullary thyroid cancer with known RET mutation status that will support the efficacy and safety of the phase III study D4200C00058. The applicant stated that the final analysis of the core phase of this study is planned for Q4 2015.

- Unmet medical needs to be fulfilled.

The applicant claims that there is a lack of approved and effective pharmacological treatment other than thyroidectomy for MTC patients and that there is a need in the MTC patient population that could be fulfilled with the proposed medicinal product.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The applicant claimed that the potential risks inherent in marketing vandetanib for the specific indication, while additional, more comprehensive data will be available in the future, would be offset by the potential benefit to the patients whose only treatment option currently available is surgery. The RMP for vandetanib in the approved indication is considered as adequate to address any identified and unknown risks.

New active Substance status

The Applicant requested the active substance vandetanib, contained in the above medicinal product, to be considered as a new active substance in itself.

Scientific Advice/Protocol Assistance

The Applicant received Scientific Advice and Protocol Assistance from the CHMP on 18 November 2005 and 2 June 2006. The Scientific Advice and Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pierre Demolis** Co-Rapporteur: **Barbara van Zwieten-Boot**

- The application was received by the EMA on 1 September 2010.

- The procedure started on 22 September 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2010.
- During the meeting on 20 January 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 January 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2011.
- The summary report of the inspection carried out at the following sites Centre Léon Bérard, Service de Médecine Nucléaire and Hamatologie/Onkologie between 15 March – 8 April 2011 was issued on 31 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 June 2011.
- During the CHMP meeting on 23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- During a meeting of a SAG on 8 September 2011, experts were convened to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 and 28 September 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 October 2011.
- During the CHMP meeting on 20 October 2011, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 November 2011
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 09 November 2011 recommending the granting of a conditional marketing authorisation.
- During the meeting on 14-17 November 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Caprelsa on 17 November 2011.

2. Scientific discussion

2.1. Introduction

Medullary Thyroid Carcinoma

Carcinoma of the thyroid is the most common malignancy of the endocrine system and include mostly (85%–95%) well-differentiated tumors (papillary or follicular), about 2.5% to 10% of thyroid cancers are medullary carcinoma and other are anaplastic, both of which carry a worse prognosis for patients. MTC is a distinct subtype, arising from the parafollicular cells (C-cells) of the thyroid, that has particular prognostic and genetic features: it presents mainly as a sporadic cancer (75% of cases) or as part of a hereditary syndrome (25%).

- The hereditary form of MTC is a rare disease commonly diagnosed in patients <20 years and characterised by Multiple Endocrine Neoplasia (MEN) with complete penetrance (virtually all patients develop MTC), but variable expressivity: Multiple Endocrine Neoplasia (MEN) type 2a, MEN type 2b, or Familial Medullary Thyroid Carcinoma (FMTC). Only 50% of patients with MEN2a and MEN2b, develop pheochromocytoma and 30% of patients with MEN2a develop parathyroid hyperplasia). All of the patients with MEN2b develop a typical ganglioneuromastosis throughout the aerodigestive tract. Patients with FMTC develop only MTC). Patients with hereditary MTC carry a germline mutation of the RET gene, leading to constitutive activation of the RET tyrosine kinase.

- The sporadic form of MTC most often presents in middle-aged patients as a solitary nodule in the thyroid. RET was found to be mutated in some tumors of patients with sporadic MTC, and 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.

Symptoms and Prognosis

Patients with MTC often have localization to the neck and mediastinum. Main symptoms are mostly diarrhoea, pain, opiod use, fatigue, respiratory symptoms, flushing, weight loss and dysphagia. Metastatic MTC spreads most often to the regional lymphatics as well as to the liver, lungs, and bones. Metastases can be anticipated by increasing levels of calcitonin and are often evident on radiographic imaging studies.

The 5-year survival for medullary cancer with regional spread is about 78%. For medullary cancer which spread to distant sites or lymph node the 5-year survival rate is approximately 40% and median overall survival is 2-3 years in patients with distant metastatic disease. Approximately 35% of patients present with tumor extending beyond the thyroid with regional lymph node involvement, and 13% have metastatic disease at initial diagnosis. Metastatic disease is the most common cause of death in patients with MTC, and approximately 90% of patients with metastatic disease die of progressive cancer.

Patients with the hereditary form of the disease generally have a better prognosis than patients with the sporadic form. However, if patients are matched for age and disease stage, no differences in survival are seen, suggesting that patients with sporadic disease may be diagnosed later with more advanced disease.

Treatment

Patients with MTC can be cured only by thyroidectomy, performed when the tumour is confined to the thyroid gland. The tumour is relatively unresponsive to conventional doses of radiation therapy and to chemotherapeutic regimens (none of which have been approved in this indication yet).

About the product

Caprelsa, vandetanib, is an orally administered tyrosine kinase inhibitor (TKI) with activity against the Rearranged during transfection (RET) proto-oncogene, the Vascular endothelial growth factor receptor (VEGFR) and Epidermal Growth Factor Receptor (EGFR).

Initially, the Applicant claimed vandetanib was indicated for the treatment of adult patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Subsequently, as a result of the evaluation procedure, the approved indication states as follows:

Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1).

Treatment should be initiated and supervised by a physician experienced in treatment of MTC and in the use of anticancer medicinal products and experienced in the assessment of electrocardiogram (ECG). Only one supply per prescription is allowed. For a further supply, a new perscription is required.

The recommended dose is one 300 mg tablet once a day, taken with or without food at about the same time each day.

If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Patients treated with Caprelsa must be given the patient alert card and be informed about the risks of Caprelsa.

Vandetanib may be administered until patients with MTC are no longer benefiting from treatment.

QTc interval should be carefully assed prior to initiation of treatment. In the event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. The 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary. The patient must be monitored appropriately. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly.

2.2. Quality aspects

2.2.1. Introduction

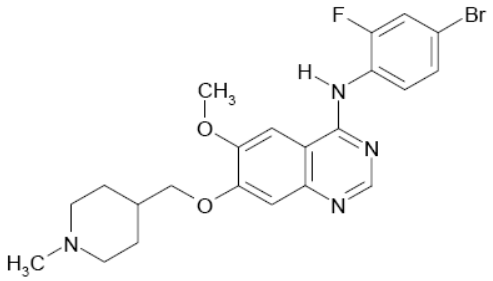
Caprelsa contains the active substance vandetanib. For other ingredients see the SmPC. The product is formulated as immediate release tablets of two strengths. The 100 mg strength is presented as a round, biconvex, white, film-coated tablet with 'Z100' impressed on one side; the other side is plain.

The 300 mg strength is presented as an oval-shaped, biconvex, white, film-coated tablet with 'Z300' impressed on one side; the other side is plain.

The product is packaged in PVC/PVDC/alu blisters.

2.2.2. Active Substance

The chemical name of the active substance is N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl) methoxy] quinazolin-4-amine.



The corresponding molecular formula is $C_{22}H_{24}BrFN_4O_2$, molecular weight is 475.36 g/mol. The compound is achiral.

The structure of vandetanib was confirmed by elemental analysis, mass spectrometry, infra red spectroscopy, nuclear magnetic resonance spectroscopy, ultraviolet spectroscopy, differential scanning calorimetry and X-ray crystallography.

Vandetanib is a white to off-white powder. The substance exhibits pH-dependent aqueous solubility (with best solubility at acidic pH) and is defined as class II (low solubility/high permeability) under the Biopharmaceutics Classification System (BCS). Vandetanib shows varied solubility in organic solvents (sparingly soluble in tetrahydrofuran and ethanol, slightly soluble in ethylacetate, very slightly soluble in acetonitrile).

Manufacture

The applicant decided to use some elements of quality by design (QbD) approach for the active substance synthesis. The manufacture of vandetanib is a seven step process starting from three starting materials. Three intermediates are key intermediates; however, only one of them is routinely controlled. Specifications for starting materials and this intermediate have been adequately justified. Regarding the other isolated intermediates, suitable specifications for skip testing have been set.

A design space with respect to impurities formation has been defined for each of the intermediates. No critical process parameters were identified, as the level of impurities remained well below the tolerated levels at all times. Consequently, the ranges established during the screening have been considered as proven acceptable ranges.

The design space boundaries have been established using a combination of prior knowledge, significant manufacturing experience and experimentation in conjunction with science-based risk management processes. The vandetanib design space boundaries are justified based on an examination of all the information from the development of the vandetanib synthetic process, the manufacture of clinical trial batches and extensive systematically designed multi factorial studies.

For the purification step of vandetanib, the applicant has also described the approach to determine process parameters and identified the region of thermodynamic stability of anhydrate. Process parameters for the distillation and residual water post-distillation have been set and impurity interaction experiments have been performed. Based on these additional data, the boundaries of the design space for the purification step correspond to the ranges explored in the design of experiments.

The applicant has agreed to verify at commercial scale any movement of the manufacturing process to a different area of the design space, other than the area of the design space already authorised, according to the agreed process verification protocol.

Specification

A number of critical quality attributes (CQA) for the active substance were considered during the establishment of the proposed vandetanib design space. Some of the CQAs are controlled in the active substance specification – these are description, identification, assay, purity, contents of residual solvents, sulphated ash and particle size. For the rest of CQAs a justification why this is not necessary was provided.

Vandetanib is routinely controlled by in-house monograph which includes appearance, identification, assay, organic impurities, residual solvents and particle size. An exhaustive discussion has been provided on impurity profile; detailed information was provided for intermediates, reaction by-products and the active substance degradants. The impurity limits are considered safe, based on toxicology data. Absence of routine control of starting materials, potential genotoxic impurities, residual solvents and heavy metals has been sufficiently justified by additional data.

Analytical methods used for the active substance control have been sufficiently described and appropriately validated.

Batch results starting from early development batches were provided. Recent production batches were manufactured within the proposed design space limits at the set points. All results conform to the active substance specification.

Stability

Stability studies according to the relevant EU/ICH stability guidelines have been submitted with late development batches. Based on stability results submitted up to 48 months at long term conditions, a retest period of 60 months can be granted with the special storage "stored in the primary packaging protected from light".

Vandetanib solid is found to be stable to both thermal and hydrolytic degradation but a small degree of degradation is observed under stressed photolytic conditions. In solution, vandetanib is degraded under acidic, oxidative and light stress conditions but it is stable under basic conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

All excipients, used in the finished product manufacture, are of compendial quality. Dibasic calcium phosphate dihydrate and microcrystalline cellulose are used as fillers, crospovidone as disintegrant, povidone as binder and magnesium stearate as lubricant. Purified water is used in wet granulation but

is not present in the finished product. The tablets are film-coated with a mixture of hypromellose, polyethylene glycol, titanium dioxide and purified water.

The applicant proposed to have flexible range in the amount of some of the excipients (dibasic calcium phosphate dihydrate, microcrystalline cellulose, magnesium stearate and the film coating). This, however, was only accepted for magnesium stearate and the film coating, based on the knowledge gained during the development. The amounts of dibasic calcium phosphate dihydrate and microcrystalline cellulose have been fixed during the procedure.

Physicochemical properties of the active substance and its compatibility with the excipients were extensively studied. Pharmaceutical development of the finished product contains QbD elements.

Both the formulation and manufacturing development have been evaluated through the use of design of experiments including the risks identified during risk assessments. A design space has been defined for the wet granulation and the dry granulate milling. Critical process parameters forming the design space are clearly set and found acceptable. Particle size reduction of vandetanib is performed prior to the finished product manufacture. Particle size within the set specification limit does not affect dissolution performance of the tablets. Data from process screening also demonstrated that dissolution performance is not affected by tablet hardness.

It has been demonstrated that dissolution is not critical for the *in vivo* performance, as the limiting factor for bioavailability is the absorption rate. Several tablet variants were prepared and tested for dissolution behaviour. In vitro dissolution tests can differentiate between these variants; however, as seen from their *in vivo* behaviour in a clinical study, they can be considered bioequivalent.

Dissolution experiments were conducted at varied conditions for the pH and use of surfactant. Dissolution rate is related to disintegration time. A discriminating dissolution method has been developed.

Adventitious agents

No materials used in the manufacture of the finished product are of human or animal origin. Magnesium stearate is of vegetable origin.

Manufacture of the product

Conventional wet granulation approach was selected as vandetanib has sub-optimal compression properties and is incorporated into the tablets in a high load. Risk assessment of individual manufacturing steps and their impact on the quality of the product was performed.

Both tablet strengths are manufactured from the common granulate.

The manufacturing process starts with dispensing of the ingredients which are then dry mixed. The mixture is granulated with purified water, the wet mass is de-lumped on a screening mill and the granulate is dried. The dried granulate is afterwards mixed with magnesium stearate and compressed into tablet cores. The tablet cores are film-coated in a coating pan. The finished product is packed into blisters.

In-process controls are performed at each step of the manufacturing process as part of the overall control strategy; the critical process parameters are tested to ensure that the product is manufactured inside the design space. Non-critical in process controls are performed to confirm continuous quality of the product on-line and to reduce testing at release. The batch size has been defined.

Traditional approach has been followed with respect to manufacturing process validation.

The manufacturing process was sufficiently described and validated to the extent required for the marketing authorisation approval. At the time of the CHMP Opinion the proposed design space was only partly verified at commercial scale. Only a target area of the restricted approved design space has been verified. This is acceptable and no concerns are raised about the capability and reproducibility of the manufacturing process, when operating in this target area. However if the applicant wishes to move to other areas of the design space, then this move should be verified with an appropriate verification scheme. It should be noted that the currently approved verification scheme has a limited value in assessing the risk of such moves. Therefore prior to moving to areas of the design space not already verified, the applicant needs to submit a revised verification scheme (submitted as a variation in section 3.2.R), including consideration of the requirement for a running-in period based on the assessment of the risk attributed to new areas of the design space.

Product specification

The critical quality attributes were defined: identity, assay, degradation products, uniformity of dosage units, dissolution and microbial purity. These are also specification parameters, together with description.

Reduced finished product testing approach, based on the results of real time testing, has been proposed for the release testing. The dissolution test will not be performed routinely at the time of release as it is controlled via the GSA and disintegration in-process tests. Nevertheless, it will be performed on stability. The uniformity of dosage units by weight variation will not be performed routinely either; however, all batches would comply with the limit if tested. The test for microbial purity has been included in the finished product control strategy. All batches would pass the test if tested.

The reduced testing at release has been accepted in principle. However, it cannot be applied before the outcome of the running-in period is available. Release testing frequency will be revised through a risk assessment process, based on the outcome of the proposed running-in-period scheme (i.e. full testing for five commercial batches per strength). The switch from parallel testing to reduced testing will be done through a variation.

Adequate descriptions of the in-house analytical methods are given. The methods are appropriately validated. Batch results starting from development batches and including clinical batches produced at the proposed commercial manufacturing site, have been provided. All results comply with the finished product specification.

Stability of the product

Three batches of vandetanib 100 mg tablets and three batches of 300 mg tablets manufactured at production scale at the commercial site were stored in the proposed commercial packaging, i.e. PVC/PVDC/alu blisters. The tablets were also tested in bulk and at stressed conditions (high temperature, light).

Samples have been tested at each time point for description, assay, dissolution, degradation products and water content. In addition, microbial purity has been tested annually.

The stability studies have been performed according to EU/ICH guidelines on stability. All parameters remained within specification during the stability testing at all storage conditions. Slight increase in water content and decrease of dissolution was observed at accelerated and intermediate conditions; no other trends are detected. No degradation was seen in the samples.

Stability studies support the shelf-life as defined in the SmPC. No special storage conditions are needed.

Comparability Exercise for Finished Medicinal Drug Product

N/A

GMO

N/A

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Initial major objections related to the design space for both the active substance and the finished product have been satisfactorily solved. The design space has been partly reduced as compared to the initial application. The boundaries of the design space are now adequately set to ensure desired quality of the finished product.

The quality of the product is considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development program comprises of pharmacology, pharmacokinetic and toxicology studies which have been performed in accordance with Good Laboratory Practices (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics *in vitro*
Vandetanib potently and selectively inhibited VEGFR-2, EGFR and RET kinase activity, which are 3 key targets in MTC.

Vandetanib more effectively inhibited phosphorylation of EGFR/L858R mutants (substitution of Leucine at codon 858 with Arginine) than wild-type EGFR. Phosphorylation of the gatekeeper mutants, EGFR/T790M (substitution of Threonine at codon 790 with Methionine) and RET/V804, showed decreased sensitivity to Vandetanib.

In *in vitro* model of angiogenesis, Vandetanib inhibited VEGF-stimulated endothelial cell migration, proliferation, survival and new blood vessel formation.

Primary pharmacodynamics *in vivo*
In vivo, Vandetanib significantly reduced VEGF-induced and tumour cell-induced angiogenesis, tumour vessel permeability and tumour microvessel density, and inhibited tumour growth and metastasis in human and murine xenograft and orthotopic models of cancer.

In various human tumour xenograft models in mice, Vandetanib significantly inhibited tumour growth and angiogenesis and induced tumour regressions. These anti-tumour effects became more pronounced as the dose increased and were independent on tumour size at the start of treatment. When treatment was stopped tumours rapidly re-grew, but growth was re-inhibited when treatment was restarted, indicating that tumours remain responsive to Vandetanib without developing resistance and that sustained treatment with Vandetanib is required to maintain inhibition of tumour growth.

In the PC-9 human lung cancer model, Vandetanib produced a more sustained anti-tumour effect, whereby PC-9 tumours did not re-grow when treatment was stopped. The antitumor activity and inhibition of angiogenesis was enhanced when Vandetanib was given in combination with taxanes.

The 2 metabolites of Vandetanib, N-desmethyl and N-oxide Vandetanib, showed similar inhibitory activity against both VEGFR-2, VEGFR-1, EGFR and FGFR-1 compared to Vandetanib. The N-oxide metabolite was less potent than the N-desmethyl metabolite against all kinase enzymes.

Vandetanib showed broad-spectrum antitumour activity in vivo. This antitumour activity extended to a range of models (subcutaneously or orthotopically implanted human tumour xenografts or syngeneic murine tumours) and histological types, including lung, colon, breast, prostate, ovarian, glioma, head and neck.

Secondary pharmacodynamic studies

In a murine model of wound healing, Vandetanib did not prevent wound healing, but was associated with a reduced skin breaking strength.

In an *in vitro* selectivity screen, Vandetanib bound significantly to 59/334 receptor or enzyme targets including several protein kinases previously identified in other screening assays. Ten receptors were bound by Vandetanib with sufficient affinity (IC_{50} < 1μM) to suggest the potential for receptor interactions. Then, next to targets directly involved in tumour proliferation and angiogenesis (VEGFR-2, EGFR and RET), Vandetanib is active against other targets.

Safety pharmacology programme

Vandetanib inhibited the hERG channel with an IC_{50} of 0.4 μM, produced an increase in action potential duration at concentrations of ≥1 μM in isolated Purkinje fibers and increased QTcV by up to 15% in anaesthetised dogs. These results suggest clearly a hERG channel-mediated risk of QT interval prolongation in humans.

When Vandetanib was given in combination with ondansetron, an anti-emetic drug, an increase in hERG channel inhibition was observed.

Vandetanib increased blood pressure in rats and dogs and then, might also have the potential to induce hypertension in humans.

In conscious rats, a single oral dose of Vandetanib up to 200 mg/kg did not affect respiratory function. At these doses, no effect in humans is expected since 40 mg/kg produced a protein free Cmax similar to that seen in patients at a therapeutic dose of 300 mg which is significant lower than the dose rates tested in this study.

Oral administration of Vandetanib caused significant inhibition of gastric emptying and intestinal transit at doses of 40, 200 and 1000 mg/kg.

Vandetanib minimally affected Central Nervous System function. In rats, Vandetanib caused a decrease in open field activities at all dose levels (40, 200 and 1000 mg/kg/day, *p.o.*) and a decrease in landing foot splay at 1000 mg/kg. However, given these high doses, these finding are not considered to be of clinical relevance.

A single oral dose of 50 mg/kg Vandetanib did not affect renal function in conscious rats.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been submitted.

2.3.3. Pharmacokinetics

Absorption

Vandetanib was absorbed slowly with a T_{max} ranged from 2 to 8 hours after single or repeated oral administration of vandetanib to rats and dogs, the oral bioavailability was generally good (50 to 90 %). The C_{max} and area under the curve (AUC_{0-24}) increased fairly dose-proportional up to about 25 mg/kg and thereafter slightly less than proportional in rats after repeated administration.

Distribution

The protein binding of ^{14}C-Vandetanib in plasma of mice, rats, rabbits dogs and human was moderate, from 83 to 90%. The tissue distribution of vandetanib and/or metabolites in pigmented and non pigmented male rats after single oral dosing was slow but extensive, and consistent with the distribution pattern of a lipophilic compound. Highest concentrations of vandetanib and/or its metabolites were seen in the majority of tissues at 6-8 hours after administration. The distribution of radioactivity to brain was evident. Retention of radioactivity was seen in pigmented tissues indicating melanin affinity. A significant distribution of radioactivity was seen in milk of lactating rats and further on in the plasma of suckling pups.

Metabolism

The metabolism of vandetanib seemed to be similar in the toxicology species, rat and dog, as well as in mouse and human. The 2 major metabolites identified in excreta, were N-desmethyl-vandetanib and vandetanib-N-oxide. In mouse, a minor metabolite was also identified as O-desalkyl-vandetanib glucuronid. A glucuronide conjugate was also detected in human urine.

Metabolism as well as biliary excretion appears to be most important for the elimination of vandetanib in preclinical species. CYP identification studies *in vitro*, suggest that CYP3A4 is involved in the formation of N-desmethyl-Vandetanib. vandetanib-N-oxide is formed via FMO1 and FMO3 (FMO=flavine mono-oxygenase). Both these enzymes are also found in kidney indicating that renal excretion might be contributed to the clearance of vandetanib.

Excretion

Excretion of ^{14}C-Vandetanib in faeces (via bile) was the major route in mouse, rat and dog with excretion in urine being a minor route. The rate of excretion was generally slow and consistent with the plasma half-lives of vandetanib. As vandetanib was the major component detected in rat faeces it is likely that N-oxide is excreted into the faeces and then reduced back to vandetanib in the gut. In dogs, the major component in faeces was unchanged vandetanib and it is possible that a similar reduction had occurred in the gut of dogs.

Pharmacokinetic Drug Interactions (in vitro)

Vandetanib and hepatic cytochromes

Vandetanib is metabolized through the CYP3A4 about 10% and the FMO1 and FMO 3, about 2%, yielded to N-desmethyl vandetanib and to vandetanib-N-oxide, respectively.

Cytochrome inhibition by vandetanib

Vandetanib produced some inhibition of CYP2D6 with IC50 and Ki values of 25 and 13 µg/mL, respectively.

Cytochrome induction by vandetanib

Induction of CYP1A2, 2C9 and 3A4 by vandetanib was evident in studies using human hepatocytes. Maximal induction of CYP1A2 activity (3-fold increase in activity, 28% of the positive control (β-naphthoflavone) response), CYP2C9 activity (2,3-fold, 38% of the positive control (rifampicin) effect) and CYP3A4 activity (17,2 -fold increase, 33% of the positive control (rifampicin) effect), occurred at 0,95 µg/mL of vandetanib, a concentration close to the therapeutic one at 300 mg, i.e. 0,81 µg/mL

Vandetanib showed a weak inhibition of P-gp (IC50 = 8.7 µg/ml) and BCRP (IC50 = 11.9 µg/ml). Considering that the steady-state concentrations of vandetanib following 100 mg and 300 mg daily dosing are approximately 0,32 µg/ml and 0,81µg/ml, respectively, it is unlikely that vandetanib will markedly affect the disposition of P-gp and BCRP substrates. However, since these transporters are located at the intestinal level and since the concentrations of vandetanib are much higher in the gastro-intestinal tract than in plasma, inhibition of P-gp and BCRP at this level cannot be excluded.

OCT2

Vandetanib was an inhibitor of OCT2 inhibiting the uptake of the selective OCT2 marker substrate [14C]-creatinine by HEK-OCT2 cells, with a mean IC50 value of approximately 2, 1 µg/ml (study KMX083).

2.3.4. Toxicology

Single dose toxicity

A single oral dose of Vandetanib at 2000 mg/kg to mice or rats was not tolerated and all animals died or were killed for humane reasons. A single oral dose of 1000 mg/kg resulted in the death of 1 out of 10 mice while in rats there were no adverse effects at this dose. An IV single dose of 50 mg/kg in mice resulted in early death in 1 of 10 mice. No IV single dose toxicity was performed in rats due to intolerance to the vehicle.

Repeat dose toxicity

Repeat dose toxicity studies were performed in rats (up to 6 months) and in dogs (up to 9 months) using the oral route. In addition, repeat dose toxicity studies up to 14 days IV dosing were performed in rats and dogs.

Dose-limiting toxicities in 1, 6 and 9 month studies included gastrointestinal effects in dogs, and skin and hepatotoxicity in rats. As a result of such toxicity, exposures in the toxicity studies in most cases did not reach margins of clinical exposure.

Key findings in the repeat dose toxicity studies included adverse signs (emesis, loose faeces/diarrhoea), hepatobiliary toxicity, dysplasia of teeth and epiphysial growth plate, folliculitis of the skin, renal papillary necrosis, phospholipidosis in variety of tissues and haematological effects and ovarian atrophy. These findings were generally in accordance with what would be expected from an inhibition of VEGFR and EGFR signalling.

Genotoxicity

Vandetanib was evaluated over a range of concentrations between 5 and 5000 µg/plate using 4 strains of Salmonella typhimurium (TA1535, TA1537, TA98 and TA100) and 2 strains of Escherichia coli (WP2P and WP2 uvrA), in the presence and absence of a rat liver-derived metabolic activation system (S9-mix). Vandetanib showed no mutagenic potential. Vandetanib was not clastogenic to cultured human lymphocytes.

Vandetanib did not increase the incidence of micronucleated polychromatic erythrocytes in the bone marrow of male rats when administered as a single oral dose of up to 1000 mg/kg.

Carcinogenicity

No carcinogenicity studies have been submitted.

Reproduction Toxicity

The reproductive toxicity of Vandetanib was investigated in a series of studies to assess embryofoetal toxicity, male and female fertility as well as pre and post-natal development.

Vandetanib significantly affected all stages of female reproduction in rats. A decrease in the number of corpora lutea was observed in the ovaries of rats dosed at 75 mg/kg/day in the 1 month toxicology study. In the absence of maternal toxicity in a female fertility study, there was a trend towards increased oestrus cycle irregularity in animals dosed at 10 or 25 mg/kg/day. A dose-related increase in early intra-uterine deaths, resulting in a reduced number of live embryos and increased post-

implantation loss, was observed at 10 and 25 mg/kg/day. Following a 4 week withdrawal period there were no effects on oestrus cycles, pre- or post-implantation losses, or on the number of lives embryos.

In the embryofetal development study in rats, heart vessel abnormalities (aortic arch interrupted or right sided, subclavian artery arising from ductus arteriosus or pulmonary arch; subclavian artery retro-oesophageal; innominate artery absent) and precocious ossification of some skull bones were observed at 25 mg/kg/day. Heart vessel abnormalities were observed also at lower doses (10 mg/kg/day and 1 mg/kg/day) and a no-effect level was not established.

In a rat pre- and post-natal development study, an increase in pre-birth loss was observed at 10 mg/kg/day. Reduced post-natal pup growth was observed in all treated groups. There were no effects on behavioural tests, mating performance, fertility and gestation of the F1 generation.

Toxicokinetic data

Toxicokinetic data was submitted for repeat dosing in rats and dogs.

Total steady state AUC_{0-24} after 100 mg/day (~1.43 mg/kg/day) dosing in humans (7530 ng.h/ml) was similar to that achieved at the highest oral dose level (10 mg/kg/day) in the rat 6 month study (8114 ng.h/ml) and ~3-fold higher than that achieved at the high dose, 15 mg/kg/day, in the 9 month dog study (2273 ng.h/ml).

Steady state AUC_{0-24} after 300 mg/day dosing, 18782 ng.h /ml, was consequently higher than those determined in the 6 and 9 month studies.

In the 6 months study in the rat, at the NOAEL (1 mg/kg/day), animals were 23.5 times less exposed (799 ng.h /ml) than human at 300 mg/day (18782 ng.h /ml). In the 9 months study in the dog at 5 mg/kg/day, animals are 18 times less exposed (1 035 ng.h /ml) than human at 300 mg/day (18782 ng.h /ml).

Local Tolerance

No local tolerance studies have been submitted.

Other toxicity studies

Phototoxicity

Vandetanib absorbs light in the wavelength of 290-700 nm and a phototoxic potential of Vandetanib was demonstrated in an *in vitro* cytotoxicity assay.

Impurities

A control strategy was developed. Some impurities (BNAN, Aminodibenzyl, Vandetanib 4-Amino MA and 2, 4-Dibromo-6-fluoroaniline) were considered as not to be genotoxic; however, assays are not in compliance to international guidelines. For the other impurities, no assays were available (Vandetanib N-Formyl and Vandetanib t-Butyl).

2.3.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name):

CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	**OECD122**	**-0.684 ; 2.21 ; 3.90**			**Not > 4.5** ; not PBT
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				
	BCF				
Persistence	DT50 or ready biodegradability				
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	**0.00001 µg/l then < 0.01 µg/l.**	µg/L			**PEC is < 0.01 then Phase II is not necessary; but the Applicant has chosen to conducte Phase II assessment.**
Other concerns (e.g. chemical class)					
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	**OPPTS 835.1110** **OECD 121**	**Adsorption to sludge** **K_{oc} = 22 700 L/kg** **Adsorption to soil** **K_{oc} = 100.000 (pH 11.5)**			Highly absorbed (> 10.000 L/kg, EMEA/CCCHMP/4447/00)
Ready Biodegradability Test	**OECD 301F**	**5% is degraded (after 28 days)**			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	**OECD 201**	NOEC	**48**	µg/L	freshwater green algae
Daphnia sp. Reproduction Test	**OECD 211**	NOEC	**300**	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	**OECD 210**	NOEC	**10**	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	**OECD 307**	60.6 –101.6% of the applied radioactivity could be recovered In soil.			
Soil Micro organisms: Nitrogen Transformation Test	**OECD 216**	NOEC	**56**	µg/kg	
Terrestrial Plants, Growth Test/*Species*	**OECD 208**	NOEC	**1000**	mg/kg	
Earthworm, Acute Toxicity Tests	**OECD 207**	NOEC	**1000**	mg/kg	*Eisenia foetida foetida*
Collembola, Reproduction Test	**ISO 11267**	NOEC	**10**	mg/kg	*Folsomia candida*
Sediment dwelling organism	OECD 218	NOEC	**100**	mg/kg	Toxicity to the freshwater midge Chironomus riparius.

No environmental risk has been identified as a consequence of the use of Vandetanib.

2.3.6. Discussion on non-clinical aspects

Vandetanib is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and Rearranged during Transfection (RET) tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase.

Vandetanib inhibits VEGF-stimulated endothelial cell migration, proliferation, and survival and new blood vessel formation in *in vitro* models of angiogenesis. In addition, vandetanib inhibits epidermal growth factor (EGF) -stimulated EGF receptor tyrosine kinase in tumour cells and endothelial cells. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival *in vitro*. Vandetanib also inhibits both wild type and the majorities of mutated, activated forms of RET, and significantly inhibits the proliferation of medullary thyroid tumour (MTC) cell lines *in vitro*.

In vivo vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability, tumour microvessel density, and inhibited tumour growth of a range of human xenograft tumour models in athymic mice. Vandetanib also inhibited the growth of MTC xenograft tumours *in vivo*.The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown

2.3.7. Conclusion on the non-clinical aspects

Vandetanib has shown no mutagenic or clastogenic potential.

In repeat-dose toxicity studies of up to 9 months duration, effects included emesis, body weight loss and diarrhoea in dogs and physeal dysplasia in young dogs and rats with open growth plates. In rats, effects on teeth, kidney and skin were noted. These findings occurred at clinically-relevant plasma concentrations, were largely reversible within 4 weeks of cessation of dosing and were attributable to inhibition of vascular endothelial growth factor receptor (VEGFR) or EGFR.

Effects noted in other studies included inhibition of human ether-a-go-go related gene (hERG) current and prolongation of QTc interval in dogs. Elevation of systolic and diastolic blood pressure were observed in rats and dogs. In mice, vandetanib was shown to delay but not prevent wound healing. Vandetanib also showed evidence of phototoxic potential in an *in vitro* cytotoxicity assay. In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. This suggests that vandetanib slows but does not prevent wound healing. The appropriate interval between discontinuation of vandetanib and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In clinical studies, a small number of patients had surgery while receiving vandetanib and there were no reported wound healing complications.

Vandetanib had no effect on fertility in male rats. In a female fertility study, there was a trend towards increased oestrus cycle irregularity, a slight reduction in pregnancy incidence and increase in implantation loss. In a repeat-dose toxicity study in rats, there was a decrease in the number of corpora lutea in the ovaries of rats given vandetanib for 1 month.

In rats, embryofoetal toxicity was evident as foetal loss, delayed foetal development, heart vessel abnormalities and precocious ossification of some skull bones. In a rat pre- and post-natal

development study, at doses producing maternal toxicity during gestation and/or lactation, vandetanib increased pre-birth loss and reduced post-natal pup growth. Vandetanib was excreted into milk in rat and found in plasma of pups following dosing to lactating rats.

As the development of vandetanib was performed only by oral route, which is the clinical route of administration, no specific local tolerance studies were performed. In line with ICH S9, no carcinogenicity studies have been conducted.

Based on the review of the data on non clinical aspect, the CHMP considers that the application is approvable and requested the inclusion of the following statements in section 4.6 of the SmPC:

- Women of childbearing potential must use effective contraception during therapy and for at least four months following the last dose.
- There is a limited amount of data on the use of vandetanib during pregnancy. Vandetanib has shown significant effects on all stages of female reproduction in rats. If vandetanib is used during pregnancy or if the patient becomes pregnant while receiving vandetanib, she should be apprised of the potential for foetal abnormalities or loss of the pregnancy.
- There are no data on the use of vandetanib in breast-feeding women. Vandetanib and/or its metabolites is excreted into milk in rats and found in plasma of pups following dosing to lactating rats. Breast-feeding is contraindicated while receiving vandetanib therapy (section 4.3 and 4.6 of the SmPC).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

The clinical pharmacokinetic documentation consists of 16 phase I studies, 3 phase II studies and 3 phase III studies. The main features of these studies are summarised in the table below.

Table 2. Summary of the clinical studies contributing PK data of vandetanib

Study No.	Study detail	Dose	Number randomized/treated and type of subjects
Study 01	Rising single dose followed by multiple dose tolerability and toxicity study (Western)	ZD6474: 50 mg, 100 mg, 200 mg, 300 mg, 500 mg, 600 mg	77/77 Patients with malignant solid tumors.
Study 43	Rising single dose followed by multiple dose tolerability and toxicity study (Japanese)	ZD6474: 100 mg, 200 mg, 300 mg, 400 mg (single doses)	0/18 Japanese patients with malignant solid tumours.

Study No.	Study detail	Dose	Number randomized/treated and type of subjects
Chinese Study 04	Rising multiple dose study to determine the PK & tolerability (Chinese)	ZD6474: 100mg every other day; 100 mg once daily and 300mg once daily	0/36 Chinese patients with malignant solid tumours.
Study 12	Safety, tolerability and PK of oral ascending doses	ZD6474: 300 mg, 400 mg, 800 mg, 1200 mg (single doses)	0/23 Healthy male volunteers.
Study 15	Effect of itraconazole (CYP3A4 inhibitor) on ZD6474 PK	ZD6474: 300 mg (single dose) Itraconazole: 200 mg	16/16 Healthy male volunteers.
Study 16	Effect of hepatic impairment on PK, safety and tolerability	ZD6474: 800 mg (single dose)	0/30 8 healthy subjects and 22 patients with hepatic impairment: 8 mild, 8 moderate, 6 severe.
Study 21	Effect on cardiac repolarisation of co-administration of a single dose of ondansetron with a single dose of ZD6474	ZD6474: 700 mg (single oral dose) Ondansetron 32 mg (single IV dose)	28/28 Healthy male volunteers.
Study 22	Effect of renal impairment on PK, safety and tolerability	ZD6474: 800 mg (single dose)	0/32 10 healthy subjects and 22 patients with renal impairment: 6 mild, 6 moderate, 10 severe.
Study 24	Effect of food on ZD6474 PK and intra-subject variability	ZD6474: 300 mg (single dose)	16/16 Healthy volunteers (15 male, 1 female).
Study 25	Absorption, metabolism and excretion	[^{14}C]-ZD6474: 800 mg (single dose)	0/4 Healthy male volunteers.
Study 26	Effect of rifampicin (CYP3A4 inducer) on ZD6474 PK	ZD6474: 300 mg (single dose)	18/18 Healthy male volunteers.
Study 30	Effect of 4 oral tablet variants and an oral solution on PK exposure	ZD6474: 300 mg (single dose)	23/23 Healthy volunteers (21 male, 2 female).
Study 50	Effect of vandetanib on vascular permeability	ZD6474: 100 mg, 300 mg (once daily doses)	24/22 Patients with advanced colorectal cancer and liver metastases.
Study 38	Safety and tolerability of ZD6474 in combination with Irinotecan, 5-FU and leucovorin (FOLFIRI) as first- or second-Line therapy in patients with metastatic colorectal adenocarcinoma	ZD6474: 100 mg, 300 mg (once daily doses) FOLFIRI: standard 14 day treatment cycles	0/21 Patients with metastatic colorectal adenocarcinoma.
Study 39	Dose-finding study to assess efficacy (objective response) and safety in Japanese patients with advanced or metastatic (stage IIIB/IV), or recurrent NSCLC who have failed 1 or 2 previous chemotherapy regimens; at least 1 of which contained platinum	ZD6474: 100, 200 and 300 mg (once daily doses)	53/53 Japanese patients with NSCLC who have failed 1 or 2 previous chemotherapy regimens.
Study 41	Safety and tolerability of ZD6474 (ascending doses) in combination with pemetrexed (ALIMTA™)	ZD6474: 100 mg, 300 mg (once daily doses) Pemetrexed: 500 mg/m^2	0/21 Patients with histologically- or cytologically-confirmed locally-advanced or metastatic NSCLC.

Study No.	Study detail	Dose	Number randomized/treated and type of subjects
Study 08	Efficacy and tolerability of ZD6474 in Patients with Locally advanced or Metastatic Hereditary Medullary Thyroid Carcinoma.	ZD6474: 300 mg (once daily doses)	0/30 Patients with Locally advanced or Metastatic Hereditary MedullaryThyroid Carcinoma MTC.
Study 68	Efficacy of ZD6474 (ZACTIMA) 100 mg Monotherapy in subjects with Locally advanced or Metastatic Hereditary Medullary Thyroid Cancer.	ZD6474: 100 mg (once daily doses)	0/19 Subjects with Locally advanced or Metastatic Hereditary Medullary Thyroid Cancer.
Study 03	Comparison of the efficacy of ZD6474 with the efficacy of ZD1839 (IRESSA™)	ZD6474: 300 mg (once daily doses) Iressa: 250 mg (once daily dose)	168/168 Patients with locally-advanced or metastatic NSCLC who had failure of either first-line and/or second-line chemotherapy, either of which was platinum-based.
Study 06	Safety, tolerability and efficacy of ZD6474 in combination with docetaxel (TAXOTERE™)	ZD6474: 100 mg, 300 mg (once daily doses) Docetaxel: 75 mg/m^2	127/144 Patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy (Note: 17 additional patients were enrolled into the run-in phase).
Study 02	Efficacy of ZD6474 in patients with metastatic breast cancer based on the objective response rate using RECIST criteria.	ZD6474: 100 mg and 300 mg	0/46 Female patients with metastatic breast cancer.
Study 58	Efficacy of ZD6474 (ZACTIMA) versus placebo in subjects with Unresectable Locally advanced or Metastatic MedullaryThyroid Cancer.	ZD6474: 300 mg (once daily oral)	Subjects with Unresectable Locally advanced or Metastatic MedullaryThyroid Cancer.
Study 57	Efficacy of ZD6474 versus erlotinib	ZD6474: 300 mg (once daily oral) Erlotinib: 150 mg (once daily oral)	1240/1237 Patients with locally-advanced or metastatic NSCLC after failure of at least 1 prior cytotoxic chemotherapy.

Method of analysis

All assays used to analyse vandetanib in plasma employed LC-MS/MS detection. Assays were also validated for vandetanib and metabolites in plasma, urine and plasma ultra-filtrate (PUF).

The calibration range for vandetanib in plasma was generally 5-1000 ng/mL, and for the metabolites 1-200 ng/mL, however, there were considerable variations between methods. The calibration range in urine was 100-50000 ng/mL and in PUF 1-200 ng/mL.

Absorption

The PK parameters after single and repeated dosing of vandetanib are presented in the table below.

Table 3. PK parameters for vandetanib after a single dose and at steady state (day 43) for 100 mg administered every other day) and 100 and 300 mg (administered once daily): Study 04

Parameter (units)	Summary statistics	Treatment group		
		Vandetanib 100 mg (every other day)	Vandetanib 100 mg (once daily)	Vandetanib 300 mg (once daily)
Single dose (Day 1)		N=12	N=12	N=12
$AUC_{0\text{-}24h}$ (ng.h/mL)	gmean (CV%)	1392 (51.53)	1294 (30.49)	5643 (58.83)
C_{max} (ng/mL)	gmean (CV%)	81.78 (48.74)	71.76 (32.26)	329.5 (69.97)
t_{max} (h)	Median (range)	6 (4 to 10)	6 (2 to 10)	8 (2 to 10)
Steady state (Day 43)		N=8[a]	N=9	N=7
AUC_{ss} (ng.h/mL)	gmean (CV%)	11767 (29.06)	10826 (40.63)	38611 (38.35)
$C_{ss,\ max}$ (ng/mL)	gmean (CV%)	342.9 (37.97)	521.7 (35.29)	2024 (39.08)
$C_{ss,\ min}$ (ng/mL)	gmean (CV%)	213.3 (24.52)	436.6 (43.99)	1497 (42.93)
$C_{ss,\ av}$ (ng/mL)	gmean (CV%)	245.2 (29.10)	451.1 (40.63)	1608 (38.34)
t_{max} (h)	Median (range)	4 (4 to 8)	6 (0 to 24)	4 (0 to 24)
CL/F (L/h)	gmean (CV%)	8.499 (29.06)	9.237 (40.63)	7.770 (38.35)
V_{dist} (L)	Population Mean		1896	
$t_{½}$ (days)[b]	Mean (±SE)	10.4 (2.2)	8.9 (0.85)	7.6 (1.76)
R_{ac}	Mean (range)	14.9 (5.3-45.1)[b]	9.138 (5.90-12.2)	.1. .29-13.1)

a) n = 9 for $C_{ss,\ max}$ and t_{max} only, b) determined from the population analysis, c) V_{dist} mean population value, R_{ac}=Accumulation ratio (index)

Bioavailability

No studies have been submitted with intravenous administration of vandetanib.

Bioequivalence

A number of formulations have been utilised throughout the clinical development of vandetanib. The commercial tablet formulation has been used in some Phase II studies and in all Phase III studies. No significant difference has been detected between the Phase I, IIa and III formulations. Alterations in particle size, process and formulation did not translate into relevant changes in exposure. Moreover, the similar concentration profile of the solution and the different tablet formulations indicate that the absorption pattern of vandetanib is not dependent on dissolution, and therefore the formulation has little impact.

Influence of food

Vandetanib rate and extent of absorption did not significantly change when taken with a high-fat breakfast (data not shown).

Distribution

The volume of distribution has not been determined in humans as no intravenous formulation has been developed. In patients, vandetanib was approximately 93% bound to plasma proteins; both albumin and α-1-acid-glycoprotein bind to vandetanib. The plasma protein binding of the N-desmethyl

metabolite is similar as for vandetanib, and the binding of the N-oxide metabolite could not be determined due to analytical difficulties. Although the bioavailability of vandetanib is not known, the Vss/F indicates immense distribution into tissues, which is also confirmed in preclinical studies.

Metabolism

The metabolism of 14C-vandetinib was investigated in 4 healthy volunteers (Study 25) following a single oral dose of 800 mg. Vandetanib represented 80% of the circulating radioactivity during the first day but this declined slowly with time. Due to the low radiochemical dose, long half-life of vandetanib and high volume of distribution, concentrations of radioactive material were low in plasma, urine and faeces. Using qualitative LC-MS, unchanged vandetanib and 2 known metabolites (vandetanib N-oxide and N-desmethyl vandetanib) were detected in plasma. N-desmethyl-vandetanib was found to be the major circulating metabolite of vandetanib; relative to vandetanib, the exposure to N-desmethyl-vandetanib was ~10 % and for N-oxide-vandetanib the exposure relative to vandetanib was <2% (studies 16, 22 and 26). The same metabolites were found in both urine and faeces, where an additional minor metabolite was also present. This was shown by mass spectroscopy to be a glucuronide conjugate. Using TLC, the ratio of vandetanib: N-desmethyl vandetanib excreted in faeces was estimated 5:1.

Vandetanib is not a substrate for P-gp, BCRP, MRP1 or OCT2. Vandetanib was found to be a weak inhibitor of P-gp and BCRP, although at concentrations higher than what are expected in plasma. Vandetanib is also an inhibitor of OCT2, a transporter involved in the excretion of creatinine.

Elimination

Plasma clearance has not been determined in humans as no intravenous formulation has been developed. CL/F is approximately 10 L/h, although highly variable.

The elimination has not been fully elucidated, and no metabolite profiling was performed in the human mass balance study. Clearance of vandetanib occurs by metabolism and excretion in urine and faeces of unchanged vandetanib. Total recovery of radioactivity was 69% after 21 days and was still ongoing, which is caused by the slow elimination of vandetanib, and twice as much radioactivity was excreted in the faeces (44%) compared to urinary (25%) excretion. Qualitative measurements identified N-desmethyl-vandetanib and vandetanib-N-oxide in plasma as well as in urine and faeces. In urine, a glucorinide conjugate was also found. No quantitative results of the concentrations of the metabolites and parent compound in plasma, urine and faeces could be provided from the mass balance study, which is considered a deficiency. However, due to the long half-life of vandetanib, only a low dose of radioactive material could be given, and thereby the concentration levels of the metabolites were too low for characterization. The approach to search for the N-desmethyl and N-oxide metabolites was based on data from mass balance studies in the pre-clinical program.

Urine concentrations were determined in a healthy volunteer study, indicating that less than 5% is excreted in urine as unchanged drug over the first 72 h. This indicates that renal excretion is not the major route of elimination. Rather, the amount excreted unchanged in urine, in combination with the large proportion radioactive material found in faeces indicated that metabolism and biliary excretion are likely important mechanisms for vandetanib elimination.

A long terminal elimination half-life (8-19 days) was observed in both single and multiple-dose studies, and is consistent with the low clearance (8.7L/h) of vandetanib. Longer half life is estimated in the target patient population (MTC) with a mean T1/2 of approximately 20 days (4-85 days). Such discrepancy is not clearly explained. The mean CL/F was approximately 10-13 L/h across studies.

Pharmacokinetics of Metabolites

Pharmacokinetics of metabolites of vandetanib has been investigated in healthy volunteers, in patients and subjects with renal and hepatic impairment. Due to the low systemic exposure, it is estimated that the active metabolite N-desmethyl-vandetanib contributes only a relatively small proportion (approximately 10%) of the overall pharmacological activity of vandetanib. This proportion may increase up to 43% in patients co-administered CYP inducers such as rifampicin (Study 26), but is not changed in patients with renal impairment (Study 22) and may be decreased in patients with hepatic impairment (Study 16).

Dose proportionality and time dependency

In healthy volunteers, the pharmacokinetics seemed to be independent of dose over the dose range 300-1200 mg single doses. There was no clear indication of non-proportionality in exposure in patients receiving 50 – 600 mg, or in patients receiving 100 mg every other day or 100 -300 mg daily, although there were a limited number of patients in several of the dose groups. Also, the variability in exposure between patients was high, which could possibly mask a dose dependency. The pharmacokinetics of vandetanib seemed to be independent of time. In the population pharmacokinetics models, the estimates of the inter-individual variability were approximately 40% for CL/F and 50% for Vc/F.

300 mg was selected as the dose with which to begin treatment in clinical studies. The rationale for the using the 300 mg dose was based primarily on: (1) preclinical data, which demonstrated that the greatest benefit (in terms of maximizing inhibition against key targets) is seen when vandetanib is used at the maximum tolerated dose (MTD), (2) the MTD of 300 mg being concluded from data in the Phase I ascending-dose Study D4200C00001 (Study 01) and the corresponding Phase I study in Japanese patients, Study D4200C00043 (Study 43), and (3) in Study 08, the phase II study of vandetanib in hereditary MTC patients, the dosing schema of beginning treatment with vandetanib 300mg allowing for dose reductions demonstrated that this was a safe and tolerable dosing plan.

Intra- and Inter-individual variability

The intra-subject variability following single oral dose of 300 mg vandetanib tablet under both fed and fasted conditions was assessed in 15 healthy volunteers using a replicate design (Study 24). Intra-subject variability in exposure to vandetanib was found to be small; the overall estimate for intra-subject variability was 8% for AUC and 11% for Cmax. In phase I studies inter-subject variability was typically approximately 30%.

Pharmacokinetics in target population

Pharmacokinetics of vandetanib in patients with MTC was evaluated by popPK analyses. The results are summarized in the table below.

Table 4. Summary of pharmacokinetic parameters estimated by popPK analysis in patients with MTC (studies 8, 58 and 68) and in healthy subject/cancer patients.

Studies	1 ,2, 3,6, 12, 15, 21, 24, 30	3, 6, 12, 15, 21, 24	58	8	68
N patients / healthy subj	251/110	219/79	191[1]	30	19
Ka (h^{-1})	3.4	0.3 (fixed)	0.3 (fixed)	0.429	0.55
$AUC_{0\text{-}24h,\ ss}$ (ng.h/ml)[1]		28698	19829	25060	7492

Cmax (ng/ml)[1]		1240	857	819	353
$t_{½}$ (days)	7.8	7.9	20		9
Cl (L/h)	11.1	10.9	13.2	11.5	13.0
Vss (L)	3210	3000	7450	7440	3850
Accumulation ratio		11.4	8.1		

[1] Summary of secondary pharmacokinetic parameters (median) from MTC patients dosed to steady state (Day 56) with 300 mg daily (study 8, 58) and 100 mg (study 68).

The PK parameter estimates between patients and healthy volunteers do not indicate large PK differences between patients and healthy volunteers. Estimated elimination half-life (~18 days) was longer in phase 3 popPK analysis than in the phase I studies (~ 8 days), in which elimination half-life was determined after single dose administration. Data across studies are comparable.

Special Populations

Population pharmacokinetic analysis predicted weight as covariates of vandetanib clearance and volume of distribution. The mean estimated clearance for median weight (68 kg) was 13.2 ± 0.306 L.h-1. A steady-state AUC on Day 56 of 13.75 µg.h/mL (27% lower than the median of all subjects that received 300 mg up to Day 56) is estimated for the heaviest patient with a body weight of 125 kg. This exposure is greater than the threshold for a probability of stable disease to be 50% (7.05 µg.h/mL) as estimated by the response analysis. The estimated weight effect is, however, modest and no dose adjustment for weight is necessary.

Pharmacokinetics of vandetanib was not different in Caucasian and Oriental patients (Studies 01, 43, 04, 58). Gender and age (Study 58) had no effect on the pharmacokinetics of vandetanib. Pharmacokinetics of vandetanib has not been studied in children.

A study in renally impaired subjects indicated a clear trend towards higher exposure with decreased renal function. Unbound vandetanib concentrations were on average 16%, 46% and 57% higher in subjects with mild, moderate and severe renal impairment. Adequate recommendations have been introduced in the SmPC regarding the use of vandetanib (not recommended) in patients with moderate or severe renal insufficiency for whom very limited data are available with the proposed 300 mg dose (and none with other doses) in patients with MTC.

In a study with hepatically impaired patients without tumours in the liver, there was no increase in AUC or C_{max} in patients with mild, moderate or severe hepatic impairment, but rather a slight decrease. The AUC and C_{max} of the N-desmethyl metabolite were decreased in hepatic impairment, while the AUC and C_{max} of the N-oxide were increased.

Pharmacokinetic Interaction Studies

The effect of inhibition of CYP3A4 by itraconazole was assessed in healthy volunteers in Study 15. The 9% increase in exposure (AUC0-504h) was not considered to be clinically meaningful.

The effect of induction of CYP3A4 by rifampicin was assessed in healthy volunteers in Study 26. The estimate of the treatment ratio for vandetanib AUC0-504h indicates a statistically significant 39.9% reduction, when taken in combination with rifampicin, compared with vandetanib alone. The presence or absence of rifampicin did not significantly influence the Cmax.

The metabolite formed by CYP3A4 metabolism has been identified as N-desmethylvandetanib and consistent with induction of CYP3A4, there was a 266% increase in the exposure (AUC) to this metabolite when vandetanib was, in combination with rifampicin compared to vandetanib alone and

the exposure relative to vandetanib increased from about 7% to 43%. Levels of vandetanib-N-oxide were low and did not allow the determination of the AUC0-504h. However, compared with vandetanib alone, the AUC determined to a common time t increased by about 100% and Cmax by about 175% when vandetanib was given in combination with rifampicin and the exposure relative to vandetanib showed a small increase from approximately 1.5% to approximately 2%.

Vandetanib exhibit pH dependent solubility: high solubility at low pH and low solubility at neutral pH. At pH 6.8 solubility of vandetanib is 0.35 mg/ml. No further data on vandetanib solubility has been submitted at different pH and notably under a value of 6.8. As proton-pump inhibitors and H2-antihistamines increase gastric pH until 5-6, one cannot exclude that this solubility could be affected.

S-warfarin (the pharmacologically more active enantiomer) is metabolized by CYP2C9 and R-warfarin is metabolized principally by CYP1A2 and to a lesser degree by CYP3A4. Vandetanib has been shown to have a moderate potential to inhibit these iso-enzymes.

Pharmacokinetics using human biomaterials

See Non-clinical pharmacokinetic drug interactions.

2.4.3. Pharmacodynamics

Mechanism of action

The role of vandetanib as a selective inhibitor of VEGF, EGFR and RET has been described in the non-clinical section of this report. In addition to this, clinical studies supporting the involvement of VEGFR and EGFR in the anti-cancer activity of vandetanib are described in the primary pharmacology section below.

Primary and Secondary Pharmacology

See Secondary Endpoints, Pharmacodynamic parameters pertinent for activity in the MTC setting.

2.4.4. Discussion on clinical pharmacology

There is a scientific rationale in MTC for vandetanib which targets two separate aspects of cancer by directly inhibiting EGFR and/or RET dependent tumour growth and indirectly inhibiting tumour growth through antiangiogenic effects on endothelial cell proliferation, migration and survival.

The long half-life of vandetanib is unfavourable for a drug which is to be dose adjusted based on adverse events, especially with regard to serious concerns about the safety profile, including marked QT prolongation (and clinical consequences) and potential deterioration of renal function, as high concentrations will remain for months after cessation of the drug. Conventional studies and popPK analysis indicated a low intra- and moderate to high inter-subject variability of vandetanib.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics of vandetanib and metabolites have been adequately investigated. Following single oral dose of vandetanib absorption appeared to be relatively slow with Cmax achieved at a median Tmax of 6 h and vandetanib is slowly cleared from the plasma (8.7 L/h) and is characterised by a long plasma half-life of 8-18 days. Consistent with the long half-life, once daily oral administration of 100 mg or 300 mg resulted in approximately 10-fold accumulation from single dose to steady-state levels.

A pharmacokinetic study in volunteers with mild, moderate and severe renal impairment shows that exposure to vandetanib after single dose is increased up to 1.5, 1.6 and 2-fold respectively in patients with mild, moderate (creatinine clearance ≥ 30 to < 50 ml/min) and severe (clearance below 30 l/min) renal impairment at baseline (see section 5.2 of the SmPC). Clinical data suggest that no change in starting dose is required in patients with mild renal impairment. There is limited data with 300 mg in patients with moderate renal impairment: discontinuation for AEs in 5/6 pts. The starting dose could be reduced to 200 mg in patients with moderate renal impairment; safety and efficacy have however not been established with 200 mg (see section 4.4 of the SmPC). Vandetanib is not recommended for use in patients with severe renal impairment since there is limited data in patients with severe renal impairment, and safety and efficacy have not been established.

Vandetanib is a weak inhibitor of the efflux pump P-gp. The co-administration of vandetanib and drugs excreted by P-gp, such as digoxin, may result in increased plasma concentrations of these drugs. Patients receiving digoxin and vandetanib may require increased digoxin blood level monitoring and appropriate dosage adjustments. The applicant has planned to study the interaction between vandetanib and digoxin further.

Vandetanib is an inhibitor of the OCT2 transporter. Therefore, vandetanib may have the potential to decrease the elimination of drugs known to be excreted by OCT2 and to increase a patient's exposure to these drugs. Metformin is a substrate of OCT2; patients who are receiving vandetanib and metformin (or other substrates of OCT2) may require more careful monitoring and possible dose adjustment of metformin. The applicant has planned to study the interaction between vandetanib and metformin further.

The effect of proton pump inhibitors and H2 antagonists on the gastrointestinal absorption of vandetanib has not been determined. Vandetanib demonstrates pH-dependent solubility; therefore, the co-administration of vandetanib with proton pump inhibitors and H2 antagonists may reduce a patient's exposure to vandetanib. The concomitant use with these therapeutic classes is therefore not recommended (see section 4.4 of the SmPC)

The co-administration of vandetanib with proton pump inhibitors and H2 antagonists may reduce a patient's exposure to vandetanib. Therefore, the applicant has planned to study this interaction further.

Vandetanib has the potential to induce the CYP3A4 enzyme system. Co-administration of vandetanib and drugs primarily metabolised by the CYP3A4 enzyme system may result in decreased plasma concentrations of these drugs that could reduce or shorten therapeutic effects. Therefore, appropriate dosage adjustments may be required. The applicant has planned to study the interaction between vandetanib and midazolam further.

The above mentioned drug-drug interaction studies are covered in the RMP.

2.5. Clinical efficacy

The clinical efficacy submission in MTC is based on one pivotal study (Study 58) with vandetanib 300 mg daily and is supported by two phase II uncontrolled studies performed with different dose regimen 100 mg (study 068) and 300 mg daily (study 008) in patients with MTC.

A recently completed study (Study D4200C00079 [Study 79]) was performed in patients with differentiated thyroid cancer and the preliminary results are also presented in the Applicant's documentation. A list of clinical efficacy studies submitted is presented in the table below.

Table 5: 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	100 mg	19	Complete
D4200C00058 (Study 58) placebo-controlled, randomised	III	MTC (hereditary and sporadic)	300 mg	331 (231 on vandetanib)	Complete
D4200C00079 (Study 79) Randomised, placebo-controlled	II	Differentiated thyroid cancer	300 mg	145 (72 on vandetanib)	Preliminary data available

2.5.1. Dose response studies

D4200C00008

Study 008 was a single-arm, open-label, uncontrolled, monotherapy Phase II study conducted to evaluate the efficacy and tolerability of vandetanib (300 mg daily) in 30 patients with hereditary locally advanced or metastatic MTC.

The ORR was 20.0% (6/30) (complete (CR) or partial response (PR) based on primary site-read assessment based on RECIST). By independent assessment there were 5 (16.7%) of patients who had an OR (modified RECIST criteria). Median PFS was 27.9 months. The median duration of response (DOR) from first response until progression or death was 10.2 months, and from first dose until progression or death was 18.5 months.

D4200C00068

Study 068 was a single-arm, open-label, uncontrolled, monotherapy Phase II study conducted to evaluate the efficacy and tolerability of vandetanib (100mg) in 19 patients with hereditary locally advanced or metastatic MTC.

The ORR (RECIST criteria, based on site-read assessment) was 15.8% (3/19) with 95% CI [3.4; 39.6]. The median DOR from the onset of response was 5.5 months

2.5.2. Main study

D4200C00058

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

Methods

Study Participants

Inclusion criteria

Patients had to fulfil all of the following criteria for inclusion in the study:

- Provision of written informed consent
- Female or male aged 18 years and over
- Previously confirmed histological diagnosis of unresectable locally advanced or metastatic hereditary or sporadic MTC. Documentation had to be provided in patient's medical chart.
- Life expectancy of 12 weeks or longer (These patients were considered most likely to be able to tolerate study procedures and treatment.)
- WHO Performance status (PS) 0-2 (These patients were considered most likely to be able to tolerate study procedures and treatment.)
- Ability to swallow study medication
- Presence of a measurable tumour as defined by (a) a solitary lesion measuring ≥2 cm or for multiple lesions, the following criteria applied:
    - A technique providing ≤5mm sections: a sum of diameters ≥2 cm (no target lesions measuring <1 cm and no lymph nodes <1.5 cm) or
    - A technique providing >5mm sections: a sum of diameters ≥4 cm (no target lesion measuring <2 cm)
- CTN ≥500 pg/mL (conventional units) or ≥146.3 pmol/L (international standard units)
- All patients (other than those with hereditary MTC who had a documented germline RET mutation) had to submit a suitable archived tumour collection sample. When this sample was not available prior to 2 weeks before randomisation, a fresh tumour sample was obtained. The tumour sample had to be obtained by the investigative site and shipped to its destination prior to randomisation.
- Negative pregnancy test for female patients of childbearing potential

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

- Brain metastases or spinal cord compression, unless treated at least 4 weeks before the first dose, and stable without steroid treatment for 10 days
- Any concomitant medications that may have affected QTc or induced CYP3A4 function (with the exception of somatostatin or somatostatin analog) and/or any prohibited medications referenced in the Amended CSP
- Major surgery within 4 weeks of randomisation
- The last dose of prior chemotherapy was received less than 4 weeks prior to randomisation
- Radiation therapy within the last 4 weeks prior to randomisation (with the exception of palliative radiotherapy)

- Serum bilirubin >1.5 x the upper limit of reference range (ULRR)
- Creatinine clearance <30 mL/min (calculated by Cockcroft-Gault formula)
- Potassium <4.0 mmol/L despite supplementation, or above the Common Terminology Criteria for Adverse Events (CTCAE) grade 1 upper limit. Magnesium below the normal range despite supplementation, or above the CTCAE grade 1 upper limit. Serum calcium above the CTCAE grade 1 upper limit. In instances when the serum calcium was below the normal range, the calcium adjusted for albumin was to be obtained and substituted for the measured serum value. Exclusion was to then be based on the calcium adjusted for albumin values falling below the normal limit. Corrected Calcium=Ca + 0.8 X (4-serum albumin)
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >2.5 × ULRR, or >5.0 × ULRR, if judged by the investigator to be related to liver metastases
- Significant cardiac event (eg, myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease ≥2, within 12 weeks before randomisation, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia
- History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (CTCAE grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication were permitted.
- Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age
- QT prolongation with other medications that required discontinuation of that medication
- Presence of left bundle branch block (LBBB)
- QTc with Bazett's correction unmeasurable or ≥480 ms on screening electrocardiogram (ECG)
- Hypertension not controlled by medical therapy (systolic blood pressure>160 millimeter of mercury [mmHg] or diastolic blood pressure >100 mmHg)
- Previous or current malignancies of other histologies within the last 5 years, with the exception of tumours associated with MEN2a and MEN2b, in situ carcinoma of the cervix, or adequately treated basal cell or squamous cell carcinoma of the skin
- Any unresolved chronic toxicity greater than CTCAE grade 2 from previous anticancer therapy
- Participation in a clinical study and/or receipt of an investigational drug during the last 30 days (participation in the survival follow-up period of a study was not an exclusion criterion)
- Previous exposure to vandetanib
- Currently pregnant or breast feeding
- Involvement in the planning and conduct of the study
- Previous randomisation or treatment in the present study

Treatments

During the blinded phase of the study, patients received either:

- vandetanib 300 mg once daily oral dose or

- placebo 300mg once daily oral dose

until they had objective disease progression, provided they did not meet any other withdrawal criteria.

Upon disease progression, patients were discontinued from blinded study treatment and given the option to begin open label treatment with vandetanib 300 mg (or receive a permanently reduced dose, if applicable), or enter follow-up for survival status.

Objectives

Primary objective:

- To demonstrate an improvement in progression-free survival (PFS) with vandetanib as compared to placebo in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC).

Secondary objectives:

- To demonstrate an improvement in the objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) with vandetanib as compared to placebo
- To demonstrate an improvement in the overall survival (OS) in patients with MTC who have been treated with vandetanib as compared to placebo
- To demonstrate an improvement in biochemical response with vandetanib as compared to placebo, as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA)
- To demonstrate a delay in time to worsening of pain (TWP) among patients with MTC after treatment with vandetanib as compared to placebo
- To determine the pharmacokinetics (PK) of vandetanib in this patient population and investigate any influence of patient demography and pathophysiology on the PK
- To assess the relationship between PK and time interval between the start of the Q wave and the end of the T wave, (corrected for heart rate) (QTc), safety, efficacy, and biomarkers
- To determine the safety and tolerability of vandetanib treatment in MTC patients
- To determine the mutational status of the rearranged during transfection (RET) proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumour samples

Outcomes/endpoints

Primary endpoint

- Progression-free survival (PFS), defined from the date of randomization to the date of objective progression or death (by any cause in the absence of progression), provided death was within 3 months from the last evaluable RECIST assessment, using data from RECIST assessments performed at baseline, during treatment and during the follow-up period. The PFS assessment was based on an independent radiological review.

Secondary endpoints

- Secondary efficacy endpoints included overall Respose Rate (ORR) by RECIST, overall survival (OS) and biochemical response rate: CTN and CEA.

Sample size

Assuming 2:1 randomisation (vandetanib: placebo), to detect a doubling of PFS at the 2-sided alpha= .050 level with 80% power, at least 90 events were required. Assuming a median PFS of 12 months in the control group, a non-linear recruitment period of 22 months, and a minimum follow-up of 6.7 months, at least 232 patients were to be recruited for the study, i.e., the total length of the study was estimated to be 28.7 months to observe 90 progression events.

Randomisation

Eligible subjects were to be randomized strictly sequentially in a 2:1 ratio.

Blinding (masking)

The study was double-blind.

Statistical methods

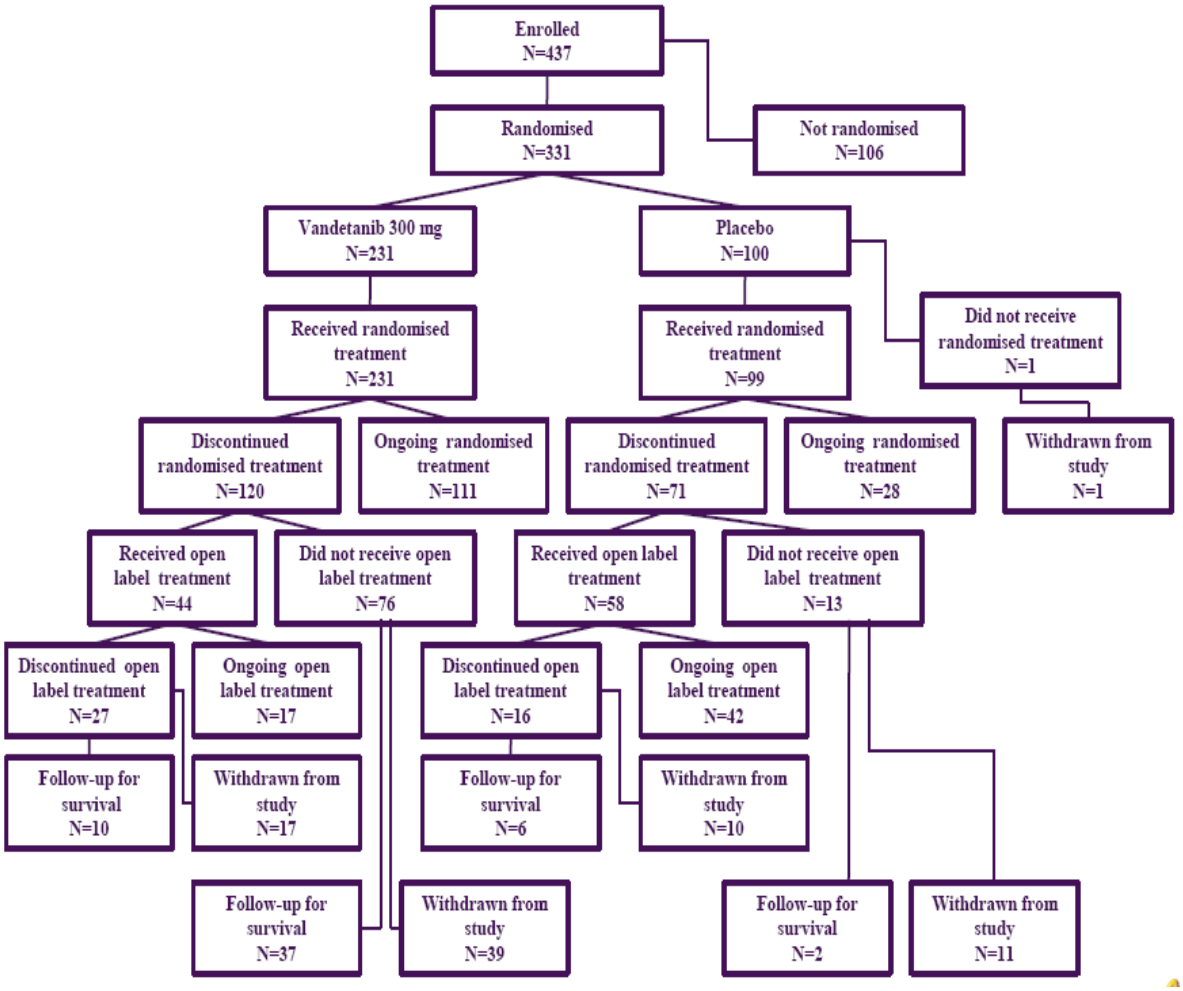
Primary endpoint analysis

The primary analysis was based on an ITT analysis of PFS data derived from all available modified RECIST assessments, which included any available information on central read RECIST scans performed whilst on randomised treatment, after discontinuation of randomised treatment and after first dose of open label treatment.

A log-rank test was planned for the primary analysis of PFS (unadjusted model with treatment factor only).

Results

Participant flow



Recruitment

The study (period from 23 November 2006 to 31 July 2009 (date of data cut-off)) was conducted at 63 study sites in Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, India, Italy, Korea, Netherlands, Mexico, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Switzerland, and the United States.

Conduct of the study

There were 7 amendments of the study protocol that occurred for 5 of them after the last patient was enrolled (data not shown).

Baseline data

Table 6 : Summary of demographic characteristics (ITT Analysis Set)

		Vandetanib 300mg (N=231)	Placebo (N=100/ = 99 for weight)	Total (N=331)
Age (years)	**Mean**	**50.7**	**53.4**	51.5
	SD	14.1	12.0	13.6
	Median	**50.0**	**52.5**	51.0
	Min	18	26	18
	Max	83	84	84
Age group	**≥18 - <40**	50 **(21.6)**	10 **(10.0)**	60 (18.1)
	≥40 - <65	132 **(57.1)**	70 **(70.0)**	202 (61.0)
	≥65 - <75	42 (18.2)	17 (17.0)	59 (17.8)
	≥75	7 (3.0)	3 (3.0)	10 (3.0)
Sex n (%)	Male	134 (58.0)	56 (56.0)	190 (57.4)
	Female	97 (42.0)	44 (44.0)	141 (42.6)
Race n (%)	Black	1 (0.4)	1 (1.0)	2 (0.6)
	Caucasian	218 (94.4)	97 (97.0)	315 (95.2)
	Oriental	8 (3.5)	1 (1.0)	9 (2.7)
	Other	4 (1.7)	1 (1.0)	5 (1.5)
Weight (kg)	Mean	70.4	70.2	70.3
	SD	17.3	16.8	17.2
	Median	68.0	69.0	68.0
	Min	38	36	36
	Max	125	115	125

A medical history of previous thyroidectomy was noted in 90.3% of patients, diarrhoea in 45.0%, and fatigue in 15.4%.

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

Numbers analysed

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

Table 7. Number analysed

	Number of patients

	Vandetanib 300 mg	Placebo	Total
Patients randomised	231	100	331
Patients included in Safety Analysis Set	231	99	330
Patients excluded from Safety Analysis Set	0	1	1
Randomised but not received blinded treatment	0	1	1
Patients included in Full Analysis Set	231	100	331
Patients included in Per-Protocol Analysis Set	215	91	307
Patients excluded from Per-Protocol Analysis Set	16	9	25
Patients included in PK Analysis Set	231	0	231
Patients excluded from PK Analysis Set	0	100	100
No evaluable PK sample	0	100	100

Outcomes and estimation

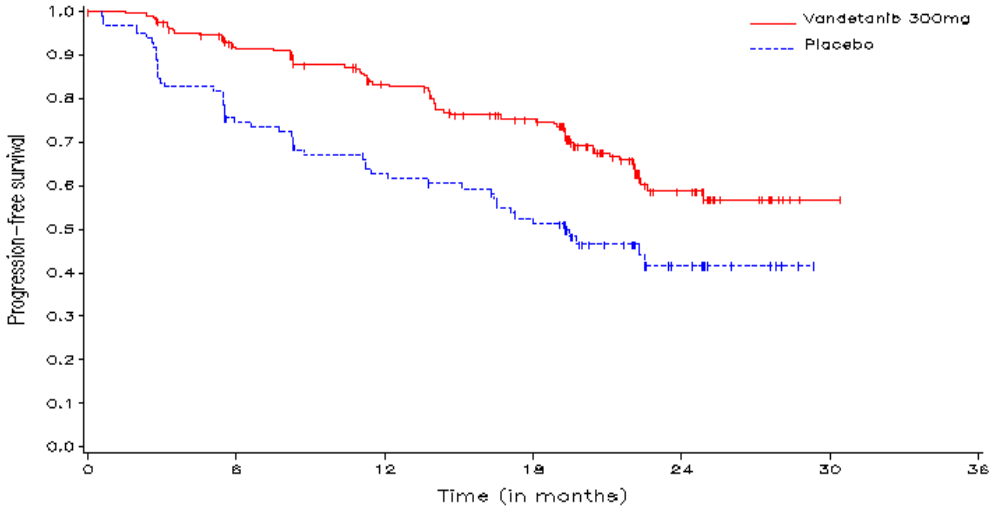
Primary endpoint

Table 8: Primary analysis of PFS (ITT)

			Treatment effect (vandetanib:placebo)		
Randomised treatment	**N**	**Number (%) of events**	**Hazard ratio**	**95% CI**	**logrank p-value**
Vandetanib 300mg	231	73 (31.6)	0.46	(0.31, 0.69)	0.0001
Placebo	100	51 (51.0)			

The median PFS in the placebo group was 19.3 months. The median PFS in the vandetanib group could not be calculated (because of an insufficient number of PFS events); a Weibull model was used to estimate the median PFS in the 2 treatment arms: the predicted median PFS for the vandetanib arm is 30.5 months.

Figure 1: Kaplan-Meier curves for the comparison of time to PFS



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

Sensitivity analyses for PFS

Table 9. Sensitivity analyses of PFS /analysis methods

Analysis set	Type of analysis	Randomised treatment	N	Number (%) of events	Treatment effect (vandetanib:placebo) -- Hazard ratio	95% CI	2-sided p-value
Per-protocol	Log rank test[a]	Vandetanib 300mg	215	71 (33.0)	0.45	(0.30, 0.68)	0.0002
		Placebo	91	48 (52.7)			
Full	Cox PH model[b]	Vandetanib 300mg	231	73 (31.6)	0.46	(0.32, 0.68)	0.0001
		Placebo	100	51 (51.0)			
Full	Whitehead method[c]	Vandetanib 300mg	231	73 (31.6)	0.51	(0.35, 0.72)	0.0002
		Placebo	100	51 (51.0)			

A hazard ratio < 1 favours vandetanib.
PFS was derived from all available central read RECIST assessments.
[a] Log rank test with treatment as the only factor in the PP analysis set.
[b] Cox proportional hazard regression model is adjusted for treatment and baseline covariates.
[c] Whitehead method used to assess the impact of a differential frequency of assessments in the treatment arms.

Table 10. Sensitivity analyses of PFS - derivations of PFS (ITT)

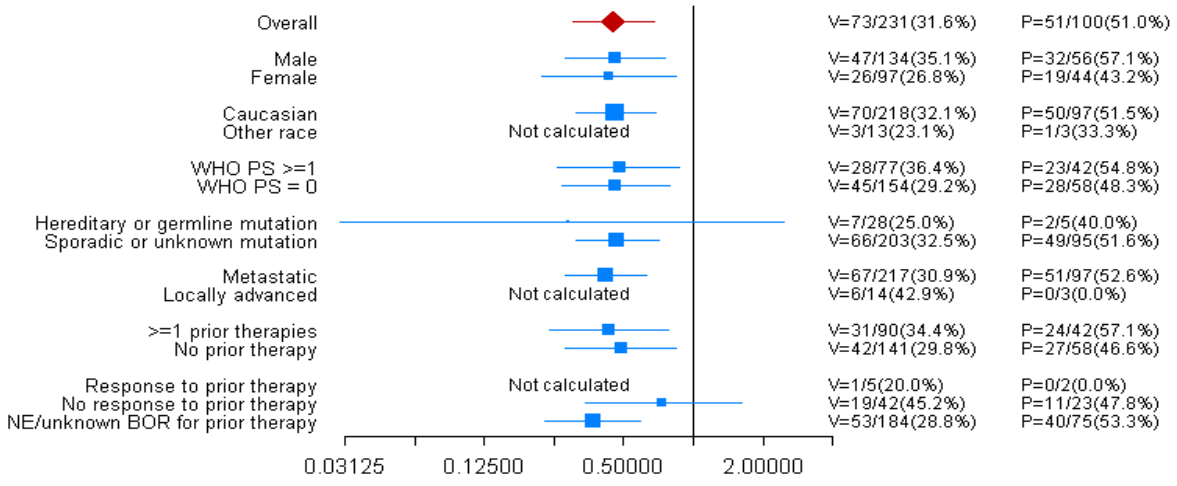
Derivation	Randomized treatment	N	Number (%) of events	Treatment effect (vandetanib:placebo) -- Hazard ratio	95% CI	2-sided p-value
Excluding open label[a]	Vandetanib 300mg	231	64 (27.7)	0.27	(0.18, 0.41)	<0.0001
	Placebo	100	59 (59.0)			
Site read[b]	Vandetanib 300mg	231	101 (43.7)	0.40	(0.27, 0.58)	<0.0001
	Placebo	100	62 (62.0)			
Hypointense lesions[c]	Vandetanib 300mg	231	78 (33.8)	0.49	(0.33, 0.72)	0.0003
	Placebo	100	52 (52.0)			
Calcified lesions[d]	Vandetanib 300mg	231	74 (32.0)	0.47	(0.31, 0.70)	0.0002
	Placebo	100	51 (51.0)			

[a] PFS was imputed for patients who took open label treatment in the absence of progression based on changes in TL size whilst on randomized treatment.
[b] PFS derivation used site read RECIST assessments, excluding any assessments of scans performed whilst on open label treatment.
[c] PFS derivation treated 1st appearance of hypointense or hypodense lesions in the 1st 2 follow-up scans as PD on that scan date.
[d] PFS derivation did not use the correction for calcified lesions.
log rank test with treatment as the only factor.

Subgroup analyses on the primary endpoint

The following subgroup analyses, pre-specified prior to unblinding, were performed using a log rank test with treatment as the only factor: Forest plots are presented below (for pre-specified RET mutation status, CTN doubling time, CEA doubling time, p-VEGF at baseline, p-VEGFR2 at baseline and p-bFGF at baseline these primary pharmacology) .

Figure 2: Subgroup analyses for PFS - Baseline characteristics and disease status (ITT)

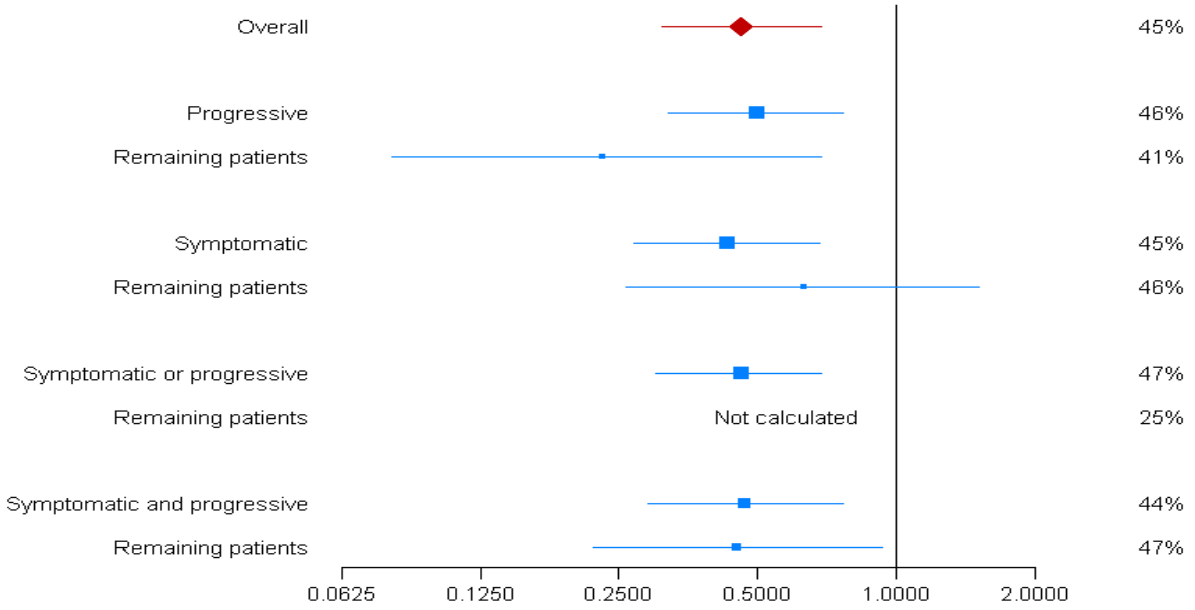


PFS was derived from all available central read RECIST assessments. Prior therapy refers to systemic anti-cancer therapy for MTC taken prior to the first dose of randomised treatment. A response to prior therapy is defined as a BOR of CR or PR to the most recent prior therapy. No response to prior therapy is defined as a BOR of SD or PD to the most recent prior therapy.

The superiority of vandetanib over placebo is consistent across all pre planned subgroups, even if not significant in all of them. No HR is greater than 1.

Most patients (all but 18 patients) had either progressive disease or symptoms at baseline (12 patients without progression and without symptoms and 6 patients with unknown progressive status and without symptoms); 25 patients were only symptomatic; 64 patients had only progressive disease; 186 patients had symptomatic and progressive disease. 307 patients were known to be progressive or symptomatic.

Figure 3: PFS and ORR for 4 Ad Hoc Subgroups based on disease status



Secondary endpoints

ORR

Table 11. ORR (ITT Set)

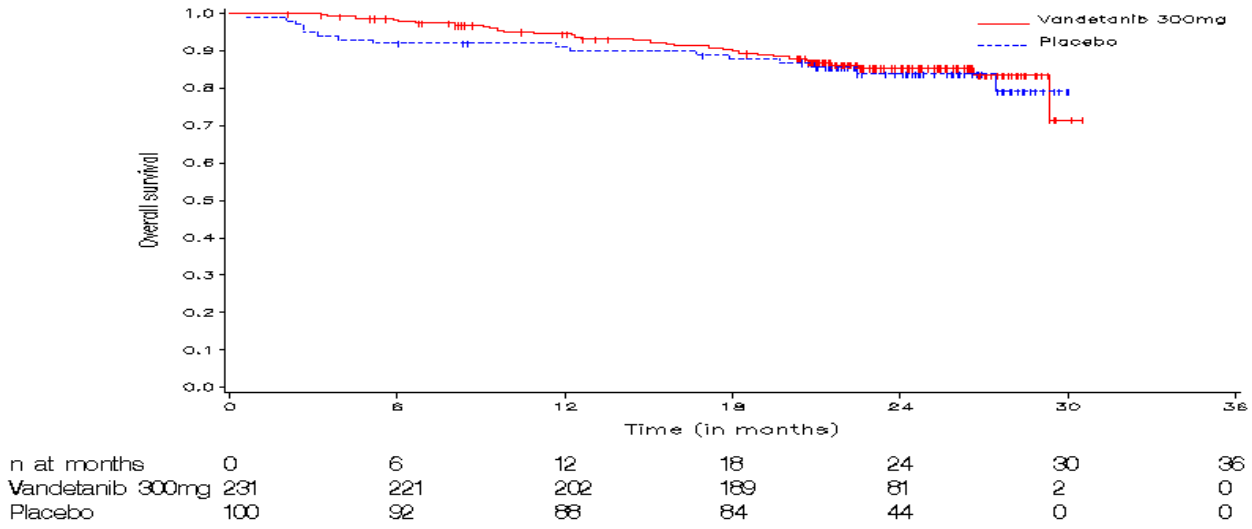
Treatment effect			**(vandetanib:placebo)**		
Randomised treatment	**N**	**Number (%) of responses**	**Odds ratio**	**95% CI**	**2-sided p-value**
(a) primary analysis using a logistic regression model with treatment as the only factor.					
Vandetanib 300mg	231	104 (45.0)	**5.48**	**(2.99, 10.79)**	**<0.0001**
Placebo	100	13 **(13.0)**			

ORR by site read assessment (excluding the open label period) was respectively 39% vs. 2.0%. None of the patients had complete response; the absence of response was due to stable disease in respectively 49.4% and 70% of the patients and disease progression 3.9% and 13.0% of the patients in the vandetanib and placebo treatment groups.

Median DOR could not be calculated for either group.

OS

Figure 4: Kaplan-Meier plot of OS (ITT)



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

No significant positive effect of vandetanib over placebo has been demonstrated on OS: HR of 0.89 (0.28, 2.85). In MTC setting, even at metastatic stage, OS is fair; one should also note that open label use of vandetanib was allowed after progression and cross-over from placebo (randomised treatment) to open label vandetanib was chosen in 58 of the 100 ITT placebo patients.

Time to worsening of pain (Patient reported outcome) and other secondary endpoints

There was an improvement in TWP (derived using the worst pain score from BPI and patient reported analgesic use) for vandetanib compared with placebo: HR 0.61, 95% CI (0.43, 0.87), p=0.0062; this was confirmed by sensitivity analyses that used the Cox proportional hazards. The median time to deterioration in worsening of pain was 7.85 months vs. 3.25 months in the placebo arm.

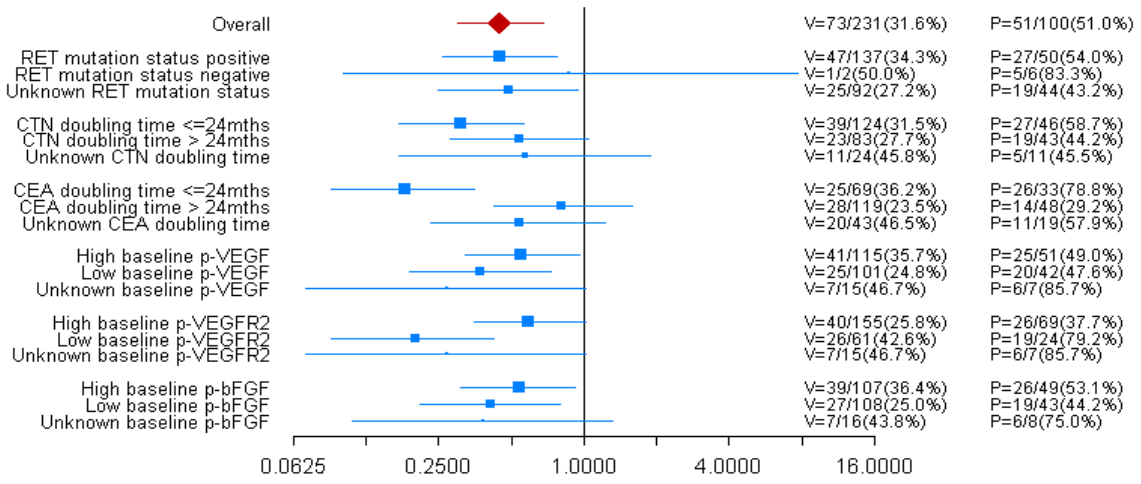
There were no observed differences between treatment groups for most exploratory variables such as time to deterioration in WHO PS [32.5 % vs. 34.0 %, HR 0.74, 95% CI (0.48, 1.14), p=0.1654, stool frequency, FACT_G score, or opioid analgesic medication use [OR 2.78, 95% CI 0.77 to 10.80, p=0.1193].

There was an improvement in weight in the vandetanib arm compared to the placebo arm [28.6% vs. 11%, OR 3.24, 95% CI 1.69 to 6.76, p=0.0003].

Pharmacodynamic parameters pertinent for activity in the MTC setting

Data from Study 58 are described in the figure below with regard to effect of vandetanib on biochemical response rate (CTN and CEA), according to RET status and other biomarkers.

Figure 5. Study 58/subgroup analyses for PFS - Biomarkers (ITT)



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.**)**

RET mutation status

RET mutation status was determined by sequencing the 6 most commonly mutated exons in MTC (10, 11, 13, 14, 15, and 16) and by evaluating for the M918T mutation using an amplification refractory mutation system (ARMS) analysis as there is no standard or routine practices for how to test for somatic RET mutations in the tumours of patients with advanced MTC.

A RET positive mutation status was defined as having a mutation either observed from the sequencing or ARMS assay. RET mutation negative status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons, and the ARMS assay negative for a M918T mutation. Unknown RET mutation status was documented when 1 or more sequencing assay was unsuccessful (non-informative), and none of the successful assays demonstrated a mutation.

All patients included in the phase II supportive trials (Studies 08 and 68) had hereditary MTC, documented as RET positive in all patients in study 08 and RET positive in 17/19 and unknown in 2/19 in study 68.

Patients included in the pivotal phase III trial (Study 58) had either sporadic or hereditary MTC. Out of 331 patients, 287 (86.7%) had sporadic MTC, 33 (10.0%) patients had hereditary MTC (more, n=28 in the vandetanib vs. n=5 in the placebo group), and 11 (3.3%) patients had unknown status. Diagnosis of hereditary MTC was based on family history if RET mutation status was unavailable. Patients with hereditary MTC who had a documented germline mutation in RET were not required to provide a mandatory tumour collection sample. All patients with sporadic MTC had to submit a suitable archived tumour sample before randomisation.

Study 058 initially had a co-primary analysis population to evaluate the efficacy of vandetanib in patients with a RET mutation as well as in the overall population which was removed when the RET could not be determined for a major proportion of patients after completion of recruitment.

Measurement of RET mutation status in the RET proto-oncogene was (after amendment) a secondary objective and was performed on a tumour samples from all patients who did not have a documented germline RET mutation.

RET mutation was positive in 187 (56.5%) patients, unknown in 138 (41.1%), and shown negative in only 8 patients (2.4%), including 2 patients in the vandetanib group. At 12 months, the progression rate (vandetanib vs. placebo) was 34.3 % (47/137) vs. 54.0 % (27/50) in patients with RET + status, 27.2 % (25/92) vs. 43.2 % (19/44) in patients with RET unknown status and 50.0 % (1/2) vs. 83.3 % (5/6) in patients with RET – status, respectively.

Correlation between RET mutation status and clinical outcome could not be clearly evaluated in study 58 because in 41.1%% of patients in study 58 RET mutation status was unknown.

Table 12. Efficacy endpoints in RET mutation positive patients and the 79 patients proven without M918T mutation and with no other RET mutation identified.

Efficacy Endpoint	RET Mutation Positive (n=187)[a]	Patients with No M918T Mutation and No Other Identified Mutation (n=79)
PFS HR (95% confidence interval)	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)
Predicted median PFS (months) (vandetanib vs. placebo)	29 vs. 18	28 vs. 18
Objective response rate (vandetanib arm)	52%	35%
Duration of response (months)	22	18

a RET mutation positive hereditary and sporadic MTC patients

Following a post-hoc analysis, efficacy endpoints were studied for seventy nine patients. These patients were identified as without M918T mutation and with no other RET mutation (71 patients with sporadic MTC previously classified as RET mutation "unknown" and 8 patients with sporadic MTC previously classified as RET mutation "negative "). Forty six patients were randomised to vandetanib and 33 patients to placebo. Table 12 compares the efficacy analysis observed in RET mutation positive patients versus RET mutation negative patients (defined as having no mutation at the most common site of RET mutation (M918T) and no other RET mutation identified)

For vandetanib in 'RET mutation negative' patients, the ORR was 35% [16 /46,] versus 52%. Absolute difference was 17%, and relative difference was 33%. Vandetanib is suggested to prolong PFS compared to placebo in that subgroup, with a HR for PFS of 0.57 [95% CI 0.29-1.13]. The results are not significant in the RET negative patients as the higher bound of the 95% CI is over 1 (1.13) and the HR for PFS is lower in RET mutation negative' patients as defined above as compared with RET positive patients [HR for PFS =0.45 95% CI 0.26-0.78]. Duration of response is 18 months instead of 22 months (absolute difference 4 months, relative difference 18 % shorter).Predicted mean PFS is similar (29 vs. 28) and longer than placebo (18 months).

Biochemical response rate: CTN and CEA

Biochemical response rate (CTN and CEA), markers of activity of vandetanib in MTC, were evaluated as secondary efficacy endpoints in the 3 clinical studies in MTC, the open phase II (Study 08 and 68) and in the pivotal phase II-III study vs. placebo (Study 58) as percentage of patients with a best biochemical response (respectively CTN / CEA) of CR or PR. CR was defined as complete normalization of the CTN level (≤10 pg/ml for men and ≤5 pg/ml for women) /CEA level (2.5 pg/ml) confirmed by a

repeat assessment > 4 weeks later. PR was define as decrease in the CTN/CEA level of at least 50% from baseline confirmed by a repeat assessment > 4 weeks later.

In the phase II study (Study 08) with vandetanib 300 mg, CTN response was observed in 80% (24/30) of patients and CEA response in 53% (16/30) of patients. In the phase II study with vandetanib 100 mg (68), CTN response was observed in 15.8% of patients (3/19 patients) who experienced a reduction in CTN of at least 50% that was sustained for at least 4 weeks; 5.3 % of patients (1/19 patients) experienced a reduction in CEA of at least 50% from baseline that was sustained for at least 4 weeks.

In the pivotal phase II-III study (58), there was a statistically significant difference between vandetanib and placebo arm for both CTN and CEA response:

- CTN (CR plus PR): OR 72.86, 95% CI (26.22, 303.2), p<0.0001
- CEA (CR plus PR): OR 52.03, 95% CI (15.95, 320.3), p<0.0001.

CTN doubling time ≤ 24 months and CEA doubling time ≤24 months are known to be markers of poor prognosis and more aggressive disease. In study 58, the efficacy of vandetanib on PFS was more marked in comparison with placebo in patients with CTN doubling time ≤ 24 months and CEA doubling time ≤24 months (statistically significant difference versus placebo in these subgroups).

Forest plots of subgroup analyses for PFS (according to baseline characteristics, disease status and biomarkers) have been submitted. As the global interaction test was not statistically significant at the 1% level (p=0.177), unplanned post hoc individual interaction tests were performed with a 10% significance level for all factors included in the forest plots.

The percentage of patients with ORR was higher in patients with CEA doubling time ≤24 months at baseline compared with CEA doubling time >24 months: 53.6% versus 37 % respectively. The percentage of patients with ORR was higher in patients with CTN doubling time ≤24 months at baseline compared with CTN doubling time >24 months: 46.8% vs. 39.8 % respectively. CEA and CTN doubling times and tumor size have been linked to the rate of objective progression in MTC. HR for PFS was in favour of vandetanib in patients with tumor size <10 cm and ≥ 10 cm, but seems somewhat better in patients with the largest tumors≥ 10 cm.

A significant effect on PFS was demonstrated in patients with tumor size ≥ 10 cm at baseline but not in patients with tumor size <10 cm .

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for pivotal Study 058

Title: An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Centre Study To Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer		
Study identifier	D4200C00058	
Design	Randomized, double-blind, placebo-controlled, multi-centre phase III study	
	Duration of main phase: Duration of Run-in phase:	Until required number of PFS events not applicable

	Duration of Extension phase:		not applicable
Hypothesis	H0: no difference between vandetanib and placebo H1: difference between vandetanib and placebo		
Treatments groups	Vandetanib		Vandetanib until objective disease progression, 300mg once daily
	Placebo		Placebo until objective disease progression, 300mg once daily
Endpoints and definitions	**Primary endpoint:** PFS	Progression Free Survival	Time from randomization to objective disease progression or death.
	Secondary endpoint: ORR	Objective Response Rate	Percentage of patients with a best objective response (BOR) of complete (CR) or partial (PR) response (RECIST criteria).
	Secondary endpoint: OS	Overall Survival	Time from date of randomisation to date of death
Database lock	31 July 2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	All randomized patients (Full Analysis Set) 103 weeks			
Descriptive statistics and estimate variability	Treatment group	Vandetanib	Placebo	
	Number of subject	231	100	
	PFS (median)	30.5 months	19.3 months	
	Hazard Ratio	0.46		
	95% CI	0.31-0.69		

Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	vandetanib *vs*. placebo
		Log rank P-value (2-sided)	0.0001
Notes	The analysis for PFS was performed using the long-rank test and was based on all the available central read assessments		

Analysis description	**Secondary Analysis**			
Analysis population and time point description	All randomized patients (Full Analysis Set) 103 weeks			
Descriptive statistics and estimate variability	Treatment group	Vandetanib	Placebo	
	Number of subject	231	100	
	ORR	45.0%	13.0%	

	OS (median)	Not reached	Not reached	
	Hazard Ratio	0.89		
	95% CI	0.28-2.85		
Notes				

Analysis performed across trials (pooled analyses and meta-analysis)

No analyses performed across trials were submitted.

Clinical studies in special populations

Preliminary dose-finding and safety results of Study 79 in 6 paediatric patients with hereditary MTC were reported, with objective response in 5 patients.

Supportive studies

Preliminary results of a phase II, placebo controlled randomised study (study 79) of vandetanib 300 mg in 145 patients with locally advanced or metastatic papillary or follicular thyroid carcinoma failing or unsuitable for radioiodine therapy found a HR of 0.62 (0.43,0.92), p=0.017 on the primary endpoint PFS without any significant difference on the secondary endpoints.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy in the present submission is based on a pivotal study (Study 58) with vandetanib 300 mg daily. Study 58 was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of vandetanib versus placebo in patients with unresectable locally advanced or metastatic MTC.

The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib as compared to placebo in patients with unresectable locally advanced or metastatic MTC. A total of 331 patients were randomized (2:1) to receive vandetanib 300 mg once daily (231 patients) or placebo (100 patients).

There was no substantial imbalance between treatment arms with respect to demographic and baseline characteristics, with the exception of age. Of 331 patients, 287 (86.7%) had sporadic MTC, 33 (10.0%) patients had hereditary MTC, and 11 (3.3%) patients had unknown status. The patients who participated in this study were generally representative of a population of patients with unresectable locally advanced or metastatic MTC population, and their demographic and baseline characteristics generally resembled those in the target population. There was a statistically significant difference at baseline in the % of patients <40 years of age in the vandetanib and placebo group, p=0.02. Age was not a pre-planned subgroup analysis for efficacy data.

A significant increase in PFS versus placebo on the primary analysis (HR=0.46, 95% CI, 0.31 to 0.69, p=0.0001) was observed. The predicted median PFS (Weibull model) for the vandetanib arm was 30.5 months, which is approximately an 11-month delay for the vandetanib arm when compared with the

19.3 months median PFS in the placebo arm. The gain in PFS was maintained over time. Post-hoc sensitivity analysis of PFS adjusting for CTN and for CEA at baseline were performed and did not show any influence of baseline imbalance in CTN values and CEA values. Except for response in terms of CEA doubling time, the superiority of vandetanib over placebo on PFS was consistent across all pre planned subgroups, even if not significant in all of them.

The results observed on PFS were supported by results on some secondary endpoints such as ORR (45 % vs. 13.0 %, OR 5.48 (2.99, 10.79), <0.0001 for the primary analysis). The results on biochemical response also supported the primary endpoint. For CTN OR = 72.86, 95% CI of 26.22, 303.2; p<0.0001 and for CEA OR = 52.03; 95% CI of 15.95, 320.3; p<0.0001 with more marked effect of vandetanib on PFS in patients with more aggressive stage of the disease characterised by CTN doubling time ≤ 24 months and CEA doubling time ≤24 months. No significant positive effect of vandetanib over placebo has been demonstrated on OS: HR of 0.89 (0.28, 2.85). It is likely that it will not be possible (even with more mature data) to establish a long term survival outcome from the pivotal study and this could be in part caused by the open label use of vandetanib after progression on randomised treatment. Because of the proposed cross-over at progression, the OS comparison in fact compares populations that differ mainly by the fact that vandetanib has been proposed early (experimental group) or later on, at progression (placebo arm).

95% of the study population had metastases at baseline. Because of the very small number of patients without metastasis treated with vandetanib (14 patients only), no firm conclusion can be made about efficacy and B/R in patients without metastasis.

Following the SAG's advice, the indication was revised to include aggressive and symptomatic disease. The choice of '*aggressive*' instead of '*progressive*' was justified by the fact that the term of "progressive" remains ambiguous (RECIST progression as in the primary criteria or including clinical, RX and biological criteria) and the term "aggressive" is likely to address patients condition with rapid deterioration, for whom an urgent treatment is required.

Only 6 patients with moderate renal failure were randomised to vandetanib (1 with severe renal impairment, NI criteria). These 6 patients were initially treated with 300 mg but the dose was reduced for AEs in 5/6 patients to 200 mg and further to 100 mg in 1 patients. The safe and effective dose in patients with moderate or severe renal failure has not been established (see sections 4.2 and 4.4 of the SmPC).

At present optimal duration of treatment remains unclear and should be left to the clinical evaluation and decision of the treating physician. A dose-finding study analyzing the safety and activity of 150mg vs 300mg due to be completed in July 2014 will address this issue (see section on Pharmacovigilance).

RET mutation status

The activity of vandetanib in RET mutation negative patients is indirectly supported by the activity of the drug observed in the subgroup of 138 patients in Study 58 whose RET status could not be successfully established. In the vandetanib arm, PFS at 12 months for this subgroup of patients was 27.2 % compared to 34.3 % in patients with RET + status.

In a post-hoc analysis, further data from 71 patients previously classified as RET mutation "unknown" and 8 patients previously classified as RET mutation "negative" showed efficacy (see Table 12) Therefore, the available evidence suggests but does not fully confirm efficacy of vandetanib in RET negative tumours.

Moreover, it is not certain that those patients tested RET negative in the post-hoc analysis are not positive for mutation on other exons. It is equally not certain that those patients tested RET negative from old tumour sample were still RET negative at the time of initiation of treatment. Therefore, it is difficult to draw an unequivocal conclusion of the size of the benefit of vandetanib in patients with RET mutation negative tumours.

Given that the precise mechanism of action of vandetanib in RET remains unclear, the absolute benefit in these patients should be more precisely/directly determined. A conditional marketing authorisation was thus recommended, taking into consideration that the risk-benefit balance of vandetanib, as defined in Article 1(28a) of Directive 2001/83/EC, is positive, to gather the missing information.

In the framework of the conditional marketing authorisation,, given the need to confirm the benefit risk balance in RET negative patients, the following statements were included in the Product Information:

- In section 4.1 of the SmPC: "'For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1)

- In section 4.4 of the SmPC: "Patients without RET mutation may have a decreased benefit from vandetanib treatment and the benefit/risk balance for this group of patients may therefore differ from that of the group with RET mutations. For patients whose RET mutation status could be negative, a possible lower benefit should be taken into account before individual treatment decisions and the use of vandetanib should be carefully considered because of the treatment related risks. Therefore RET mutation testing is recommended. When establishing RET mutation status, tissue samples should be obtained if possible at the time of initiation of treatment rather than at the time of diagnosis (see sections 4.1 and 5.1)

- In section 5.1 of the SmPC: "In Study 58, RET mutation testing was performed by using the polymerase chain reaction (PCR) based Amplification Refractory Mutation System (ARMS) assay for the M918T mutation, and direct sequencing of DNA for mutations in exons 10, 11, 13, 14, 15 and 16 (site of M918T mutation) on all sporadic patients where DNA was available (297/298).

  However, RET status could not be tested in a large proportion of patients (mainly because of unavailable results for direct sequencing of DNA) and response rate was somewhat lower in the patients with unknown RET status compared with RET mutation positive status: 51.8% vs. 35.9 % respectively. In the blinded comparison of vandetanib vs. placebo, only 2 patients known to be RET negative at all 6 exons received vandetanib and none demonstrated responses.

  A post-hoc subgroup analysis of RET negative status based on absence of M918T mutation of the pivotal study 58 was performed. A patient was considered to have a RET mutation if either an M918T mutation by the ARMS assay, or a RET mutation in any exons sequenced was present in the tumour. Actually 79 patients were identified by absence of an M918T mutation and no RET mutation identified at any of the other 6 exons tested but in 71 of such patients sequencing of the 6 exons was incomplete. M918T mutation is the most frequent mutation observed inpatients with sporadic MTC; however it cannot be ruled out that some patients tested RET negative for M918T mutation might be positive for mutation on other exons.

Results according to RET status (positive, unknown and RET M918T mutation negative definition) are presented in Table 3, Section 5.1 of the SmPC.

- The SmPc and Package Leaflet have also been amended, referring to the medicinal product as having been authorized under the conditional approval scheme.

Additional expert consultation

The SAG was requested to define the restricted population of patients in whom the absolute benefit in terms of progression prevention would compensate for the overall safety profile of vandetanib and to comment on whether other possible methods as FISH or RNA studies would be more sensitive and specific to determine RET status.

In view of the associated risks, the SAG considered that it was important to limit treatment with vandetanib to patients who are in real need for treatment. This can be established based on clinical and biological criteria. From a clinical point of view, this corresponds to patients that can be identified as having a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need for treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin and/or CEA as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence the treatment. Similarly, imaging data alone is not expected to be useful in identifying patients in need for treatment. From a biological point of view, the efficacy of vandetanib has been established only in patients with RET mutation-positive tumours. The efficacy is unknown in RET mutation-negative tumours. Further studies are needed, using biopsy material in the metastatic setting, to study the effect in RET mutation-negative tumours and to clarify the exact mechanism of action of the drug.

Additional efficacy data needed in the context of a conditional MA

Current evidence supports the use of vandetanib in patients with unresectable locally advanced or metastatic medullary thyroid cancer. However, from a quantitative point of view, the specific benefit in RET – MTC patients might be less as compared with what was observed in RET+ MTC tumours. Therefore, based on the available evidence, there is a need to further investigate any quantitative differences in terms of efficacy in RET negative patients with vandetanib that are not known at present. As a result, the CHMP considered the following measure necessary to address the missing clinical data in the context of a conditional MA:

A non-randomised study of vandetanib in patients with sporadic medullary thyroid cancer with known RET mutation status to include 60% of patients who receive vandetanib in the CHMP approved indication within the EU. Patients will be followed for 2 years and an interim analysis will be presented 12 months after first inclusion. Data will be collected and analyzed at pre-specified times.

The inclusion criteria will be based on the SmPC indication, sporadic medullary thyroid cancer and known RET mutation status. RET mutation negative patients who do not receive vandetanib due to RET status or contraindication should also be to enrolled and followed in order to have a control group for patients with RET negative status. Exclusion criteria should be limited as much as possible to contra-indications outlined in section 4.3 of the SmPC.

Patients will not be required to have a fresh tissue biopsy to determine RET status before enrolment. However RET status must be determined and a recent determination of such status should be obtained as often as possible even in patients previously tested at an earlier stage of their disease. Determination of RET status should be made preferably just prior to the initiation of treatment. Tissue type used for assay, date of tissue biopsy, assay type and definition used for RET mutation positive and negative will be collected.

Efficacy endpoints will include ORR, DCR and PFS. The main analysis will compare efficacy parameters of vandetanib in RET mutation positive and RET mutation negative patients, with reference to the respective outcomes observed in RET mutation positive and RET mutation negative patients who do not receive treatment. Safety analyses will be determined for the overall population, RET mutation negative and RET mutation positive patients. At each visit, a safety assessment will be conducted including QT prolongation information.

Efficacy assessments will be performed at 3 month intervals. PFS hazard ratio will be calculated for RET mutation positive versus RET mutation negative patients. The magnitude of the hazard ratio should be interpreted in the context of the non-randomized grouping of patients by RET mutation status.

The final analysis will be performed when at least 40 patients identified with RET mutation and 40 patients identified without evidence of RET mutation have been enrolled into the study and received vandetanib for 14 months. The total duration of the study is expected to be 38 months.

The applicant confirmed that it would be able to provide the clinical data requested as part of the specific obligation, set out in section 4 Recommendations.

2.5.4. Conclusions on the clinical efficacy

A randomized, double-blind, placebo-controlled study (Study 58) was conducted to demonstrate safety and efficacy of vandetanib 300 mg versus placebo. The result of the primary analysis of PFS showed 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).

The CHMP considers that an open label trial comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib, based on a CHMP approved protocol is necessary to address the missing efficacy data in the context of a conditional MA:

2.6. Clinical safety

The safety data submitted corresponds primarily to the safety analysis set in Study 58.

Patient exposure

The total estimated exposure to vandetanib (at all doses, and with concomitant chemotherapy as well as monotherapy) from clinical studies in healthy volunteers and patients is approximately 4000 patients. As of the data cut-off date of 19 October 2009, 1839 patients had received 300 mg

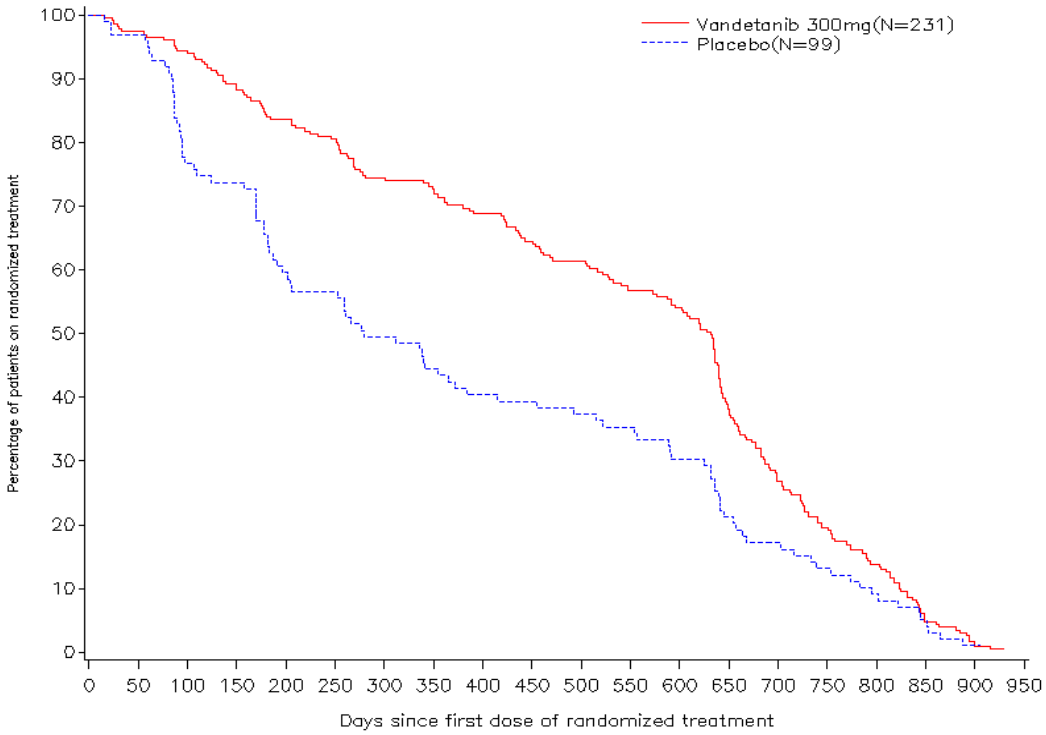
vandetanib in the pooled monotherapy clinical studies: 274 patients for at least 1 year and 84 patients for at least 2 years.

In pivotal study 58, patients were randomised to receive vandetanib 300 mg or placebo, continuing on blinded treatment until objective disease progression. A total of 231 patients were treated with vandetanib 300 mg monotherapy and 99 patients received placebo in the randomised phase.

Upon disease progression, patients were discontinued from blinded study treatment and then unblinded and given the option to receive post-progression open label treatment with vandetanib 300 mg (or receive a permanently reduced dose, if applicable), or enter follow-up for survival status. A total of 58 (58%) of randomised placebo patients and 44 (19%) randomised vandetanib patients received vandetanib during the open label treatment. Overall, there were no substantial imbalance regarding patients characteristics, except in the percentage of patients ≤ 40 y at baseline in the vandetanib arm.

The mean duration of exposure was longer for vandetanib 300 mg (75.0 weeks for total exposure and 73.6 weeks for actual exposure) than for placebo (53.9 weeks for total exposure and 53.7 weeks for actual exposure) (See Figure X below).

Figure 6. Percentage of patients by exposure on randomised treatment in Study 58 (safety analysis set)



At the date of data cut-off, of the 231 patients randomised in vandetanib 300 mg arm, 162 patients had been treated with vandetanib for at least 12 months, and 51 patients had been treated for at least 24 months. A total of 49.4% had a dose reduction or interruption: while 30.3% remained on 300 mg, 35.1% were reduced to 200 mg, 0.9% reduced directly to 100 mg and 33.7% discontinued (22.0 % due to disease progression; 6.1% due to AE, without having a dose reduction; 5.6% for other reasons).

The reasons for discontinuation of randomised treatment were:

- AEs in 12.1% of vandetanib patients and 3.0% of placebo patients.

- Disease progression in 30.7% vandetanib patients versus 55.0% placebo patients.

While randomized placebo patients remained on placebo therapy for a median of 265 days:

- Patients who remained on initial 300 mg dose remained on therapy for a median of 339 days

- Patients who had their dose reduced to 200 mg remained on therapy for a median of 502 days

- Patients who had their dose reduced to 100 mg remained on therapy for a median of 545.5 days

A summary of patients who had dose reductions and/or interruptions whilst on randomised treatment is provided below.

Table 14. Summary of patients who had dose reductions and/or interruptions whilst on randomised treatment (Safety Analysis Set)

	Actual dose level	**Reason for dose change**	**Vandetanib N=231 (%)**	**Placebo N=99 (%)**	**Total N=330 (%)**
Original dose level	300 mg /day		231 (100.0)	99 (100.0)	330 (100.0)
Dose reduction or dose interruption		Total	114 (49.4)	15 (15.2)	129 (39.1)
Dose reductions	**200 mg /day**	**Total**	**81 (35.1)**	**3 (3.0)**	**84 (25.5)**
		AE < grade 3	19 (8.2)	1 (1.0)	20 (6.1)
		AE ≥ grade 3	19 (8.2)	0 (0.0)	19 (5.8)
		Diarrhoea < grade 3	5 (2.2)	0 (0.0)	5 (1.5)
		Diarrhoea ≥ grade 3	5 (2.2)	1 (1.0)	6 (1.8)
		QTc Prolongation	16 (6.9)	0 (0.0)	16 (4.8)
		Rash < grade 3	9 (3.9)	0 (0.0)	9 (2.7)
		Rash ≥ grade 3	6 (2.6)	0 (0.0)	6 (1.8)
		Other	9 (3.9)	1 (1.0)	10 (3.0)
	200 mg every other day	Total	1 (0.4)	0 (0.0)	1 (0.3)
		AE ≥ grade 3	1 (0.4)	0 (0.0)	1 (0.3)
	100 mg / day	**Total**	**32 (13.9)**	**0 (0.0)**	**32 (9.7)**
		AE < grade 3	9 (3.9)	0 (0.0)	9 (2.7)
		AE ≥ grade 3	6 (2.6)	0 (0.0)	6 (1.8)
		Diarrhoea < grade 3	1 (0.4)	0 (0.0)	1 (0.3)
		Diarrhoea ≥ grade 3	4 (1.7)	0 (0.0)	4 (1.2)
		QTc Prolongation	8 (3.5)	0 (0.0)	8 (2.4)
		Rash < grade 3	3 (1.3)	0 (0.0)	3 (0.9)
		Rash ≥ grade 3	2 (0.9)	0 (0.0)	2 (0.6)
		Other	2 (0.9)	0 (0.0)	2 (0.6)
Dose interruptions	**0 mg**	**Total**	**109 (47.2)**	**15 (15.2)**	**124 (37.6)**
		AE < grade 3	33 (14.3)	7 (7.1)	40 (12.1)
		AE ≥ grade 3	46 (19.9)	4 (4.0)	50 (15.2)
		Diarrhoea <grade 3	7 (3.0)	2 (2.0)	9 (2.7)
		Diarrhoea ≥ grade 3	10 (4.3)	1 (1.0)	11 (3.3)
		Non-compliance	2 (0.9)	0 (0.0)	2 (0.6)
		QTc Prolongation	19 (8.2)	0 (0.0)	19 (5.8)
		Rash < grade 3	3 (1.3)	0 (0.0)	3 (0.9)
		Rash ≥ grade 3	12 (5.2)	0 (0.0)	12 (3.6)

		Other	9 (3.9)	4 (4.0)	13 (3.9)

A patient could have been dose reduced more than once, but was counted only once at each reduced dose.
Reasons for dose reduction/interruption are not mutually exclusive.

Adverse events

During the randomized treatment phase (study 58), a total of 3149 AEs including 289 grade 3-4 AEs, 141 SAEs and 6 fatal SAEs have been reported in 99.6% vandetanib patients. In placebo arm: 666 AEs including 46 grade 3-4 AEs, 19 SAEs and 2 fatal SAEs have been reported in 90.9% patients. The same pattern of AEs events identified during the clinical development of vandetanib is retrieved in study 58. The 5 most frequently reported AEs were diarrhoea, rash, nausea, hypertension, and headache. The percentage of patients with grade ≥ 3 AEs was 2.3 fold higher in vandetanib than in placebo arms: 55.4% vs 24.2%. (See table below).

Table 15. Summary of patients who had at least 1 AE in any category whilst on randomized treatment (Safety analysis set)

AE category	Vandetanib 300mg (N=231) (%) [a]	Placebo (N=99) (%) [a]	Total number (%) of patients (N=330)
Any AEs	230 (99.6)	90 (90.9)	320 (97.0)
Any vandetanib causally[b] related AE	222 (96.1)	59 (59.6)	281 (85.2)
Any AEs of grade 3 and higher	128 (55.4)	24 (24.2)	152 (46.1)
Any SAEs (including events with outcome = death)	71 (30.7)	13 (13.1)	84 (25.5)
Any SAEs with outcome = death	5 (2.2)	2 (2.0)	7 (2.1)
Any AEs leading to discontinuation of vandetanib	28 (12.1)	3 (3.0)	31 (9.4)
Any other significant AEs[c]	0 (0.0)	0 (0.0)	0 (0.0)

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As assessed by the Investigator.
[c] Any AE deemed by the sponsor to be significant.
AEs that occurred at any time during study, excluding any AEs that occurred during or after open label treatment.

The following adverse reactions were identified during the randomized treatment phase of study 58

Table 16 .Summary of grouped AEs whilst on randomized treatment - based on MedDRA groupings (Safety analysis set)

		__Vandetanib 300mg (N=231)__		__Placebo (N=99)__		
Grouped event type	Maximum CTCAE Grade	Number (%) of patients[a]	Event rate (per 1000 pt years)	Number (%) of patients[a]	Event rate (per 1000 pt years)	Total number (%) of patients (N=330)
Rash	Total	205 (88.7)	3942.9	23 (23.2)	279.5	228 (69.1)
	Grade 1	112 (48.5)	591.3	22 (22.2)	265.8	134 (40.6)
	Grade 2	77 (33.3)	346.3	1 (1.0)	9.8	78 (23.6)
	Grade 3	15 (6.5)	48.1	0 (0.0)	0.0	15 (4.5)
	Grade 4	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Diarrhoea	Total	131 (56.7)	845.4	27 (27.3)	334.5	158 (47.9)
	Grade 1	60 (26.0)	237.3	17 (17.2)	194.1	77 (23.3)

Grouped event type	Maximum CTCAE Grade	__Vandetanib 300mg (N=231)__ Number (%) of patients[a]	Event rate (per 1000 pt years)	__Placebo (N=99)__ Number (%) of patients[a]	Event rate (per 1000 pt years)	Total number (%) of patients (N=330)
	Grade 2	46 (19.9)	167.8	8 (8.1)	82.6	54 (16.4)
	Grade 3	24 (10.4)	80.6	2 (2.0)	19.7	26 (7.9)
	Grade 4	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Nausea/vomiting	Total	84 (36.4)	372.0	20 (20.2)	224.9	104 (31.5)
	Grade 1	54 (23.4)	204.3	18 (18.2)	201.9	72 (21.8)
	Grade 2	26 (11.3)	87.0	2 (2.0)	19.6	28 (8.5)
	Grade 3	4 (1.7)	12.2	0 (0.0)	0.0	4 (1.2)
Haemorrhages	Total	36 (15.6)	123.8	11 (11.1)	111.7	47 (14.2)
	Grade 1	25 (10.8)	83.4	5 (5.1)	50.5	30 (9.1)
	Grade 2	9 (3.9)	27.7	3 (3.0)	29.5	12 (3.6)
	Grade 3	2 (0.9)	6.1	1 (1.0)	9.8	3 (0.9)
	Grade 4	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
	Grade 5	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
QTc related events	Total	36 (15.6)	125.6	4 (4.0)	40.2	40 (12.1)
	Grade 1	8 (3.5)	24.8	1 (1.0)	10.0	9 (2.7)
	Grade 2	8 (3.5)	25.0	0 (0.0)	0.0	8 (2.4)
	Grade 3	19 (8.2)	61.4	2 (2.0)	19.6	21 (6.4)
	Grade 4	1 (0.4)	3.0	1 (1.0)	9.8	2 (0.6)
Ischaemic heart disease	Total	5 (2.2)	15.4	2 (2.0)	19.7	7 (2.1)
	Grade 1	4 (1.7)	12.3	2 (2.0)	19.7	6 (1.8)
	Grade 3	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Ischaemic cerebrovascular conditions	Total	3 (1.3)	9.1	0 (0.0)	0.0	3 (0.9)
	Grade 3	3 (1.3)	9.1	0 (0.0)	0.0	3 (0.9)
Embolic and thrombotic events, venous	Total	2 (0.9)	6.1	4 (4.0)	39.7	6 (1.8)
	Grade 1	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
	Grade 2	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
	Grade 3	2 (0.9)	6.1	1 (1.0)	9.8	3 (0.9)
	Grade 4	0 (0.0)	0.0	1 (1.0)	9.9	1 (0.3)
ILD and similar events	Total	2 (0.9)	6.0	0 (0.0)	0.0	2 (0.6)
	Grade 3	2 (0.9)	6.0	0 (0.0)	0.0	2 (0.6)
Seizures	Total	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
	Grade 1	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)

Derived from Table 11.3.2.9.1.
SOC = System Organ Class, PT = Preferred Term.
a Number (%) of patients with AEs, sorted by group, 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 following adverse reactions were identified in clinical studies with patients receiving vandetanib as treatment for medullary thyroid cancer.

Table 17. Adverse drug reactions and system organ class

System Organ Class	Very commom	Common	Uncommon
Infection and infestation disorders	Nasopharyngitis bronchitis, upper respiratory tract infections, urinary tract infections	Pneumonia, sepsis, influenza, cystitis, sinusitis, laryngitis, folliculitis, furuncle, fungal infection, pyelonephritis	Appendicitis, staphloccocal infection, diverticulitis, cellulitis, abdominal wall abscess
Endocrine disorders		Hypothyroidism	
Metabolism and nutrition disorders	Appetite decreased, Hypocalcaemia	Hypokalaemia, hypercalcaemia, hyperglycemia, dehydration, hyponatremia	Malnutrition
Psychiatric disorders	Insomnia, Depression	Anxiety	
Nervous sytem disorders	Headache, parasthesia, dysaesthesia, dizziness	Tremor, lethargy, loss of consciousness, balance disorders, dysgeusia	Convulsion, clonus, brain oedema
Eye disorders	Vision blurred, corneal structural change (including corneal deposits and corneal opacity)	Visual impairment, halo vision, photopsia, glaucoma, conjunctivitis, dry eye, keratopathy	Cataract, accomodation disorders
Cardiac disorders	Prolongation of ECG QT interval(*)(**)		Heart failure, acute heart failure, rate and rhythm disorders, cardiac conduction disorders, ventricular arrhythmia and cardiac arrest
Vascular disorders	Hypertension	Hypertensive crisis, ischemic cerebrovascular conditions	
Respiratory, thoracic and mediastinal disorders		Epistaxis, hemoptysis, pneumonitis	Respiratory failure, pneumonia aspiration
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, vomiting, dyspepsia	Colitis, dry mouth, stomatitis, dysphagia, constipation, gastritis, gastrointestinal haemorrhage	Pancreatitis, peritonitis, ileus, intestinal perforation, faecal incontinence
Hepatobiliary disorders		Cholelithiasis	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash and other skin rections (including acne, dry skin, dermatitis, pruritis), nail disorders	Palmar-plantar erythrodysaesthiesia syndrome, alopecia	Bullous dermatitis
Renal and urinary disorders	Proteinuria, nephrolithiasis	Dysuria, hematuria, renal failure, pollakiuria, micturition urgency	Chromaturia, anuria

General disorders and administration site conditions	Asthenia, fatigue, pain, oedema	Pyrexia	Impaired healing
Investigations	ECG Qt interval prolonged	Increase of serum ALT and AST, weight decreased blood creatinine increased	Increased haemoglobin

* 13.4% vandetanib patients had QTc (Bazett's) ≥500 ms compared with 1.0% placebo patients. QTcF prolongation was >20ms in over 91% of patients, [20ms to 49ms] in 45.5%, [50ms to 99ms] in 44.2%, > 60ms in 35%, >100ms in 1.7%.

** including two sudden deaths in patients with QTc >550 ms

Serious adverse event/deaths/other significant events

Serious Adverse Events

The percentage of patients who had at least 1 SAE was higher in the vandetanib arm than in the placebo arm (30.7% vs 13.1%). There were 141 SAEs in vandetanib arm versus 19 in placebo arm. As displayed in the table below, the most commonly reported SAEs in the vandetanib arm pertained to the following SOCs:

- SOC infections: 32 SAEs (7 pneumonia, 5 Urinary tract infection, 4 pyelonephritis, 2 staphylococcal infections…)
- SOC GI disorders: 20 SAEs (5 diarrhoea, 1 pancreatitis, 1 colitis, 1 ileus…)
- Metabolism and nutrition disorder 16 SAEs (hypercalcaemia, decreased appetite, dehydration...)
- SOC vascular disorders: 11 SAEs (4 HTA, 4 hypertensive crisis, 1 accelerated HTA)
- Respiratory disorders 11 SAEs (3 pneumonitis, 2 fatal cases respiratory arrest/failure...)

Deaths

In the Safety Analysis Set, a total of 14.2% (47) patients had died at the time of data cut-off (31 July 2009): 13.9% of patients in the vandetanib arm and 15.2% of patients in the placebo arm.

Within 60 day safety follow-up

A total of 17 vandetanib patients and 11 placebo patients died within the 60-day safety follow up after vandetanib discontinuation. Out of these cases, there were 6 sudden deaths in the vandetanib arm: 2 related to prolonged QTc, and 4 additional suspected sudden deaths in patients still on treatment or <4 days after discontinuation There was 1 death related to pneumonia, 2 deaths related to nutrition disorders (malnutrition, dysphagia and anorexia leading to aspiration pneumonia), and 1 death related to cardiopulmonary insufficiency. There was a fatal case with ongoing suspected RPLS, and 3 additional deaths while ongoing SAE (staphylococcal infection, gastritis, pancreatitis). The fatal cause was assessed as unknown or due to MTC according to investigator. In the end, there were 3 deaths with objective progressive disease.

In contrast, in Placebo arm, there were 2 deaths related to gastrointestinal SAE, 5 deaths with objective progression, and 4 deaths that would be due to MTC (no objective progression).

After the 60-day safety follow-up,

A total of 15 vandetanib patients and 4 placebo patients died. Although most deaths (10/15) were assessed as related to MTC/disease progression by the investigator, there was an additional fatal case with ongoing suspected RPLS (no MRI performed). In contrast, in placebo arm, there were 3 deaths related to MTC or disease progression and one death due to suicide.

MTC was documented as the cause of death of 10.4% vandetanib patients and 14.1% placebo patients.

Furthermore, during the open label phase, there were no fatal cases among the first 58 randomized placebo patients while 2 occurred in the first vandetanib randomized patient group (pneumonia aspiration, suicide).

Other Significant Events

Skin and subcutaneous disorders

Almost 90% of patients developed a skin reaction whilst on vandetanib compared with 23% in placebo patients. Overall, rash (including acne, dermatitis acneiform) was reported in 80% vandetanib patients. In addition, photosensitivity reactions occurred in 13% patients who developed a rash only in sun-exposed areas. Patients were recommended to follow a program of skin protective measures. Two AEs of palmar-plantar erythrodysesthesia were reported.

Two cases of bullous dermatitis were reported, including 1 grade 3-4 AE. Steven Johnson syndromes and TEN have been previously reported in other vandetanib clinical trials (0.7%), some were fatal and represent an identified risk.

Gastrointestinal disorders

During the randomized phase, 80.5% vandetanib patients experienced a total of 595 gastrointestinal AES including 51 AEs grade ≥3 and 20 SAEs, compared with 56.6% placebo patients (108 AEs, 1 SAE gastrointestinal haemorrhage). Among the SAEs reported in vandetanib arm, there were: 1 pancreatitis, 1 ileus, 1 pneumatosis intestinalis, 1 small intestinal perforation, 1 colitis, 1 peritonitis, 2 dysphagia, 1 gastritis, 5 diarrhoea:

- Diarrhoea, which is one of the frequent symptoms of MTC, especially in patients with high CTN levels, was reported in 56% of vandetanib patients at all grades in study 58, i.e. a 2-fold increased percentage compared with placebo. It was the most common grade ≥3 AE reported in vandetanib patients (# 11%), with a time to onset of 151 days (range 9 to 415). At least, two patients experienced a SAE. Overall, the prevalence of diarrhea reaches approximately 40% at 3 months for all grades and does not increase after the first 3 months. The median duration was 267.5 days for the vandetanib arm and 49.5 days for the placebo arm. The management of diarrhea and vomiting which should include the monitoring of electrolytes is a major concern because of the increased risk of QTc prolongation.

- A bowel perforation occurred in a patient with a history of diverticulosis, 16 months after the start of vandetanib. Intestinal perforation is a identified risk in MTC patients receiving vandetanib.
- 3 cases of pancreatitis have been reported with vandetanib during the study: one in the randomised phase and 2 during the open label phase.

Cardiac disorders

A total of 35 cardiac AEs including 5 SAEs (4 deaths) have been reported in 30 vandetanib patients. In placebo arm, 16 AEs have been reported in 13 placebo patients including 2 SAEs (1 pericardial effusion, 1 pericardial haemorrhage), none were fatal.

Among the 35 AEs reported in vandetanib arm, there were: 2 cardiac failures (1 fatal), 2 Atrial Fibrillation (1 fatal), 1 Supraventricular Extrasystoles, 7 supraventricular arrhythmias (1 fatal), 4 Sinus Bradycardia, 3 Bundle Branch Block Left, 1 arrhythmia (1 fatal), 4 Bradycardia (1 fatal), 2 Tachycardia (1 SAE), 1 Nodal Arrhythmia, 1 Ventricular Tachycardia.

QTc prolongation

Overall, 31 (13.4%) vandetanib patients had QTc (Bazett's) ≥500 ms compared with 1.0% placebo patients, and 8 (3.47%) vandetanib patients had QTc ≥550 ms or increase from baseline ≥100 ms, based on a single value during randomised treatment.

Over 91% of patients experienced QTcF prolongation >20ms:

- In 45.5%: QTcF prolongation [20ms to 49ms]
- In 44.2%: QTcF prolongation [50ms to 99ms]
- In 35%: QTcF prolongation > 60ms
- In 1.7%: QTcF prolongation >100ms

In patients with QTc≥500msec:

- There was one fatal case
- Sex ratio: 8 male versus 23 female patients
- Age range: 23-83 years
- mean age: 50 years
- Baseline QTc: 408 – 476 msec
- Time to prolonged QTc: 1 week to 633 days.

Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28msec, median 35 msec). First QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time. The effect does not lessen over time. Prolonged QTc≥500msec was more frequent in female patients (75% versus 25% in male),

and the frequency of QTc≥500msec was increased in subgroups of patients with hypertension (20%), diarrhoea (>20%), serum Mg<LLN (31.3%) and with baseline cardiac impairment (32.1%).

Arrhythmia and QT prolonged AEs

There were 2 sudden deaths (in patients with QTc >550 ms), and 4 suspected sudden deaths.

Cardiac failure

One vandetanib patient had a Grade 1 AE of cardiac failure (following a grade 3 event of abnormal left ventricular function) and 1 patient had a Grade 5 SAE of cardiac failure acute during the randomised treatment period; no patients in the placebo arm reported these events.

Ischaemic heart disease

Ischaemic heart disease grouped events were reported in 2.2% vandetanib patients versus 2.0% in the placebo arm. In the vandetanib arm, 4 patients had events of grade 1 and 1 patient had an event of grade 3. Both patients in the placebo arm had grade 1 events.

Vascular disorders

A total of 39.0% vandetanib patients experienced an AE from the SOC Vascular disorders (vs 11.1% placebo patients).

- Hypertension which is a common side effect was reported in 31.6% vandetanib patients (versus 5.1% placebo), including 8.7% patients with Grade ≥3 events of hypertension, hypertensive crisis (1.7%), or accelerated hypertension. Two patients (0.9%) discontinued due to AEs of hypertension (1 patient with Grade 4 and 1 with Grade 2 hypertension). The prevalence of hypertension, hypertensive crisis, or accelerated hypertension was approximately 20% for the vandetanib arm within 3 months of treatment and this appeared to increase slightly over time throughout Study 58. The median duration of hypertension, hypertensive crisis, or accelerated hypertension was 261.5 days for the vandetanib arm and 188 days for placebo. The upper quartile durations were 609.5 and 259 days, respectively.
- Three (1.3%) patients, all in the vandetanib arm, had AEs of ischaemic cerebrovascular conditions, all of which were grade 3, while no patient in the placebo arm had these events.
- Thromboembolic events were reported less frequently in the vandetanib arm than in the placebo arm (0.9% vs 4.0%). Both events in the vandetanib arm were grade 3.

Nervous system disorders

A total of 256 AEs have been reported in 112 (48.5%) vandetanib patients. There were 16 reported AEs grade≥3 (2 headaches, 1 dizziness, 1 tremor, 1 disturbance in attention, 1 hyperesthesia, 1 motor dysfunction) and 9 SAEs: 1 brain edema, 1 cerebral ischemia, 1 peripheral sensorimotor neuropathy, 1 depressed level of consciousness, 2 loss of consciousness, 3 transient ischemic attacks).

In contrast, 40 AES have been reported in 32 placebo patients (32%): 4 AEs grade 3-4: 2 syncopes and 2 SAEs: 1 neuralgia, 1 hemiparesis. A total of 5 ischemic cerebrovascular events have been

reported in vandetanib arm versus none in placebo. Cerebrovascular event is an identified risk in the safety database of vandetanib.

Peripheral neurotoxicity

A total of 49 AEs related to paraesthesia, peripheral hypoesthesia, sensory neuropathy, neuropathy peripheral or tremor have been reported in vandetanib arm versus 9 AEs in placebo arm.

Reversible posterior leukoencephalopathy

Headache was reported more frequently in 25.5% vandetanib patients compared with 9.1% placebo patients and was subsequent to elevated blood pressure. There were no reported cases of RPLS in patients receiving 300 mg monotherapy. However, a total of 4 cases of RPLS have occurred in the vandetanib programme. One case occurred in Study 32 in a patient who received vandetanib 100 mg daily in combination with chemotherapy for NSCLC. Two cases occurred in paediatric patients with primary brain tumours receiving vandetanib with concomitant radiotherapy in investigator-sponsored (Study IRUSZACT0051). One case occurred in Study IRUSZACT0070 in a patient receiving vandetanib in combination with gemcitabine + oxaliplatin for transitional cell cancer.

Infections disorders

In 115 (49.8%) vandetanib patients (23 grade 3-4 AEs and 32 SAEs) versus 54 AEs in 36 (36.4%) placebo patients (5 AEs grade 3-4 and 2 SAEs including one fatal). Among the 32 SAEs reported under the SOC infection in vandetanib patients, there were 3 pneumonitis, 1 chylothorax, 1 pneumo-mediastinum, 1 pulmonary edema and 11 pneumonia (7 SAEs, one was fatal).

ILD and Pneumonia are an identified risk in the 3,000-patient vandetanib safety data base. In the monotherapy pool of 1839 patients, the majority of whom have lung cancer, the most common fatal event was pneumonia with 14 deaths. In all there were 110 events of pneumonia with 58 ≥Grade 3 and 73 serious. There were 15 cases of pneumonitis (6 ≥Grade 3, 8 serious, 2 fatal) and 7 cases of interstitial lung disease (1 ≥Grade 3, 6 serious, 2 fatal).

Respiratory disorders

During the randomized phase study, there were 165 AEs reported in 89 (38.5%) vandetanib patients (including 11 SAEs: 2 dyspnea, 1 hemoptysis, 3 pneumonitis, 1 bronchospasm, 1 respiratory failure, 1 pneumonia aspiration, 1 chylothorax, 1 respiratory arrest,) versus 75 AEs in 33 (33.3%) placebo patients (including 3 SAEs: 1 hemoptysis, 1 pleural effusion, 1 pulmonary thrombosis).

Globally, the number of AEs and the nature of the most frequent AEs reported in vandetanib arm compare well with those reported in placebo arm. Aspiration pneumonia, hemoptysis were reported by 1 patient in each treatment arm. However, there were 3 pneumonitis, 1 chylothorax, 1 pneumo-mediastinum, 1 pulmonary edema in vandetanib. Of note, there were only 2 pneumonitis grade ≥3 reported in the initial submission, while no SAE was mentioned.

No event of ILD occurred during randomised treatment. However, there was 1 cases of ILD reported in patients taking vandetanib in the open-label phase. No cases have been reported in the placebo arm. Although none of these reported cases were considered by the investigator to be related to vandetanib, ILD remains an identified risk in MTC patients.

Renal disorders

Overall, 24.7% of patients in the vandetanib arm compared with 10.1% of patients in the placebo arm experienced an AE in the SOC renal disorders.

- AEs of renal failure or renal insufficiency were reported in 5 vandetanib patients versus 1 placebo patient. In all cases an aggravating condition was present: vomiting in the case of the placebo patient; hypercalcaemia, dehydration, diarrhoea or pre-existing moderate renal insufficiency with diabetes in the patients receiving vandetanib.
- Nephrolithiasis was reported in 9 vandetanib patients and 1 placebo patient
- One related acute case of interstitial nephritis led to temporary withdrawal and a reduced 200 mg dose after resolving.
- Proteinuria was reported in 10% of vandetanib patients (26 AEs versus 3 in placebo arm).
- During randomised treatment, mean creatinine was consistently higher over time in the vandetanib arm than in the placebo arm. Furthermore, 90.9% vandetanib patients had a proteinuria on dipstick versus 28.3% placebo patients.

The number of patients who experienced an AE in the renal SOC was significantly higher in the vandetanib arm. Furthermore, during randomised treatment, mean creatinine was consistently higher over time in the vandetanib arm than in the placebo arm, 90.9% vandetanib patients had a proteinuria on dipstick versus 28.3% placebo patients.

Table 18. Shift table of creatinine clearance at baseline against maximum percentage decrease in creatinine clearance whilst on randomised treatment (Study 48)

Table 51 **Shift table of creatinine clearance at baseline against maximum percentage decrease in creatinine clearance whilst on randomised treatment (Study 58)**

		Maximum percentage decrease in creatinine clearance, N (%)				
Actual treatment	**Creatinine clearance at baseline**	**0-10**	**>10-20**	**>20-30**	**>30**	**Total**
Vandetanib 300 mg	Normal	4 (1.7)	15 (6.5)	28 (12.1)	21 (9.1)	68 (29.4)
	Mild impairment	0	29 (12.6)	53 (22.9)	66 (28.6)	148 (64.1)
	Moderate impairment	0	0	1 (0.4)	14 (6.1)	15 (6.5)
	Total	4 (1.7)	44 (19.0)	82 (35.5)	101 (43.7)	231 (100.0)
Placebo	Normal	15 (15.2)	6 (6.1)	1 (1.0)	0	22 (22.2)
	Mild impairment	34 (34.3)	21 (21.2)	3 (3.0)	4 (4.0)	62 (62.6)
	Moderate impairment	1 (1.0)	3 (3.0)	1 (1.0)	1 (1.0)	6 (3.1)
	Total	50 (50.5)	30 (30.3)	5 (5.1)	5 (5.1)	90 (90.9)

This table only contains patients who had either no change in creatinine clearance level, or patients who experienced a decrease in creatinine clearance level.
Data source: Clinical Appendix A: Table 120.68.1.

Based on the table above, 21% patients with a normal renal function had a decreased creatinine clearance > 20% (decrease>30% in 9% patients). Furthermore, 51.5% mild renal impaired patients had a decreased creatinine clearance > 20% (decrease> 30% in 28.6% patients). These figures show evidence of the vandetanib nephrotoxicity.

Psychiatric disorders

Reported incidences of insomnia and depression were more frequently reported in vandetanib patients than in placebo arm. Importantly, one patient died of a suicide 103 days after receiving his last dose of vandetanib during open-label treatment.

Hepatobiliary disorders

Overall 3.9% vandetanib patients compared with 1.0% placebo patients experienced a hepatobiliary disorders AE. Eventually, 3 patients who had a history of metastatic hepatic disease including gall bladder experienced bile duct stone, cholelithiasis and cholecystitis. None of the events were considered related to therapy with vandetanib.

Metabolism and nutrition disorders

A total of 35.1% vandetanib patients experienced 131 AEs (24 AEs grade 3-4 and 16 SAEs) versus 24 AEs (1 SAE) in 20.2% placebo patients. The sole serious AE grade 3-4 reported in placebo arm was diabetes mellitus. In contrast, 5 SAEs decreased appetite or malnutrition, 2 SAEs hypokaliema, 1 SAE hyperkaliemia, 2 SAEs hypocalcaemia, 3 SAEs hypercalcaemia, 2 SAEs dehydration, and 1 SAE hyponatremia were reported in vandetanib patients.

Based on the 5 narratives of fatal cases provided by the applicant, at least two patients died after a Grade 4 anorexia, one of malnutrition and respiratory failure (not documented), and one of pneumonia aspiration (not documented).

Patients with advanced MTC often have airway and esophageal compromise as a result of bulky disease around the neck—deaths from respiratory arrest and aspiration are not unexpected. However, a causal relationship between treatment with vandetanib and Patients 0009003 and 2801012 deaths cannot be ruled out.

Eye disorders

Abnormalities from visual assessment were more common in the vandetanib arm than the placebo arm, (83.6% versus 61.5%). The most notable difference between treatment arms was in abnormalities of the epithelium, which were observed in 49.7% vandetanib patients compared with 3.8% placebo patients. Vandetanib patients also had a higher frequency of stroma abnormalities (17.6% vs 3.8%) and abnormalities of the conjunctiva (7.5% vs 3.8%). Vandetanib patients had a lower frequency of abnormalities of blood vessels (6.9% vs 11.5%) and colour vision (7.5% vs 17.3%) relative to patients in the placebo arm. Six (5.9%) patients had AEs leading to discontinuation of open-label treatment, including 1 patient with blurred vision. 30.8% vandetanib patients who underwent ophthalmologic examinations had vortex keratopathy, compared with no patients in the placebo arm.

Drug Interactions

In Study 58, co-administration of drugs known to prolong ECG QT interval, whether or not clearly associated with Torsades de Pointes, was associated with a higher incidence of prolongation of the ECG QTc interval than when vandetanib was given without such drugs.

The potential for a PD interaction with respect to QTc between vandetanib and ondansetron was assessed in Study 21, a four-way cross-over study. Ondansetron 32 mg iv was administered alone or 6

hours after vandetanib 700 mg was administered. The mean effect of 32 mg ondansetron on QTc interval when given alone was 12.45 ms. The mean effect of 700 mg vandetanib 6 hours after administration was 17.29 ms. The combined effect of ondansetron, infusion 6 hours after 700 mg vandetanib, was 22.3 ms. These results point to an additive or slightly less than additive effect on mean QTc when ondansetron (32 mg) was administered as a 15-minute infusion to healthy volunteers who had received a single oral dose of 700 mg vandetanib.

Safety during open-label treatment in Study 58

A total of 102 patients had received open-label treatment with vandetanib by the data cut-off date of 19 October 2009. A total of 58 placebo patients received vandetanib during the open label study phase, and 42 of them were continuing at the time of the cut-off data. The reported incidence of AEs in the open label phase is similar in number and type to that seen in patients who initially received vandetanib in the randomised phase.

There were no fatal cases among the 58 placebo patients while 2 occurred in the vandetanib randomized patients. One patient died of an SAE of pneumonia aspiration during the open-label phase. One additional patient died of a suicide 103 days after receiving his last dose of vandetanib during open-label treatment. The event was not considered related to treatment by the investigator.

Laboratory findings

Table 19. Laboratory findings

Laboratory finding	
Protein in urine by dipstick[1]	Very common
Blood in urine by dipstick[1]	Very common
Increased serum TSH	Very common
Increased serum amylase	Very common
Increased serum lipase	Very common
Increased haemoglobin	Very common
Increased serum creatinine [2]	Very common

[1] Incidence of laboratory findings in a randomised clinical trial in medullary thyroid cancer, not of reported adverse events.

[2] The increases in serum creatinine were CTCAE grade 1-2, and may be related to inhibition of the human transport protein OCT2.

Haemoglobin

Mean values for haemoglobin were consistently higher with vandetanib compared with placebo in both males and females. The differences between treatment arms in mean haemoglobin values were more pronounced in females than males. In males these mean levels were higher by approximately 5 to 10 g/L in the vandetanib arm up to Week 72, when the differences between treatment arms diminished. In females the mean levels of haemoglobin were higher in the vandetanib arm by ≥10 g/L at the majority of time points.

One (0.4%) patient in the vandetanib arm and 2 (2.0%) patients in the placebo arm had CTCAE Grade 3 reductions in haemoglobin. There were no important differences with respect to mean values over time for haematology parameters other than haemoglobin.

ALT

Mean ALT values increased from baseline to Week 12 during randomised treatment before decreasing to the baseline level by Week 120. Mean ALT values during randomised treatment were consistently higher over time through Week 108 in the vandetanib arm compared with the placebo arm. Similar results were observed for median values. A higher percentage of patients in the vandetanib arm than the placebo arm shifted from baseline to a higher CTCAE grade for ALT during randomised treatment.

Liver function test (LFT) elevations were reported as an AE more frequently in the vandetanib arm than the placebo arm. These included alanine aminotransferase increased (9 [3.9%] vs 1 [1.0%] in the vandetanib and placebo arms, aspartate aminotransferase increased (10 [4.3%] vs 1 [1.0%]), transaminases increased (4 [1.7%] vs 0), and liver function test abnormal (1[0.4%] vs 0 patients). No patient had a concomitant bilirubin elevation.

Four (1.7%) patients in the vandetanib arm had laboratory findings for ALT of CTCAE grade 3 or 4 whilst on randomised treatment, compared with no patients in the placebo arm. Of 28 patients in the vandetanib arm who had an ALT elevation of grade 2 or higher, 21 patients returned to normal value (18 patients) or grade 1 ALT elevation (3 patients) without any change in vandetanib dose. In 3 patients ALT normalised (2 patients) or improved to grade 1 (1 patient) after dose reduction or interruption. Four patients still had an ALT of grade 2 at data cut-off. No patient had both an ALT elevation of 3 x ULN and a bilirubin elevation of 2 x ULN. No patient in the vandetanib arm discontinued due to AEs related to LFT elevations.

Creatinine

The mean creatinine level increased from 73.6 µmol/L at baseline to 91.6 µmol/L at Week 1 and remained relatively stable through Week 108 before decreasing slightly. Mean creatinine was consistently higher over time in the vandetanib arm than in the placebo arm. A higher percentage of patients in the vandetanib arm than the placebo arm shifted from baseline to a higher CTCAE grade for creatinine during randomised treatment.

No patient in either treatment arm had laboratory findings for creatinine of CTCAE grade 3 or 4 whilst on randomised treatment. There were 6 CTCAE grade 2 elevations in serum creatinine in the vandetanib arm versus none in the placebo arm. Of these 6 patients, 4 normalised or improved with dose interruption, reduction, or discontinuation, 1 patient had recurrent episodes of nephrolithiasis and pyelonephritis, and 1 patient continued to have elevated creatinine at the date of data cut-off.

A total of 9 (3.9%) patients in the vandetanib arm had an AE of blood creatinine increased, while no patient in the placebo arm had this AE. Two (0.9%) of these patients discontinued vandetanib treatment due to AEs of blood creatinine increased.

Calcium

The percentage of patients with laboratory variables for low calcium of CTCAE grade 3 or 4 whilst on randomised treatment was higher for the vandetanib arm than for the placebo arm (5.6% vs 3.0%).

Sodium

The percentage of patients with laboratory variables of high sodium for CTCAE grade 3 or 4 whilst on randomised treatment was higher for the vandetanib arm than for the placebo arm (1.7% vs 0%).

Thyroid Stimulating Hormone (TSH)

Median values of TSH during the randomised treatment phase of Study 58 were higher in the vandetanib arm than those in the placebo arm at virtually all time points, with the highest median value for vandetanib occurring at Week 12, after which the median values declined in this treatment arm at all time points except one.

For patients with normal TSH at baseline, elevated TSH was defined as a TSH value above 3x upper limit of normal (ULN) on at least 2 separate follow-up assessments. For patients with an abnormal TSH value at baseline, elevated TSH was defined as a TSH value above 3x the baseline value on at least 2 separate follow-up assessments. The definition was based on the findings of a study by deGroot et al 2005. By this definition, 43 (18.6%) patients in the vandetanib arm had elevated TSH values during treatment, compared with 1 (1.0%) patient in the placebo group. The median time to TSH elevation in the vandetanib arm was 57 days (range, 14 to 502).

Hypothyroidism was reported as an AE in 15 (6.5%) patients in the vandetanib arm and no patients in the placebo arm. All of the AEs of hypothyroidism were grade 1 or 2. A total of 114 (49.3%) and 17 (17.2%) of patients on the vandetanib and placebo arms respectively, required an increase in thyroid hormone replacement therapy while on randomised treatment.

Urinalysis

The percentage of patients with newly developed proteinuria or deterioration of existing proteinuria during randomised treatment was higher in the vandetanib arm (210 [90.9%] patients) compared with the placebo arm (28 [28.3%] patients), as was the percentage of patients with newly developed haematuria or deterioration of existing haematuria (79 [34.2%] vs (22 [22.2%] patients).

Among the 210 patients in the vandetanib treatment arm who developed proteinuria or had deterioration of existing proteinuria during randomised treatment, 54 (23.4%) patients had a concurrent or subsequent AE of hypertension, compared with 1 (1%) of 28 patients in the placebo

arm. None of these same patients in the 2 treatment arms had a concurrent or subsequent elevated blood pressure.

Among the 79 patients who developed haematuria or had deterioration of existing haematuria during treatment with vandetanib, 16 (6.9%) patients had a concurrent or subsequent AE of hypertension, compared with compared with 1 (1%) of 22 patients in the placebo arm. None of these same patients in the 2 treatment arm had a concurrent or subsequent elevated blood pressure.

Safety in special populations

Effect of gender

99.3% of males and 100% of females in the vandetanib arm, and 92.7% of males and 88.6% of females in the placebo arm, had an AE. The reported incidences of rash (40.3% versus 51.5%), diarrhoea (53.0% versus 60.8%), hypertension (27.6% versus 37.1%), and fatigue (19.4% versus 29.9%) were higher in females than in males in the vandetanib arm; the incidence of asthenia (17.2% versus 11.3%) was lower. Incidences in the placebo arm were similar between genders. These differences do not significantly change the safety profile.

Effect of age

The safety profile of vandetanib was examined across the following age ranges: <40 years of age, ≥40 to <65 years of age; ≥65 to <75 years of age; and ≥75 years of age. Elderly patients were defined as those patients ≥65 years of age. For the first 3 groups, the safety profile was similar except that among skin reactions, acne was reported more frequently in patients <40 years of age. There were too few patients ≥75 years of age to define a safety profile in that group.

Renal impairment

Patients with severe renal impairment (creatinine clearance <30 ml/min) were excluded from all vandetanib Phase III studies. Mild renal impairment was defined as baseline creatinine clearance values of 50 to 80 ml/min, and moderate impairment was 30 to 50 ml/min. In Study 58, 1 patient had mild renal impairment at baseline and had an event of interstitial nephritis.

The safety profile of vandetanib in patients with both mild and moderate renal impairment was similar to that of the overall study population. The incidences of the events of rash, diarrhoea, hypertension, fatigue, and asthenia were 45.9%, 58.1%, 34.5%, 23%, and 14.2%, respectively, in patients with mild renal failure, and 46.7%, 40%, 26.7%, 20%, and 13.3%, respectively, in patients with moderate renal failure. These data indicate no adjustment in starting dose is needed in patients with mild-to-moderate renal impairment.

Clinical data and PK data in healthy subjects suggest that no change in starting dose is required in volunteers with mild or moderate renal impairment; in healthy subjects with severe renal impairment, exposure to vandetanib may be increased up to 2-fold.

Hepatic impairment

There is limited clinical data in patients with hepatic impairment treated with vandetanib for MTC; only 5 such patients were enrolled in Study 58. Clinical data and PK data in healthy subjects suggests that no change in starting dose is required for mild, moderate, or severe hepatic impairment.

Cardiac impairment

Thirty-eight (11.5%) patients with cardiac impairment were recruited into Study 58. Patients with previous cardiovascular abnormalities recorded on their medical history CRF were defined as having cardiac impairment. A total of 21.4% of patients in the vandetanib arm with cardiac impairment at baseline had protocol-defined QT prolongation, compared with 14.3% of all patients treated with vandetanib.

Fertility, pregnancy and lactation

Pregnant or lactating women have been excluded from participation in vandetanib studies. Therefore, there is no adequate clinical information in pregnant women using vandetanib.

Safety related to drug-drug interactions and other interactions

A total of 3 (9.7%) of 31 patients in the vandetanib arm who were treated with a Group 1 concomitant medication had protocol-defined QTc prolongation during randomised treatment and 1 (3.2%) of 4 patients had this event after randomised treatment. Of those taking Group 2 concomitant medications, 5 (8.8%) patients in the vandetanib arm had QTc prolongation during randomised treatment and 2 (3.5%) patients had QTc prolongation after randomised treatment.

Discontinuation due to adverse events

One case of discontinuation was reported in blinded phase of Study 58 for safety reasons, in the vandetanib group.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Regarding the pro-arrhythmogenic effect of vandetanib, Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28msec, median 35 msec). First QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time. Actually, this effect does not lessen over time and the half-life of vandetanib (19 days) renders this prolongation in QTc interval particularly problematic. Prolonged QTc≥500msec was more frequent in female patients (75% versus 25% in male). The frequency of QTc≥500msec was particularly increased in subgroups of patients with hypertension (20%), diarrhoea (>20%), serum Mg<LLN (31.3%) and with baseline cardiac impairment (32.1%).

Overall, 31 (13.4%) vandetanib patients had QTc (Bazett's) ≥500 ms compared with 1.0% placebo patients, and 8 (3.47%) vandetanib patients had QTc ≥550 ms or increase from baseline ≥100 ms,

based on a single value during randomised treatment. Globally, there was no difference between the different groups regarding sex ration and median age. However, when it comes up to patients with QTc≥500msec, the sex ratio is different (M/F=0.33) (25% M / 75% F).

QTc increase is an AE. The mechanism of action and both preclinical and pharmacological studies in humans have shown an explanation for the concentration related increase in QTc. Torsades de Pointes have been observed. Cases of sudden death have also been observed not linked to cases of Torsades de Pointes nor exposure. This risk is of further concern in a drug with a very long half life (19 days) and as diarrhoea is one of the main disease related symptom and side-effect of the drug. Another additional risk factor is the further risk of dehydration and consequent renal impairment; in addition, vandetanib has also shown a deterioration of renal function (increase in creatinine). Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing further major Cardiac SAEs including Torsades de Pointes.

There were 35 AEs reported under the cardiac SOC, including 6 SAEs and 5 fatal SAEs. It appears that there were 2 Atrial Fibrillation (1 fatal), 1 Supraventricular Extrasystoles, 7 supraventricular arrhythmia (1 fatal), 4 Sinus Bradycardia, 3 Bundle Branch Block Left, 1 arrhythmia (1 fatal), 4 Bradycardia (1 fatal), 2 Tachycardia (1 SAE), 1 Nodal Arrhythmia, 1 Ventricular Tachycardia. Furthermore, there were 2 sudden deaths (in patients with QTc >550 ms), and 4 suspected sudden deaths.

Although no Torsades de Pointes have been reported as such in study 58, 5 cases have been reported to the Clinical Trial Unit of Afssaps.

Additional expert consultations

Considering vandetanib induced QTcF-prolongation and the observed cardiac events and sudden deaths in the pivotal study as well as Torsades de Pointes in other indications, the SAG was asked to discuss the importance of QTcF prolongation and its clinical consequences in this clinical setting. The SAG was also asked to discuss specific measures that could be recommended to prevent, limit and control the specific cardiac risk in clinical practice in an oncology unit, and specifically whether such treatment should be administered in relation with specialised cardiological advice/follow-up.

SAG's conclusion:

The QT interval is an important measurement to identify patients at risk of developing ventricular arrhythmias and sudden death. Pharmacological and clinical observations (interference with potassium channels, mechanism of Torsades de Pointes, clinical observation of Torsades de Pointes, and cardiac deaths even if judged as unrelated to the study drug) provide strong evidence of an important association between vandetanib and increased risk of clinically significant cardiac events. Of particular concern are the long half-life of the drug, the drug-related diarrhoea potentially inducing hypokalemia, drug-drug interactions such as with SSRIs, deterioration of renal function, and the long treatment duration, all of which may contribute to increase the risk of arrhythmias and sudden death. Selected patients could a priori have an increased risk, such as those with a genetically determined long QTc interval.

A prerequisite for commencing treatment with vandetanib is the correct measurement of QT interval, if necessary by experienced cardiologists. The QTcF interval should be <480 msec prior to start. Patients

with a QT interval of >480 msec are at increased risk of arrhythmias and sudden death, but the precise magnitude of the risk is unknown. Patients who develop QTcF >480 msec should be referred to a cardiologist for identification of risk factors and follow-up.

Adequate information should be provided to patients and health care professionals on minimising concomitant risks, such as the need to identify increased diarrhoea and the need to strictly control diarrhoea in view of the risk of developing hypokalemia, monitoring of renal function and serum potassium at appropriate intervals, avoiding adverse drug-drug interactions, prompt referral to a cardiologist in case of patients at increased risk of arrhythmias and sudden death.

Although it is difficult to try to restrict use of vandetanib to specialised centres, it is important to recommend that treating oncologists should have extensive experience in identifying and managing the risk of ventricular arrhythmias and sudden death associated to vandetanib, and that specialist cardiologic advice be available promptly when needed. Overall, the SAG agreed on the risk minimisation measures presented.

2.6.2. Conclusions on the clinical safety

To prevent and limit the safety concerns, the following aspects have been reflected into the Product Information:

- A recommendation in section 4.2 of the SmPC with regards to treatment initiation and supervision by a physician experienced in treatment of MTC and in the use of anticancer medicinal products and experienced in the assessment of ECG.
- A contraindication in section 4.3 of the SmPC with regards to congenital long QTc syndrome, patients with an increased QTc interval over 480 msec and the concomitant use of vandetanib with drugs known to also prolong the QT interval and / or induce Torsades de Pointes (arsenic, cisapride, erythromycine IV, toremifene, mizolastine, moxifloxacine, Class IA and III antiarrhythmics).
- a precaution in section 4.4 of the SmPC with regards to QTc prolongation. Patients who develop a single value of a QTc interval of greater than 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- a statement in section 4.5 of the SmPC noting that Vandetanib has been shown to prolong the ECG QT interval and Torsades de Pointes have been uncommonly reported. Therefore, the concomitant use of vandetanib with drugs known to also prolong the QT interval and / or induce Torsades de Pointes is either contra-indicated or not recommended depending on existing alternative therapies:

    - Combinations contraindicated: cisapride, erythromycine IV, toremifen, mizolastine, moxifloxacine, arsenic, ,Class I A and III antiarrhythmics

- Combinations not recommended: methadone, haloperidol, amisulpride, chlorpromazine, sulpiride, and zuclopenthixol), halofantrine, pentamidine and lumefantrine.

If there is no appropriate alternative therapy, not recommended combinations of such medicinal products with vandetanib may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea.

- a statement in section 4.5 of the SmPC noting that Posterior reversible encephalopathy syndrome, PRES (Reversible posterior leukoencephalopathy syndrome-RPLS) has been observed infrequently with vandetanib treatment in combination with chemotherapy. PRES has also been observed in patients receiving vandetanib as monotherapy. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.

In addition to this, extensive physician and patient information with regard to the risks of QTc prolongation, Torsades de Pointes, PRES/RPLS and their management will be provided.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 20. Summary of the risk management plan

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks:		
Appetite decreased	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates that frequency of appetite decreased is very common.
Cerebrovascular events	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates that frequency of cerebrovascular events is common.
Cholelithiasis	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of cholelithiasis is common.

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Diarrhoea	Routine pharmacovigilance practices, signal identification, and review	Section 4.4 of the SmPC states: Diarrhoea is a disease related symptom as well as a known undesirable effect of vandetanib and gives information on the additional ECG monitoring of the QTc interval, electrolytes and the additional vigilance required if onset or worsening of diarrhoea occurs. It also gives recommendation for the treatment of diarrhoea and the action to be taken if severe diarrhoea (CTCAE grade 3 4) develops. Section 4.8 of the SmPC indicates that frequency of diarrhoea is very common
Dysphagia	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of dysphagia is common.
Heart failure	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists for HCPs	Section 4.4 of the SmPC states: Heart failure has been observed in patients who received vandetanib. Temporary or permanent discontinuation of therapy may be necessary in patients with heart failure. It may not be reversible on stopping vandetanib. Some cases have been fatal. Section 4.8 of the SmPC indicates the frequency of heart failure is uncommon
Hypertension	Routine pharmacovigilance practices, signal identification, and review	Section 4.4 of the SmPC states: Hypertension, including hypertensive crisis, has been observed in patients treated with vandetanib and gives information on the monitoring and control of hypertension, together with the action to be taken if high blood pressure cannot be controlled with medical management. Section 4.8 of the SmPC indicates the frequency of hypertension is very common.
Hypocalcaemia	Routine pharmacovigilance practices, signal identification, and review	Section 4.4 of the SmPC states: serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Section 4.8 of the SmPC indicates the frequency of hypocalcaemia is very common.

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Infections	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of nasopharyngitis, bronchitis, upper respiratory tract infections, and urinary tract infections is very common. Section 4.8 of the SmPC indicates the frequency of pneumonia, sepsis, influenza, cystitis, sinusitis, laryngitis, folliculitis, furuncle, fungal infection, and pyelonephritis is common. Section 4.8 of the SmPC indicates the frequency of appendicitis, staphylococcal infection, diverticulitis, cellulitis, and abdominal wall abscess is uncommon.
Interstitial Lung Disease and pneumonitis	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists	Section 4.8 of the SmPC states: interstitial lung disease has occurred in patients treated with vandetanib monotherapy. It is expected that this would be an uncommon adverse reaction in patients receiving vandetanib for MTC. Section 4.8 of the SmPC also indicates the frequency of pneumonitis is common.
Intestinal perforation and/or obstruction	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of intestinal perforation is uncommon and ileus is uncommon.
Pancreatitis	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of pancreatitis is uncommon.
Phototoxicity	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists	Section 4.4 of the SmPC gives information about the care to be taken with sun exposure. Section 4.8 of the SmPC indicates the frequency of photosensitivity reaction is very common.
Pneumonia	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of pneumonia is common.

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Posterior reversible encephalopathy syndrome	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists. The use of educational materials for physicians and patients, and the implementation of yearly surveys to Caprelsa prescribers to assess the effectiveness of these educational materials. (See Annex 8)	Section 4.4 of the SmPC states: PRES is a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain, has been observed infrequently with vandetanib treatment in combination with chemotherapy. PRES has also been observed in patients receiving vandetanib as monotherapy. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status. Section 4.8 of the SmPC states: PRES has occurred in patients treated with vandetanib monotherapy. It is expected that this would be an uncommon adverse reaction in patients receiving vandetanib for MTC. Provide risk minimisation tool (educational materials) to reinforce the prescriber's awareness about the risk of PRES and awareness about performing an MRI for symptoms suggestive of PRES. Provide patient alert card to educate the patient to recognise symptoms associated with PRES. All potential prescribers will be provided, before launch and thereafter, with enough patient alert cards to distribute to their patients with each prescription
QTc prolongation / torsades de pointes	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists. The use of educational materials for physicians and patients, and the implementation of yearly surveys to Caprelsa prescribers to assess the effectiveness of these educational materials. (See Annex 8)	Section 4.4 of the SmPC states: Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec). Torsades de pointes and ventricular tachycardia have been uncommonly reported in patients administered vandetanib 300 mg daily. The risk of Torsades may be increased in patients with electrolyte imbalance Section 4.4 also gives further details on the occurrence and features of QTc prolongation observed with vandetanib and the precautions for use of

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		vandetanib Section 4.5 of the SmPC states: Vandetanib has been shown to prolong the ECG QTc interval; Torsades de pointes has been uncommonly reported. Therefore the concomitant use of vandetanib with medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes is either contraindicated or not recommended depending on existing alternative therapies. Section 4.8 of the SmPC indicates the frequency of QTc prolongation is very common. Provide risk minimisation tool (educational materials) to reinforce the prescriber's awareness about the risk of QTc prolongation and Torsades de pointes. Provide patient alert card to educate the patient to recognise symptoms associated with QTc prolongation and Torsades de pointes. All potential prescribers will be provided, before launch and thereafter, with enough patient alert cards to distribute to their patients with each prescription
Renal toxicity	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists	Section 4.8 of the SmPC indicates the frequency of proteinuria and nephrolithiasis is very common; the frequency of dysuria, haematuria, renal failure, pollakiuria, and micturition urgency is common; and the frequency of chromaturia and anuria is uncommon.

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Toxic epidermal necrolysis, toxic skin eruption, exfoliative dermatitis, and other skin reactions	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists	Section 4.4 of the SmPC gives information on the management of mild, moderate and severe skin reactions, and the care to be taken with sun exposure. Section 4.8 of the SmPC indicates the frequency of photosensitivity reaction, rash and other skin reactions (including acne, dry skin, dermatitis, pruritis) and nail disorders is very common; the frequency of palmar plantar erythrodysaesthiesia syndrome and alopecia is common; and the frequency of bullous dermatitis is uncommon.
Weight decreased	Routine pharmacovigilance practices, signal identification, and review	Section 4.8 of the SmPC indicates the frequency of decreased weight is common.
Important potential risks:		
Drug-drug interactions	Routine pharmacovigilance practices, signal identification, and review Additional studies to explore potential drug-drug interactions with vandetanib have been planned: **Vandetanib co administered with digoxin** **Vandetanib co administered with metformin** **Vandetanib co administered with omeprazole (proton pump inhibitor) or ranitidine (histidine antagonist)** **Vandetanib co administered with midazolam**	Section 4.4 of the SmPC states: The administration of vandetanib with substances known to prolong the ECG QTc interval is contraindicated, or not recommended. The concomitant use of vandetanib with ondansetron is not recommended. The concomitant use of vandetanib with strong CYP3A4 inducers (such as rifampicin, St Johns' Wort, carbamazepine, phenobarbital) should be avoided. Section 4.5 of the SmPC addresses pharmacokinetic and pharmacodynamic interactions, and specifically states: If there is no appropriate alternative therapy, combinations not recommended with vandetanib may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea.
Hepatic failure	In addition to routine pharmacovigilance practices, signal identification, and review, HCP contacted and enhanced follow-up conducted using follow-up checklists	No specific risk minimisation activities identified.
Reproductive toxicity	Routine pharmacovigilance practices, signal identification, and review and follow-up on pregnancy outcome for all reports of exposure to vandetanib during pregnancy	Information relating to women of childbearing potential, pregnancy, breast-feeding and fertility is provided in the SmPC Section 4.6

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important missing information:		
Long-term use	Routine pharmacovigilance practices, signal identification, and review	No specific risk minimisation activities identified.
Use during pregnancy	Routine pharmacovigilance practices, signal identification, and review	Section 4.2 of the SmPC states: Section 4.2 of the SmPC states: If vandetanib is used during pregnancy or if the patient becomes pregnant while receiving vandetanib, she should be apprised of the potential for foetal abnormalities or loss of the pregnancy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the foetus. There are no data on the use of vandetanib in breast feeding women. Vandetanib and/or its metabolites is excreted into milk in rats and found in plasma of pups following dosing to lactating rats. Breast feeding is contraindicated while receiving vandetanib therapy.
Use in elderly patient population	Routine pharmacovigilance practices, signal identification, and review	The SmPC states in section 4.2: No adjustment in starting dose is required for elderly patients. There is limited clinical data with vandetanib in patients with MTC aged over 75.
Use in non-Caucasian patient population	Routine pharmacovigilance practices, signal identification, and review	No specific risk minimisation activities identified.
Use in patients with cardiac impairment	Routine pharmacovigilance practices, signal identification, and review	No specific risk minimisation activities identified.
Use in patients with hepatic impairment	Routine pharmacovigilance practices, signal identification, and review	Section 4.2 of the SmPC states: Vandetanib is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established. Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment.

Safety concern/missing information	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Use in patients with moderate to severe renal impairment	Routine pharmacovigilance practices, signal identification, and review	Section 4.2 of the SmPC states: Clinical data suggest that no change in starting dose is required in patients with mild renal impairment. There is limited data with 300 mg in patients with moderate renal impairment: the dose needed to be lowered to 200 mg in 5 out of 6 patients. The starting dose could be reduced to 200 mg in patients with moderate (creatinine clearance ≥30 and <50 ml/min) renal impairment; safety and efficacy have however not been established with 200 mg. Vandetanib is not recommended for use in patients with severe (creatinine clearance below 30 ml/min) renal impairment since there is limited data in patients with severe renal impairment, and safety and efficacy have not been established.
Use in paediatric patient population	Routine pharmacovigilance practices, signal identification, and review Two paediatric studies (IRUZACT0004, and IRUZACT0098) are ongoing.	The safety and efficacy in children has not been established. Therefore vandetanib is not indicated for use in paediatric patients.

HCP Healthcare professional; ILD Interstitial lung disease; PRES Posterior Reversible Encephalopathy Syndrome.

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Study D4200C00097, an international, double-blind, two-arm study to evaluate the safety and efficacy of vandetanib 150mg and 300mg/day in patients with unresectable locally advanced or metastatic medullary thyroid carcinoma with progressive or symptomatic disease.	October 2015
Study IRUZACT0004, a Phase I Study of the Combination of Vandetanib and Dasatinib Administered During and After Radiation Therapy in Children with Diffuse Intrinsic Pontine Glioma is being conducted in patients between the ages of 18 and 24 who will be dosed with vandetanib 50 to 110 mg/m^2/d.	July 2013
Study IRUZACT0098, a Phase I/II Trial of Vandetanib in Children and Adolescents with Hereditary Medullary Thyroid Cancer recruits patients between the ages of 5 to 18 years. Patients will begin on vandetanib 100 mg/m^2/d, and will be escalated to vandetanib 150 mg/m^2/d if the lower dose is tolerated	May 2015
Vandetanib coadministered with digoxin. Vandetanib is a weak inhibitor of the	June 2013

Description	Due date
efflux pump P-glycoprotein (P-gp). The co-administration of vandetanib and medicinal products excreted by P-gp, such as dabigatran or digoxin, may result in increased plasma concentrations of these medicinal products. Patients receiving dabigatran or digoxin and vandetanib may require increased clinical and biological surveillance and appropriate dose adjustments, if needed.	
Vandetanib coadministered with metformin. Vandetanib is an inhibitor of the organic cation transporter 2 (OCT2). Therefore, vandetanib may have the potential to decrease the elimination of medicinal products known to be excreted by OCT2 and to increase a patient's exposure to these medicinal products. Metformin is a substrate of OCT2; patients who are receiving vandetanib and metformin (or other substrate of OCT2) may require more careful monitoring and possible dose adjustment of metformin.	June 2013
Vandetanib coadministered with antacids (omeprazole or ranitidine). The effect of proton pump inhibitors or histamine agonists on the gastrointestinal absorption of vandetanib has not been determined. Vandetanib demonstrates pH-dependent solubility; therefore, the co-administration of vandetanib with proton pump inhibitors or histamine agonists may reduce a patient's exposure to vandetanib.	June 2013
Vandetanib coadministered with midazolam. Vandetanib has the potential to induce the CYP3A4 enzyme system. Co-administration of vandetanib and medicinal products primarily metabolised by the CYP3A4 enzyme system may result in decreased plasma concentrations of these medicinal products that could reduce or shorten therapeutic effects. Therefore, appropriate dose adjustments may be required.	June 2013

The following additional risk minimisation activities were required:

- Before and after product launch, the MAH must provide the SmPC, sufficient Patient Alert Cards (see Annex 10) for each prescription, and health care professional (HCP) educational material about the risks of QTc prolongation, Torsades de Pointes and PRES and their management according to the SmPC, to all HCPs who are expected to prescribe the product. The MAH shall agree the educational material with the national competent authority before launch of the product in the authority's state.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the current submission, the Applicant has mainly provided results taken from one pivotal study (Study 58). Two supportive studies (Studies 08 and 68) were also submitted, both performed in a limited number of patients with hereditary medullary thyroid cancer.

Study 58 was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of vandetanib versus placebo in patients with unresectable locally advanced or metastatic MTC. In the primary analysis, the superiority of vandetanib as compared to placebo was demonstrated, with a 11.2 months increase (19.3 vs 30.5 months) of median PFS (HR=0.46, 95% CI, 0.31 to 0.69, p=0.0001).

The superiority of vandetanib over placebo is clinically significant and quite consistent across all pre planned subgroups. More benefit from vandetanib was seen in patients with a CTN or CEA doubling time < 24 months compared to patients with a longer doubling time and in patients with symptoms at baseline.

The terms "symptomatic and aggressive" disease correspond to a rapid deterioration of clinical condition (clinical, biological and radiological signs) i.e., patients at urgent need of treatment

Uncertainty in the knowledge about the beneficial effects.

The activity of vandetanib in RET mutation negative patients is indirectly supported by the activity of the drug observed in the subgroup of patients with RET unknown status. Further data from study 58 provided in the post-hoc analysis of RET negative patients (including those patients classified as RET unknown, with the M918T mutation) showed efficacy. Therefore, the available evidence supports the efficacy of vandetanib in RET negative tumours using the most frequent mutation (80%-92%). . It is not certain however that those patients tested RET negative for M918T mutation are not positive for mutation on other exons. It is equally not certain that those patients tested RET negative from old tumour sample were still RET negative at the time of initiation of treatment. Therefore, it is difficult to draw an unequivocal conclusion of the size of the benefit of vandetanib in patients with RET mutation negative tumours. Given that the precise mechanism of action of vandetanib in RET remains unclear, the absolute benefit in these patients should be more precisely/directly determined.

Risks

Unfavourable effects

The most commonly reported adverse drug reactions have been diarrhoea, rash, nausea, hypertension, and headache. Regarding the pro-arrhythmogenic effect, Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28msec, median 35 msec). First QT prolongations occurred most often in the first 3 months of treatment, but continued to first occur after this time. This effect does not lessen over time. Prolonged QTc ≥ msec was more frequent in female patients (75% versus 25% in male), Frequency of QTc msec was particularly increased in subgroups of patients with hypertension (20%), diarrhoea (>20%), serum Mg<LLN (31.3%) and with baseline cardiac impairment (32.1%).

The mechanism of action and both preclinical and pharmacological studies have shown an explanation for the concentration related increase in QTc. Torsades de Pointes have been observed. Cases of sudden death have also been observed not linked to cases of Torsades de Pointes nor exposure. This risk is of further concern in a drug with a very long half life (19 days) and with diarrhoea as one of the main disease related symptoms. Another additional risk factor is the further risk of dehydration and consequent renal impairment; in addition, vandetanib has also shown a deterioration of renal function (increase in creatinine).

Uncertainty in the knowledge about the unfavourable effects

In view of the toxicity profile of vandetanib at the 300 mg dose, at least in some patients the safety of the 300 mg dose may be a concern; there is a need to further study the optimal dose with the aim to maximise the benefit-risk balance, Additional data on safety and activity of a lower dose will be provided through a randomized dose-finding trial looking at safety and activity of 150mg vs 300mg dose of vandetanib (Study D4200C00097), with overall response rate as the primary endpoint. The trial is due to be completed in October 2015. (see Section 2.7 Pharmacovigilance)

Benefit-risk balance

Importance of favourable and unfavourable effects

In the overall population, improvement in PFS, ORR and DCR are of importance as well as a positive effect on some PRO. The management of the risk of QT prolongation and associated clinical consequences and renal risks associated with vandetanib are particularly important.

Benefit-risk balance

The restriction of the indication to patients with symptomatic and aggressive disease allows to select patients who are at urgent need of treatment for medullary thyroid cancer. It is in this patient population that the benefits outweigh the important risks outlined.

Discussion on the benefit-risk balance

To prevent and limit the concern on QT prolongation and clinical consequences associated with vandetanib, the following measures have been implemented in the Product Information. :

- A recommendation in section 4.2 of the SmPC with regards to treatment initiation and supervision by a physician experienced in treatment of MTC and in the use of anticancer medicinal products and experienced in the assessment of ECG.
- A contraindication in section 4.3 of the SmPC with regards to congenital long QTc syndrome, patients with an increased QTc interval over 480 msec and the concomitant use of vandetanib with drugs known to also prolong the QT interval and / or induce Torsades de Pointes (arsenic, cisapride, erythromycine IV, toremifene, mizolastine, moxifloxacine, Class IA and III antiarrhythmics).
- a precaution in section 4.4 of the SmPC with regards to QTc prolongation. Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.

- a statement in section 4.5 of the SmPC noting that Vandetanib has been shown to prolong the ECG QT interval and Torsades de Pointes have been uncommonly reported. Therefore, the concomitant use of vandetanib with drugs known to also prolong the QT interval and / or induce Torsades de Pointes is either contra-indicated or not recommended depending on existing alternative therapies.

  If there is no appropriate alternative therapy, not recommended combinations of such medicinal products with vandetanib may be made with additional ECG monitoring of the QTc interval, evaluation of electrolytes and further control at onset or worsening of diarrhoea.

In addition to this, extensive physician and patient information with regard to the risks of QTc prolongation, Torsades de Pointes and their management will be provided.

Although the results of the randomised, placebo controlled, phase III trial fully support the positive balance of benefits and risks, there is still the need to obtain further data to confirm the magnitude of the effect of vandetanib in patients with RET mutation negative tumours.

Following consultation with the applicant, the CHMP considered the granting of a conditional marketing authorisation vandetanib. Vandetanib aims at the treatment of seriously debilitating diseases or life-threatening diseases and falls within the scope of Commission Regulation 507/2006 on the conditional marketing authorisation. The Committee found that although comprehensive clinical data referring to the efficacy of the medicinal product had not been supplied, all of the following requirements were met:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive

Based on the randomized, double-blind, placebo-controlled study presented in patients with unresectable locally advanced or metastatic MTC, the superiority of vandetanib was demonstrated compared to placebo, with a 11.2 months increase (19.3 vs 30.5 months) of median PFS (HR=0.46, 95% CI, 0.31 to 0.69, p=0.0001). The benefit risk balance of vandetanib in patients with unresectable locally advanced or metastatic medullary thyroid cancer is therefore considered to be positive.

From a quantitative viewpoint, the specific benefit in patients with RET - tumours might be less as compared with what was observed in RET+ tumours. There is a need to further confirm such differences in terms of efficacy in RET negative patients with vandetanib,

- It is likely that the applicant will in a position to provide comprehensive clinical data

Comprehensive clinical data will be provided through an open label study of vandetanib in patients with sporadic medullary thyroid cancer with known RET mutation status. Data will be collected and analyzed at pre-specified times. The final analysis will be performed when at least 40 patients identified with RET mutation and 40 patients identified without evidence of RET mutation have been enrolled into the study and received vandetanib for 14 months. This study will include 50 - 60% of patients who receive vandetanib within the EU. Patients will be followed for 2 years and an interim analysis will be presented 12 months after first inclusion. The study is considered feasible and it is therefore likely that the applicant will in a position to provide comprehensive clinical data.

- Unmet medical needs to be fulfilled

Patients with MTC can be cured only by thyroidectomy, performed when the tumour is confined to the thyroid gland. The tumour is relatively unresponsive to conventional doses of radiation therapy and to chemotherapeutic regimens (none of which have been approved in this indication yet). Caprelsa is intended for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. The CHMP concluded that the product fulfils an unmet medical need due to the lack of available alternative treatments in this population.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

The CHMP considered that the potential risks inherent in marketing vandetanib for the specific indication while additional, more comprehensive data will be available in the future would be offset by the benefit to patients with aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. The CHMP agreed that the RMP for vandetanib in the approved indication was adequate to address any identified and unknown risks.

The CHMP concluded that all the requirements for the granting of a conditional marketing authorisation had been met.

4 Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Caprelsa in the treatment of "aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease (For patients win whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision(see important information in sections 4.4 and 5.1))" is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a half yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe Caprelsa are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Package Leaflet
- Educational material for Healthcare Professionals
- Patient Alert Cards (text as agreed by the CHMP)

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de Pointes and sudden death
- Vandetanib treatment must not be started in patients:
    - whose ECG QTc interval is greater than 480 msec
    - Who have congenital long QTc syndrome
    - Who have a history of Torsades de Pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)

- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take
- The role and use of the Patient Alert Card

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU. Inclusion criteria: to meet criteria based on SmPC indication. In addition, RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. Exclusion Criteria: limited to contraindications outlined in section 4.3 of the SmPC Data to be collected on study: • History and physical examination • RET mutation status • Patients not required to have tissue biopsy to determine RET status for enrolment RET mutation status: Patients will not be required to have a fresh tissue biopsy to determine RET status before enrolment. However investigator should be strongly requested to obtain a recent sample for determination of the RET status as often as possible, even in patients previously tested at an earlier stage of their disease. Determination of RET status should be made preferably just prior to the initiation of treatment. Tissue type used for assay, date of tissue biopsy, assay type and definition used for RET mutation positive and negative will be collected. RET mutation negative patients who do not receive vandetanib due to RET status or contraindication will be allowed to enrol and followed. RET mutation status should be assessed according to pre-defined mutational analysis, where type of test and exons to be analyzed are protocol pre-specified. • Safety Assessments at each visit including QT prolongation information. • Objective tumour responses / duration of response progression • Assessed in accordance with study physicians normal medical practice • Within a centre, patients will be assessed for efficacy in a consistent manner, irrespective of their RET status at pre-defined time points • Method used for assessment (e.g. CT, MRI) • Disease status at each efficacy visit: objective response, stable disease or progressive disease. • The final analysis will be performed when at least 40 patients identified with RET mutation and 40 patients identified without evidence of RET mutation have been enrolled into the study and received vandetanib for 14 months.	December 2015

The total duration of the study is expected to be 38 months. Analyses: • The study will run for 2 years and at pre-specified times, the data will be collected and analyzed (e.g., 12 months and 24 months) • Objective response rate, progression status and DCR in the overall population, RET mutation negative and RET mutation positive patients • Safety analyses in the overall population, RET mutation negative and RET mutation positive patients	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe Caprelsa are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Package Leaflet
- Educational material for Healthcare Professionals
- Patient Alert Cards (text as agreed by the CHMP)

The educational material for Healthcare Professionals should contain the following key elements:

- Vandetanib prolongs the QTc interval and can cause Torsades de Pointes and sudden death
- Vandetanib treatment must not be started in patients:
    - whose ECG QTc interval is greater than 480 msec
    - Who have congenital long QTc syndrome
    - Who have a history of Torsades de Pointes unless all risk factors that contributed to Torsades have been corrected.
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed
- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pretreatment status has been confirmed and correction of possible electrolyte imbalance has been made.

- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought.
- Details of medicinal products where the co-administration of vandetanib is either contraindicated or not recommended.
- That vandetanib may cause Posterior reversible encephalopathy syndrome (PRES) also known as Reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status.
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take
- The role and use of the Patient Alert Card

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that vandetanib is to be qualified as a new active substance (see Appendix 1).