SANOFI

Non-Interventional Study (NIS) Protocol

NIS Name/Code	D4200C00104 (Sanofi-Genzyme OBS14778)
Edition Number	3.0
Date	21 June 2019

International Observational, Study to Evaluate the Benefit/Risk of Vandetanib (Caprelsa™) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer

Sponsor:

Genzyme Corporation, 50 Binney Street, Cambridge, MA 02142, USA

The following Amendment(s) have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	29 February 2016		
2	21 June 2019		

NAMES AND ADRESSES OF:

MONITORING TEAM'S REPRESENTATIVE

Name: Address: Tel: Fax: E-mail	

SPONSOR

Name:	Genzyme Corporation
Address:	50 Binney Street Cambridge, MA 02142, USA

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	21 June 2019, version 3.0 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	29 February 2016, version 2.0 (electronic 1.0)
Original Protocol		11 March 2013, version 1

Amended protocol 02 (21 June 2019)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) (because it will significantly impact the scientific value of the study due to the addition of a new specific population [retrospective patients]).

OVERALL RATIONALE FOR THE AMENDMENT

The Study D4200C00104 is conducted to fulfill the specific obligation (SOB) 001 post-authorization linked to the conditional marketing authorization of vandetanib (Caprelsa). The objective of Study D4200C00104 is to confirm in the real-life setting the benefit/risk ratio of vandetanib 300 mg, in both in Rearranged During Transfection (RET) mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC).

Recruitment started in 2014 (first patient in:17 February 2014), had faced a number of challenges including the rarity of the disease under study, and the existing medical practice standards. These factors made clear the extreme scarcity of RET mutation negative patients and the low use of RET status in clinical practice. The initial sample size was to include 40 RET mutation positive and 40 RET mutation negative patients.

As of 02 Aug 2018, 34 patients were enrolled into Study D4200C00104. Twenty six were RET mutation positive and only 8 were RET mutation negative. No new prospective patients were included after 30 June 2017. On 15 June 2017, a meeting was held with the European medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) Rapporteur (France) and CHMP Co-Rapporteur (Netherlands) to discuss the SOB. During this meeting it was discussed that the Marketing Authorization Holder (MAH) believes there is no longer any scientific and clinical value in completing Study D4200C00104. Then, the EMA and CHMP (Co) Rapporteurs advised to submit a type II variation to request the switch from a conditional to a standard marketing authorization (not subject to SOBs) and to include the data

presented during the meeting in the variation dossier, as consequence Study D4200C00104 would be prematurely terminated.

The MAH submitted a type II variation to request the switch of the marketing authorization from conditional to standard on 28 September 2017. At the time of the assessment of the second response document to a Request of Supplementary Information, the EMA provided the following answer (18 October 2018): "The data provided by the MAH are still considered insufficient to confirm efficacy of Caprelsa in the RET negative population. As a result, the specific obligation is not considered fulfilled. Furthermore, the data provided are considered too immature and limited to support the proposed changes in the SmPC. Considering the slow recruitment in Study D4200C00104 (SOB), the applicant is requested to present a revised plan to provide confirmatory data in RET negative patients in a reasonable timeframe."

The plan submitted by MAH and accepted by EMA on the 28 February 2019 (CHMP Positive Opinion) consists of the following 2 main strategies:

- A re-analysis of archived tumor samples from patients included in the pivotal Study D4200C00058 (LPS14811), aimed at better determining RET mutation status for patients with RET mutation "unknown" at time of Study D4200C00058.
- An amendment to current Study D4200C00104 in order to allow the inclusion of retrospective RET mutation negative patients treated with vandetanib, within current involved centers and potential new centers. The retrospective data collection will include the following:
    - Retrieval of more RET mutation negative patients by adapting the inclusion and exclusion criteria for retrospective data collection (eg, no informed consent form [ICF], no age restrictions, a determination of RET mutation negative status independent from vandetanib) treatment initiation [administration start date]).
    - An extended recruitment period into the past (before study start).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page Study Title	Removed the word " prospective " and abbreviation “MTC” from the study title. Removed the word “European” from study title and added “International”.	Update of title in consideration of the addition of retrospective patients and a minor consistency change. Added “International” as recruitment sites can be outside of European Union (EU) as well.
Names and addresses of Sponsor	Added current address of Sponsor.	Street address updated.
Overall rationale of the amendment	Added clarifying language and information.	Regulatory details were updated.
Synopsis Study Title	Removed the word "prospective " from the study title. Removed word “European” from study title and added “International”.	Update of title in consideration of the addition of retrospective patients. Added “International” as recruitment sites can be outside of EU as well.
Synopsis Study Site(s), number of patients and countries planned	Removed the words “from Europe”. Removed the number “40”.	Updated as recruitment sites can be outside of EU as well. The objective is now to recruit 20 to 25 Rearranged During Transfection (RET) mutation positive and 20 to 25 RET mutation negative patients.
Synopsis Total planned Study period	Added information regarding “Estimated date of clinical study report (CSR) addendum”.	Study period planned dates updated.
Synopsis Study Design	Added information related to addition of retrospective patients in the study design.	The changes made describes that this is a multinational, multicenter, Non-Interventional (observational), prospective (for patients with RET mutation positive or negative status), and retrospective (for patients with RET mutation negative status) study. The decision to prescribe vandetanib is taken independently of the enrollment into this study and is in line with the respective (local) prescribing information. The study is observational, meaning that vandetanib treatment initiation should never be delayed in order to meet any inclusion criteria of the study. Similarly, performing interventions on the patients that would specifically be for the study and would not be carried out in the "real-life" setting is not permitted, eg, a biopsy. European countries where vandetanib is on the market (up to 2012) will participate in this study.
Synopsis Target patient population	Added information related to inclusion of a new specific population (retrospective patients) in the study design/target patient population.	The changes made describes that patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC), treated with vandetanib 300 mg/once daily, at any time, and with a RET mutation negative status, will be allowed to enter the study retrospectively. In addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC not prescribed vandetanib 300 mg but who have RET mutation negative status will be allowed to enter the study both retrospectively and prospectively.
Synopsis Study variable(s)	Added clarifying language for prospective and retrospective patients relating to study variables.	The change made describes collection of safety data, disease assessment, death/lost to follow-up, and treatment information for retrospective and prospective patients.

Section # and Name	Description of Change	Brief Rationale
Synopsis Statistical Methods	Added sample size, statistical analysis methods and safety evaluation for study population.	The changes made describes that in addition to the original study population, two other groups of patients: a retrospective group and a group of patients from the Study D4200C00058 whose RET data were re-analyzed with the aim to categorize them as RET mutation positive or RET mutation negative. The criteria for selecting these data are intended to assure that the populations are comparable, and hence, may be pooled. In order to confirm comparability, all analyses will report the descriptive statistics for each of these groups as well as the pooled data both for RET mutation positive and RET mutation negative patients.
List of Abbreviations	Format changed as per the new template	Updated to DOMASYS style
Section 1.1 Background	Reference format changed as per the new template and minor changes. Clarifying language added in Table 3 footnote.	References updated as per DOMASYS style and replaced “Study 58” with “Study D4200C00058”. The changes made (footnote) describes that the table shows the results of the analysis performed by AstraZeneca in 2012-2014.
Section 1.2 Rationale for conducting this NIS	Added information regarding inclusion of retrospective patients.	The change made describes that this Non-Interventional study(NIS) will provide information on the clinical benefit/risk between these groups of patients based on the actual clinical practice of physicians who are prescribing vandetanib.
Section 3.1 Overall study design and flow chart	Added information regarding inclusion of retrospective patients in the study design.	The changes made describes that this study will include patients treated with vandetanib and with a RET mutation positive or negative status including RET mutation negative patients who never received vandetanib (as many patients as possible, with no restriction on the numbers of RET mutation negative patients). Patients will be either prospectively followed, or in addition, patients with a RET mutation negative status, will be allowed to enter the study retrospectively. Twenty to twenty-five vandetanib RET mutation positive and 20 to 25 vandetanib RET mutation negative patients will be enrolled in the study. For retrospective patients (only MTC patients with RET mutation negative status), data collection reporting time points will include a baseline time point before the start of their treatment for MTC (vandetanib or another treatment) where the eligibility of the patient will be confirmed, plus all subsequent time points that may be available in the patient file. Diagnosis could be as early as 1995-2000, but the centers will search databases (for the prevalent MTC patients) and review the records to consider recruitment using 2010 as a cutoff, without any limitation for the date of diagnosis. The prescription frequency of vandetanib or any other treatment for MTC should be reported.
Figure 1 Study flow chart	Added information regarding retrospective patients in the study flow chart.	The changes made describes study design/data collection time points for retrospective patients: Diagnosis date up to 2010 (footnote updated as “Diagnosis could be as early as 1995-2000, but the centers will search databases [for the prevalent MTC patients] and review the records to consider recruitment using 2010 as a cutoff, without any limitation for the date of diagnosis”); Reporting data collection until disease progression or end of study.

Section # and Name	Description of Change	Brief Rationale
Table 2 Study Plan	Added information regarding retrospective patients in the study plan (Table 2).	The change made describes that for retrospective patients a waiver of informed consent will be requested and RET mutation negative status may have been performed before or after start of the treatment of MTC (vandetanib or another treatment). Disease assessment should be consistent (same time frequency and method) within a site across the study for prospective patients, but not necessarily for retrospective patients.
Section 3.2 RET mutation analysis procedure	Added clarifying language to RET mutation analysis procedure for retrospective patients.	The changes made describes that the assay to determine mutational status will be done or may have been done (in case of retrospective patients) in certified laboratories and must be based on sequencing, PCR (polymerase chain reaction) including Amplification Refractory Mutation System (ARMS) methodology, and comparative genomic hybridization (CGH).
Section 4.2 Inclusion Criteria	Added clarifying language to inclusion criteria 1, 2, 3, 4, 6 and 7 for the prospective and retrospective parts of the study.	The changes made describes that for retrospective patients no signed informed consent, instead a waiver will be requested and there will be no age restriction for inclusion in the study. For retrospective patients, (prevalent MTC patients) diagnosis could be as early as possible, without any limitation for the date of diagnosis. For retrospective patients prescribed with vandetanib, the RET mutation status will be negative and RET mutation negative status could have been determined before or after start of treatment (with vandetanib or another drug). Also, the prescription may or may not have been issued according to the Summary of Product Characteristics (SmPC) for these patients.
Section 4.3 Exclusion criteria	Added clarifying language to exclusion criteria 1, 2, and 3 for the prospective and retrospective parts of the study.	The changes made describe that exclusion criteria 1, 2, and 3 (B) are not applicable for retrospective patients. Also, contraindications according to the vandetanib SmPC, are not applicable for patients who do not receive vandetanib. Exclusion criteria 3 (B), (C), (D), (E) and (F) are not applicable for patients who do not receive vandetanib.
Section 5.1 Criteria for Withdrawal	Added clarifying language to criteria for withdrawal 1 and 3 for the retrospective patients of the study.	The changes made describe that criteria for withdrawal 1 and 3 are not applicable for retrospective patients. Also, discontinuation of the patient treatment is not a criterion for withdrawal from the study. In this case, the patient can continue in the study, until death, loss to follow-up, or end of study.
Section 5.2 Procedure for withdrawal	Added information relating to retrospective and prospective patients.	The changes made describes that prospective patients who were not included (eg, for restrictive inclusion/exclusion criteria) or withdrawn from the study (eg, withdrawn for adverse event [AE] but continuation of assessment and treatment according to routine practice) will still be considered for the retrospective data collection: if they meet the inclusion criteria for the retrospective data collection, the same patient ID will be used in the study database and the patient will be classified as retrospective patient for data analyses.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Therapeutic Strategy of a Non-Interventional study	Added information relating to Sponsor reimbursement, retrospective patients and follow-up of both prospective and retrospective patients.	Due to the Non-Interventional nature of this study, only the laboratory analyses on biopsy samples already available can be reimbursed. In any case, all data available in the patient charts will be reported and described into the electronic case report form (eCRF) for the retrospective patients, even if not prescribed according to the SmPC. There is limited data with 300 mg in patients with moderate renal impairment. The starting dose could be reduced to 200 mg in prospectively recruited patients with moderate renal impairment; safety and efficacy have however not been established with 200 mg. All included patients (prospective and retrospective) will be followed until death, loss to follow-up, or end of the study.
Section 7.1 Patient Enrollment	Added clarifying language and additional information regarding prospective and retrospective patient enrollment in the study. .	The changes made describe that signed informed consent is not applicable for retrospective patients and RET mutation negative status will be verified for retrospective patients. The RET determination will be performed in those patients where it is needed to confirm eligibility for prospective patients, provided that a biopsy sample is available and provided that no intervention is needed that would not have been done otherwise to obtain this sample. The Investigator will register in the study Web-based Data Capture (WBDC) system, immediately after known, the information related to eligibility of the patient, even if some of these information are incomplete in the beginning. For retrospective patients, the site will search the databases for the prevalent MTC patients and review the records to consider recruitment using 2010 as a cutoff without any limitation for the date of diagnosis, and identify among these patients all those who were RET mutation negative, all of whom should be included into the study (unless if there is a contract with another company for a clinical trial that precludes this). For the cases where the RET test needs to be done on an available biopsy sample to confirm eligibility for the study, without any intervention that would not have been done otherwise, a signed informed consent should be always obtained prior to performing the laboratory analyses on the available sample (except for retrospective patients). An informed consent is never needed for the intervention itself, since this intervention should never be related to the study. The Sponsor will reimburse the costs associated to the RET determination when the test is solely performed to confirm eligibility for the study, provided that the intervention allowing to collect the sample (biopsy) was not done specifically for the study.
Section 7.2 Patient follow-up	Added clarifying language regarding follow-up or time points for retrospective patients.	The changes made describes that once the patient is enrolled in the study, every time he/she attends the office/clinic/hospital for routine visits, the Investigator will create a visit in the eCRF and record all the available information required for study purposes, together with the dates of these routine visits. Follow-up (labelled as “time points” for retrospective patients) of each patient and collection of data for the study will cease at the death of the patient, loss to follow-up, or at the end of study (whichever occurs first).

Section # and Name	Description of Change	Brief Rationale
Section 8.1 Benefit /risk	Added clarifying language for prospective and retrospective patients relating to study variables.	The changes made describes collection of safety data for retrospective and prospective patients. “Pulse” was removed and “heart rate “was added in vital signs category.
Section 8.2 Patient Characteristics	Added clarifying language for prospective and retrospective patients relating to study variables.	The changes made describes disease assessment, death/lost to follow-up and treatment information for retrospective and prospective patients.
Section 9.2.1 Time period for collection of adverse events	Added clarifying language regarding AE collection for prospective and retrospective patients.	The changes made describes that AEs will be collected throughout the study for prospective patients and retrospectively for retrospective RET mutation negative patients, from informed consent form (ICF) signature (or start of vandetanib treatment for retrospective patients where no ICF is required) until the end of the study follow-up period. For patients who discontinue or have discontinued (retrospective patients) the treatment with vandetanib before the end of the study follow-up period, AE will be collected up to 60 days after the last dose received. Serious AEs (SAE’s) occurring in the follow-up period should be reported to the Sponsor in the usual manner as described in Section 9.3.1.
Section 9.3.1	Section heading revised	To be consistent with text related to AE’s.
Section 9.3.1 Reporting of serious adverse events	Added information related to reporting of AE and serious adverse event (SAE) for retrospective patients.	The change made describes that the AEs will be collected throughout the study for prospective patients and retrospectively for retrospective RET mutation negative patients. All AEs defined in Section 9.1.2 will be recorded in the eCRF. If any SAE occurs in the course of the study, then Investigators or other site personnel will inform appropriate Sponsor representatives within 24 hours ie, immediately from awareness and if any non-SAE occurs, no later than 30 calendar days from awareness. The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to Global Pharmacovigilance (GPV) within 24 hours for SAE and within 5 calendar days for non-SAE.
Section 9.3.3 Deaths	Added information related to retrospective patients.	The changes made describes that all dead patients will be considered for the retrospective data collection, with no exception.
Section 10.2 Patient Informed Consent	Added clarifying language regarding informed consent for prospective and retrospective patients.	The changes made describes that for retrospective patients, a waiver of informed consent is requested due to retrospective and Non-Interventional nature of this study.
Section 10.3 Patient data protection	Added information regarding data protection for retrospective patients.	The changes made describes that for retrospective patients, access to the WBDC system will be controlled via a hierarchical user-name and password control. Patient data will be pseudonymized through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, or center-assigned patient identifiers. Only trained site staff will enter data into the eCRFs. Patient’s ages in range of 5 years, but not date of birth, will be entered. Patient identifiers used by sites will not be entered; rather the WBDC program will automatically assign a study ID to each patient. The pseudonymized data as entered into the WBDC system will be visible to the Clinical Research Organization (CRO) and the Sponsor, but only center staff will be able to trace a study ID number back to a patient identity, a necessary measure to allow center staff to respond to data queries raised by the CRO later. Eventually, once the database will be frozen, the sites will destroy this correspondence between study ID and their own identifiers.

Section # and Name	Description of Change	Brief Rationale
Section 11.1 Monitoring, quality control and archiving	Additional information regarding monitoring, quality control, and archiving for this study was added along with clarifying language related to Non-Interventional nature of this study, and prospective patients.	The changes made describes that before the first patient is recruited into the study, the local Marketing Company (MC) representative or delegate will: Establish the adequacy of the facilities and the Investigator's capability to appropriately collect the sample, which should always be done in the frame of an intervention that was already planned independently from the study. During the study the local MC representative or delegate can implement different activities to assure compliance with Sponsor standards of quality. Contacts with the sites to: Ensure that the screening is performed properly and thoroughly, so that no patient who may be eligible is missed from the systematic screening process; Monitoring activities for: Must ensure that the screening is performed properly and thoroughly, so that no patient who may be eligible is missed from the systematic screening process. Source data verification (SDV): Screening log must be checked thoroughly against the information from any sources of data available at the site, including admission logs, discharge logs, hospital databases, laboratory databases, etc.
Section 11.3 NIS timetable and end of study	Added information regarding "Estimated date of CSR addendum"	Study period planned dates updated.
Section 13 Statistical Methods and sample size determination	Added Sample size, statistical analysis methods, and safety evaluation for study population.	The change made describes sample size, statistical analysis methods (primary and secondary), and safety evaluation for RET mutation negative and RET mutation positive patients in the study.
Protocol amendment synopsis and body text	Brand name Caprelsa introduced only once as "Vandetanib (Caprelsa)" in the text.	Minor consistency change.
Appendix B	SMPC text added	Latest approved SMPC in EU.
All Appendices	Tables and references reformatted to DOMASYS style and corrected inconsistencies.	Consistency changes.

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

International Observational, Study to Evaluate the Benefit/Risk of Vandetanib (Caprelsa™) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer

Study Site(s), number of patients and countries planned

It is estimated that 6 countries and 30 Investigator sites ~~s~~hall participate in the study and will provide at least 20 to 25 Rearranged During Transfection (RET) mutation positive and 20 to 25 RET mutation negative patients treated with vandetanib for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic medullary thyroid cancer (MTC). In addition, symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC patients who are RET mutation negative but not prescribed vandetanib 300 mg will be allowed to enter the study.

Total planned study period	
Estimated date of first patient in	1Q2013
Estimated date of last patient in	3Q2019
Estimated date of last patient last visit	4Q2020
Estimated date of data base lock	2Q2020
Estimated date of clinical study report (CSR)	3Q2020
Estimated date of CSR addendum	3Q2021

Medicinal Products (type, dose, mode of administration) and concomitant medication

Vandetanib 300 mg/once daily, film-coated tablets.

The starting dose could be reduced to 200 mg in patients with moderate renal impairment.

Rationale

The Study D4200C00104 is conducted to fulfill the specific obligation linked to the conditional marketing authorization of vandetanib. The objective of Study D4200C00104 is to confirm in the real-life setting the benefit/risk ratio of vandetanib 300 mg, in both RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. The clinical benefit of vandetanib 300 mg has previously been established in a clinical trial (Study D4200C00058) on the basis of a clinically and statistically significant advantage in progression free survival (PFS) which was supported by a high response rate and substantial duration of response.

Objectives of this NIS

A) To determine the Objective Response Rate (ORR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

A) To determine the Disease Control Rate (DCR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

B) To assess the duration of response and time to response for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

C) To explore the clinical outcomes (including but not limited to PFS and ORR) amongst RET mutation negative patients not treated with vandetanib.

D) To evaluate the incidence of QT (The interval between Q and T on electrocardiogram [ECG]) interval corrected for heart rate (QTc) prolongation and associated risks for QTc prolongation in patients receiving vandetanib who are RET mutation positive and RET mutation negative. In addition, the incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation of vandetanib will be assessed.

E) To compare PFS for patients treated with vandetanib who are RET mutation positive to patients treated with vandetanib who are RET mutation negative.

Study design

This is a multinational, multicenter, Non-Interventional (observational), prospective (for patients with RET mutation positive or negative status) and retrospective (for patients with RET mutation negative status) study. The decision to prescribe vandetanib is taken independently of the enrollment into this study and is in line with the respective (local) prescribing information. The study is observational, meaning that vandetanib treatment initiation should never be delayed in order to meet any inclusion criteria of the study. Similarly, performing interventions on the patients that would specifically be for the study and would not be carried out in the "real-life" setting is not permitted eg, a biopsy. European countries where vandetanib is on the market (up to 2012) will participate in the study.

Target patient population

Patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib 300 mg/once daily and with a RET mutation positive or negative status, prospectively. In addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib 300 mg/once daily, at any time, and with a RET mutation negative status, will be allowed to enter the study retrospectively. Also, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC not prescribed vandetanib 300 mg but who are RET mutation negative will be allowed to enter the study both retrospectively and prospectively.

Study variable(s):

Benefit/risk

- ORR (using Response Evaluation Criteria in Solid Tumors [RECIST] 1.1)
- DCR (using RECIST 1.1)
- PFS derived (using RECIST 1.1)
- Duration of response and time to response
- Safety:

  All efforts will be made to collect the following safety data, for prospective (RET mutation positive or negative) and for retrospective (RET mutation negative) patients:
  - AE: All AEs (for patients treated with vandetanib), will be collected actively throughout the study, and retrospectively for retrospective RET mutation negative patients
  - ECGs: QTc prolongation
  - Vital signs: blood pressure, heart rate
  - Laboratory data:
    - Electrolyte: serum potassium, calcium and magnesium
    - Thyroid stimulating hormone (TSH) at baseline
    - Renal function: creatinine clearance value (Cockcroft Gault formula)
    - Hepatic function: serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and albumin

Patient demographics and medical history

- Age
- Sex
- Co-morbidities
- Chronic drug therapy related to relevant medical conditions at baseline

Disease characteristics

- First diagnosis of sporadic MTC date
- Date of diagnosis of sporadic, unresectable, locally advanced/metastatic MTC
- Investigator´s assessment of symptomatic and aggressive (clinical deterioration, calcitonin [CTN], carcinoembryonic antigen [CEA] doubling time, change of tumor volume, other)
- Date of last determination of disease progression
- RET determination (if more than one determination has been done, information from all will be collected):
    - Date of RET assay
    - Mutational status
    - Assay type
    - Tissue type used for assay
    - Date of tissue biopsy
    - Exons analyzed
- Disease assessment (including number/sites of disease locations): at baseline (for all patients and before treatment with vandetanib for the patients who received vandetanib) and at follow-up visits for prospective patients or at any time point for retrospective patients (whenever performed)
- Date of measurements
- Symptoms at baseline (before treatment with vandetanib for the patients who received vandetanib) and at every disease assessment time point (lump at the base of the neck, dysphagia, respiratory difficulty, hoarseness, diarrhea, weight loss, lethargy, asthenia, anorexia and bone pain)
- CTN and CEA doubling time at baseline
- CTN and CEA at every disease assessment time point

Death/Lost to follow-up

- Date and cause

Treatment information:

- Previous treatments received for the sporadic MTC (including non-pharmacologic)
- <u>For prospective (RET mutation negative or positive) patients prescribed vandetanib at entry</u>: current and any subsequent treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: date of treatment start and stop (if available)
- <u>For retrospective (RET mutation negative) patients diagnosed with MTC and prescribed vandetanib at any time, or never prescribed vandetanib:</u> previous, current and any further treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: dates of treatments start and stop (if available)

- For RET mutation negative patients not treated with vandetanib at entry: current and subsequent treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: dates of start and stop (if available)
- Dose adjustments/discontinuations during follow-up (dates of adjustments and doses)
- Opioid use: Dates, doses, and routes by generic name

Statistical methods

All statistical analyses will be performed by Worldwide Clinical Trials Limited (WCT), 172 Tottenham Court Road, London W1T7NS, United Kingdom under the supervision of the Sponsor Study Scientific leader.

A comprehensive Statistical Analysis Plan (SAP) will be prepared before first patient in.

Determination of sample size

The Sponsor and the EMA agreed that a sample size between 40 and 50 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC receiving vandetanib: 20 to 25 RET mutation negative and 20 to 25 RET mutation positive would be appropriate. If the ORR is 35% with a standard deviation (SD) of 0.4770, then Table 1 below shows the 95% confidence interval (CI) for different sample sizes:

Table 1 - Confidence interval (95% CI) according to sample size per type of mutation for an Objective Response Rate of 35%

Sample size per type of mutation	Objcetive Response Rate	95% (CI)
20	35%	(14.1%, 55.9%)
25	35%	(16.3%, 53.7%)
30	35%	(17.9%, 52.1%)

Statistical Analysis

The changes implemented in the protocol amendment define, in addition to the original study population, 2 other groups of patients: a retrospective group and a group of patients from the Study D4200C00058 whose RET data were re-analyzed with aim to categorize them as RET mutation positive or RET mutation negative. The criteria for selecting these data, described elsewhere in this amended protocol, are intended to assure that the populations are comparable, and hence, may be pooled. In order to confirm comparability, all analyses will report the descriptive statistics for each of these groups as well as the pooled data both for RET mutation positive and RET mutation negative patients, as presented in Table 2 below.

Table 2 - Summary of baseline characteristics

	RET mutation positive				RET mutation negative				All
	Prospective	Study D4200C00058	Retrospective	All	Prospective	Study D4200C00058	Retrospective	All	
Variable	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	

Table content will adapt to the type of variable as defined below:

Qualitative variables will be described by number of observed values, percentage and number of missing values (patients with missing data will not be included in the percentage calculation).

Quantitative variables will be described by number of observed values, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum.

For time-to-event, the median time to event and, number and percentage of each group remaining at risk at the last point of observation will be provided.

Statistical analyses will be conducted with SAS Software version 9.3 or upper.

Analysis of Primary Criteria

Estimate ORR, DCR rates for RET positive and negative

The ORR and DCR will be summarized as qualitative variables.

Time to response and Duration of response for RET positive and negative

The time to response and duration of response will be summarized as time-to-event data. Kaplan-Meier curves will be produced. A waterfall plot of the best percentage change in the sum of the longest diameters of the target lesions from baseline will be produced split by RET mutation status.

Analysis of Secondary Criteria

PFS and ORR exploration for RET positive and negative

A Kaplan-Meier plot of PFS split by RET mutation status will be presented. Median PFS will be presented, where possible, in the 2 groups.

Subgroup analyses will be performed for PFS by CTN doubling time and CEA doubling time at baseline.

QTc prolongation under vandetanib for RET positive and negative

QTc will be treated as a continuous variable.

The following will be executed without formal testing:

- The frequency and percentage of patients with symptoms at each time point will be summarized by RET mutation status. Opioid analgesic use will be summarized descriptively by RET mutation status.
- Data for RET mutation negative patients not treated with vandetanib will be summarized with 95% CIs presented when appropriate.

Safety Evaluation

SAE and AE leading to discontinuation – summary by RET mutation *positive and RET mutation negative*

Safety data will be presented by RET mutation status. Caution will be used when interpreting safety data in RET mutation negative patients who are not treated with vandetanib, that cannot be compared with safety data from the RET mutation negative patients who are treated with vandetanib.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this NIS Protocol.

ADR:	adverse drug reaction
AE:	adverse event
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ARMS:	amplification refractory mutation system
AST:	aspartate aminotransferase
CEA:	carcinoembryonic antigen
CGH:	comparative genomic hybridization
CHMP:	Committee For Medicinal Products for Human Use
CRO:	clinical research organisation
CSR:	clinical study report
CT:	computed tomography
CTCAE:	common terminology criteria for adverse events
CTN:	calcitonin
ECG:	electrocardiogram
eCRF:	case report form (electronic)
EU:	European Union
GCP:	good clinical practice
GGT:	gamma-glutamyltransferase
GPV:	Global Pharmacovigilance
ICF:	informed consent form
ICH:	International conference on Harmonisation
M918T:	mutation in RET result in an amino acid substitution at position 918, from methionine to threonine
MC:	Marketing Company
MRI:	magnetic resonance imaging
MTC:	medullary thyroid cancer
NIS:	non-interventional study
NISA:	Non-Interventional Study Agreement
ORR:	objective response rate
PCR:	polymerase chain reaction
PFS:	progression free survival
QT:	the interval between Q and C on ECG
QTc:	QT interval corrected for heart rate
RECIST:	response evaluation criteria in solid tumors
RET:	rearranged during transfection
RMP:	risk managment plan
SAE:	serious adverse event
SAP:	statistical analysis plan

SDV:	source data verification
SmPC:	summary of product characteristics
TSH:	thyroid stimulating hormone
ULN:	upper limit of normal
ULRR:	upper limit of reference range
WBDC:	web-based data capture

1 INTRODUCTION

1.1 BACKGROUND

In Study D4200C00058 (the pivotal clinical trial in which the efficacy and safety of vandetanib 300 mg were compared to placebo in patients with medullary thyroid cancer (MTC), Rearranged During Transfection (RET) mutation testing was performed by performing a polymerase chain reaction (PCR)-based assay called the Amplification Refractory Mutation System (ARMS) assay to detect the most common mutation in sporadic MTC (the M918T mutation) and by sequencing the 6 most commonly mutated exons in RET (10, 11, 13, 14, 15, and 16). A tumor was considered to have a RET mutation if it either had an M918T mutation by the ARMS assay, or a RET mutation in any of exons 10, 11, 13 to16. A RET mutation negative tumor was defined as having no M918T mutation by ARMS and a wild-type RET sequence in each of exons 10, 11, 13 to16. The mutation status was considered to be unknown in tumors where an assay failed to yield a sequence at any of the tested exons (by sequencing or ARMS assay), and none of the successful assays demonstrated a mutation.

Therefore, the criteria for defining a patient as RET mutation negative were very stringent - all 7 assays had to have been successful and demonstrated no mutation. Conversely, only one assay had to demonstrate a RET mutation for the patient to be considered RET mutation positive. Because many of the tumor samples were in poor condition and the stringent criteria for defining patients as RET mutation negative, a high percentage of patients had an unknown RET mutation status and only a small percentage of patients were identified as RET mutation negative.

The mutation status outcome in Study D4200C00058 (N=331) was as follows:

- 57% of patients were defined as RET mutation positive
- 41% had an unknown RET mutation status
- 2% (8) patients were identified as being RET mutation negative based on the protocol definition for RET mutation status.

To better define the efficacy of vandetanib 300 mg in patients who were RET mutation negative, a post-hoc subgroup analysis of RET mutation negative status based on absence of M918T mutation of the pivotal Study D4200C00058 was performed. Based on a recent study with a data base consisting of 100 sporadic MTC tumors whose complete exon sequencing was done at all 6 RET exons where RET mutations have been described (1), it is estimated that if a patient does not have the M918T mutation, there is an 86% likelihood that the patient will not have a RET mutation at all; this is also supported by other studies (2). In Study D4200C00058, it was also established that 86% of patients without an M918T mutation had no other RET mutation identified (79 sporadic patients were identified without a M918T mutation and no RET mutation identified at any of the other 6 exons tested in 71 of these patients) (3).

Thus, patients with the sporadic form of MTC without the M918T mutation have nearly a 90% probability of being RET mutation negative. Table 3 summarizes the results of the post hoc analysis of efficacy endpoints in patients with a documented RET mutation and patients who were M918T mutation negative and other mutations not tested or negative.

Table 3 - Summary of efficacy findings in a segment of patients according to RET mutation status[a]

	Patients with documented RET mutation (n=187)	Patients with no M918T mutation and other mutations not tested or negative (n=79)[b]
ORR (vandetanib arm)	52%	35%
Efficacy Endpoint PFS		
HR (95% CI)	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)

a The table shows the results of the analysis performed by Astra Zeneca in 2012-2014.
b RET mutation status was obtained at the time of diagnosis in a majority of patients and could have changed since.
CI= Confidence Interval, HR= Hazard ratio, ORR= Objective response rate, PFS= Progression free survival, RET= Rearranged during transfection

1.2 RATIONALE FOR CONDUCTING THIS NON-INTERVENTIONAL STUDY

This Study D4200C00104 is being conducted to fulfill the specific obligation (SOB) post-authorization linked to the conditional marketing authorization of vandetanib. It is carried on to confirm in real-life conditions the benefit/risk of vandetanib 300 mg, both in RET mutation negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC.

Previously in a clinical trial (Study D4200C00058) the clinical benefit of vandetanib 300 mg had been established based on clinically and statistically significant advantage in progression free survival (PFS) supported by a high response rate and substantial duration of response.

When comparing the groups of patients, some considerations will be taken into account: the RET mutation positive and RET mutation negative population may not be part of a homogenous patient population. The RET mutation negative and RET mutation positive patients may have different clinical courses based on factors other than the RET status.

A non-interventional study (NIS) is an appropriate approach because this type of study will provide information on the clinical benefit/risk between these groups of patients based on the actual clinical practice of physicians who are prescribing vandetanib.

Moreover, it is very important for the study objectives that the management of the disease is not modified in comparison to standard of care. Therefore, delays of vandetanib treatment initiation time, no extra procedures, interventions or extra visits over and above the standard of care will be required for study purposes.

Conducting this real world NIS as described above will lead to a more thorough understanding of the benefit/risk profile of vandetanib in RET mutation positive and negative patients based on the actual clinical practice with vandetanib. A NIS is a study in which no additional diagnostic or monitoring procedures shall be applied to the patients.

2 NON-INTERVENTIONAL STUDY OBJECTIVES

A) To determine the Objective Response Rate (ORR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

B) To determine the Disease Control Rate (DCR) for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

C) To assess the duration of response and time to response for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative.

D) To explore the clinical outcomes (including but not limited to PFS and ORR) among RET mutation negative patients not treated with vandetanib.

E) To evaluate the incidence of QT (the interval between Q and T on electrocardiogram [ECG]) interval corrected for heart rate (QTc) prolongation and associated risks for QTc prolongation in patients receiving vandetanib who are RET mutation positive and RET mutation negative. In addition, the incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation of vandetanib will be assessed.

F) To compare PFS for patients treated with vandetanib who are RET mutation positive to patients treated with vandetanib who are RET mutation negative.

3 STUDY PLAN AND PROCEDURES

This NIS protocol has been subject to an internal review according to Sponsor internal procedures.

3.1 OVERALL STUDY DESIGN AND FLOW CHART

This is a multinational, multicenter, Non-Interventional, study of patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib 300 mg/once daily and with a RET mutation positive or negative status including RET mutation negative patients who never received vandetanib (as many patients as possible, with no restriction on the numbers of RET mutation negative patients). Patients will be either prospectively followed, or in addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC and with a RET mutation negative status, will be allowed to enter the study retrospectively.

Twenty to twenty-five vandetanib RET mutation positive and 20 to 25 vandetanib RET mutation negative patients will be enrolled in the study.

For prospective patients (patients with RET mutation positive or negative): study visits will include a screening visit and/or enrollment visit, where the eligibility of the patient will be confirmed, plus additional follow-up visits:

- For effectiveness measurement purposes, Investigators are strongly recommended to perform a complete disease assessment (biomarkers, symptoms and imaging) at least every 6 months according to both site normal clinical practice and International MTC guidelines (4, 5). Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be used as a base for calculation for disease assessment.
- For patients prescribed with vandetanib, prescription frequency and safety assessments should be done according to specifications in the Summary of Product Characteristics (SmPC) (see Appendix B).

Patients will be followed until objective progression or until the end of study (whichever occurs first).

For retrospective patients (only MTC patients with RET mutation negative status):

Data collection reporting time points will include a baseline time point before the start of their treatment for MTC (vandetanib or another treatment) where the eligibility of the patient will be confirmed, plus all subsequent time points that may be available in the patient file.

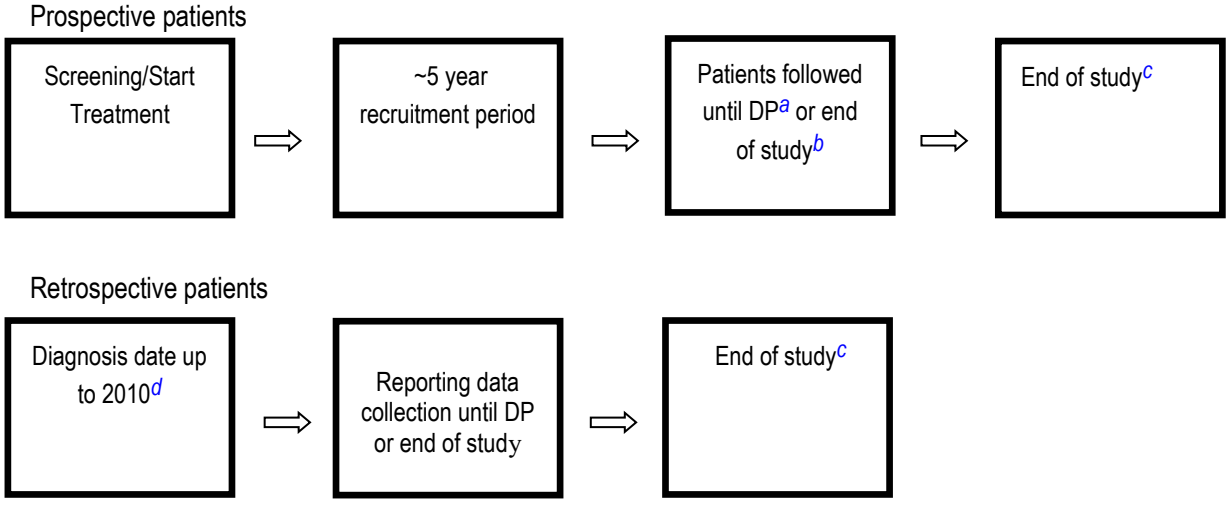
- Complete disease assessment (biomarkers, symptoms, and imaging) according to both site normal clinical practice and international MTC guidelines will be reported (4, 5). RECIST 1.1 will be used as a base for calculation for disease assessment.

- Diagnosis of MTC could be as early as 1995-2000. The centers will search their databases for the prevalent MTC patients and review the records to consider recruitment using 2010 as a cutoff, without any limitation for the date of diagnosis. The prescription frequency of vandetanib or any other treatment for MTC should be reported. All efforts will be made to report safety assessments according to specifications in the SmPC, based on the data that will be available in the patient charts (see Appendix B).

Data collection and reporting will be performed until objective progression, or until the end of study (whichever occurs first). For all patients end of study is defined as 14 months after the last prospective patient has been enrolled in the study and when at least 10 events in each treatment group have been observed. If all patients have progressed prior to 14 months after the last patient is recruited, the study will stop.

The minimum follow-up time period of 14 months for prospective arm (not retrospective) is appropriate because approximately 80% of patients who had an objective response in a pivotal Phase III study achieved their response within 14 months of starting vandetanib (3).

Figure 1 - Study flow chart



a DP = Disease progression
b Whichever occurs first
c End of study is defined as 14 months after the last prospective patient has been enrolled in the study and when at least 10 events in each treatment group have been observed. If all patients have progressed prior to 14 months after the last patient is recruited, the study will stop.
d Diagnosis could be as early as 1995-2000, but the centers will search databases (for the prevalent MTC patients) and review the records to consider recruitment using 2010 as a cutoff, without any limitation for the date of diagnosis.

Detailed study assessments are described in Table 4.

Table 4 - Study plan

Time	Screening/Enrollment visit or baseline time point	Follow-up visits for prospective patients or follow-up time points for retrospective patients
Obtain Informed Consent[a]	X	-
Inclusion/exclusion criteria assessment	X	-
Patient Characteristics, including RET status[b]	X	-
Disease assessment[c]	X	X
Treatment information	X	X
Safety information Laboratory[d]	X	X

a Waiver for retrospective patients

b For retrospective patients: RET mutation negative status may have been performed before or after start of the treatment of medullary thyroid cancer (MTC) (Vandetanib or another treatment).

c Disease assessment should be consistent (same time frequency and method) within a site across the study for prospective patients, but not necessarily for retrospective patients.

d Potassium, creatinine, calcium, magnesium and thyroid stimulating hormone (TSH) will be collected at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for one year.

RET= Rearranged during transfection

3.2 RET MUTATION ANALYSIS PROCEDURE

The assay to determine mutation status will be done or may have been done (in case of retrospective patients) in certified laboratories and must be based on one of these 3 tests:

- Sequencing
- PCR including ARMS methodology
- Comparative genomic hybridization (CGH)

For this study, the criteria for definition of the RET status is as follows:

- If mutation is present in M918T (exon 16) or any other additional exon tested where RET mutations have been described (10, 11, 13 to16), then the patient is RET mutation positive.
- If mutation is absent in M918T (exon 16), and in any of the other additional exons where RET mutations have been described (10, 11, 13 to 16), then the patient is RET mutation negative.

4 SELECTION OF PATIENT POPULATION

4.1 INVESTIGATORS

Investigators experienced in the treatment of symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC and based in European Union (EU) countries where vandetanib is approved and available for use in the treatment of MTC.

4.2 INCLUSION CRITERIA

The patient population that will be included in the NIS must fulfill all the following criteria:

I 01. Signed informed consent for prospective patients. No need for signed informed consent for retrospective patients (waiver).

I 02. Male or female aged 18 years or above for prospective patients. No age restriction for retrospective patients.

I 03. Histological diagnosis of MTC (for retrospective patients [prevalent MTC patients] diagnosis could be as early as possible, without any limitation for the date of diagnosis).

I 04. Patients with symptomatic and aggressive sporadic MTC, who have unresectable, locally advanced/metastatic disease. (The factors considered by the Investigator to determine a patient's disease to be symptomatic and aggressive will be recorded in the electronic case report form [eCRF], allowing for missing data for the retrospective patients).

I 05. Measurable disease:

- Assessment confirmed within the 12 weeks previous to start of treatment, and
- Defined according to RECIST 1.1: at least 1 lesion, not irradiated, that can be accurately measured as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. Measurable lesions with calcifications should not be assessed as target lesions unless no other measurable lesion is available.

Known definite RET mutation status (definition according to Section 3.2). The status should be:

- For prospective patients prescribed with vandetanib: positive or negative.
- For prospective patients not prescribed with vandetanib: negative.
- For retrospective patients prescribed or not prescribed with vandetanib: negative.

- For prospective patients: RET mutation status must be determined from a tumor sample obtained within 18 months prior to enrollment. It is strongly recommended that a tissue sample obtained within 6 months prior to enrollment is used. For retrospective patients: RET mutation negative mutation status could have been determined within 18 months before or after start of treatment (with vandetanib or another drug). In case of retrospective patient treated with another drug, the patient should have been treated with vandetanib at any time.

I 06. For prospective patients newly prescribed vandetanib 300 mg, the prescription should be issued according to marketing authorization and following the vandetanib SmPC (Appendix B). The starting dose could be reduced to 200 mg in patients with moderate renal impairment. For retrospective patients, the prescription may or may not have been issued according to the SmPC.

I 07. Note: The **prescription of the medicinal product is clearly separated from the decision to include the patient** in the NIS. The study is observational, meaning that vandetanib treatment initiation should never be delayed in order to meet any inclusion criteria of the study.

4.3 EXCLUSION CRITERIA

E 01. Current or planned inclusion/participation in a clinical trial, not applicable for retrospective patients.

E 02. Patients already receiving vandetanib or who have received vandetanib for their MTC before the study first visit, not applicable for retrospective patients.

E 03. Contraindications according to the vandetanib SmPC, not applicable for retrospective patients and for patients who do not receive vandetanib:

A) Patients with a QTc interval over 480 msec:
   - Congenital long QT syndrome
   - Concomitant use of vandetanib with the following medicinal products known to also prolong the QT interval and/or induce Torsades de pointes: Arsenic, cisapride, erythromycin intravenous, toremifene, mizolastine, moxifloxacine, Class IA and III antiarrhythmics

A) Currently pregnant or breast-feeding, not applicable for retrospective patients.

B) Hypersensitivity to the active substance or to any of the excipients, not applicable for patients who do not receive vandetanib.

C) Severe renal impairment: creatinine clearance <30 mL/minute calculated by Cockcroft-Gault formula, not applicable for patients who do not receive vandetanib (See Appendix D).

D) Serum bilirubin greater than 1.5 × the upper limit of reference range (ULRR), not applicable for patients who do not receive vandetanib.

E) Potassium, magnesium or calcium outside the normal laboratory range, not applicable for patients who do not receive vandetanib.

5 WITHDRAWAL OF PATIENTS

5.1 CRITERIA FOR WITHDRAWAL

Patients may be withdrawn from the NIS at any time. Specific reasons for withdrawing a patient from this NIS are:

1. Voluntary withdrawal by the patient who is at any time free to withdraw his/her participation in the NIS, without prejudice to further treatment (not applicable for retrospective patients).
2. Incorrect enrollment (inclusion/exclusion criteria are not fulfilled).
3. Inclusion in a clinical trial at any time during the study (not applicable for retrospective patients).

Discontinuation of the patient treatment is not a criterion for withdrawal from the study. In this case, the patient can continue in the study, until death, loss to follow-up, or end of study.

5.2 PROCEDURES FOR WITHDRAWAL

For prospective patients: patients who withdraw should be asked about the reason(s) for their withdrawal. No specific procedures after withdrawal are required per study but continuation of patient assessment and treatment according to routine clinical practice.

No further data will be collected on prospective patients following withdrawal from the study.

Prospective patients who were not included (eg, for restrictive inclusion/exclusion criteria) or withdrawn from the study (eg, withdrawn due to AE but continuation of assessment and treatment according to routine practice) will still be considered for the retrospective data collection: if they meet the inclusion criteria for the retrospective data collection, the same patient ID will be used in the study database and the patient will be classified as retrospective patient for data analyses.

6 THERAPEUTIC STRATEGY

6.1 THERAPEUTIC STRATEGY OF A NON-INTERVENTIONAL STUDY

The assignment of a patient to a particular therapeutic strategy is not decided in advance by the protocol but falls within current practice. Therefore, the Sponsor will not reimburse vandetanib or any other medication, or any intervention or related expenses (due to the Non-Interventional nature of this study, only the laboratory analyses on biopsy samples already available can be reimbursed).

- Trade name and generic name: Caprelsa, vandetanib
- Dosage, form and strength: 300 mg/once daily, film-coated tablets

For prospective patients, doses and treatment regimens of vandetanib 300 mg, and other treatments for MTC, and concomitant medication should be or should have been prescribed according to the instructions in the SmPC (see Appendix B) and current practice.
In any case, all data available in the patient charts will be reported and described into the eCRF for the retrospective patients, even if not prescribed according to the SmPC.

There is limited data with 300 mg in patients with moderate renal impairment. The starting dose could be reduced to 200 mg in prospectively recruited patients with moderate renal impairment; safety and efficacy have however not been established with 200 mg.
All patients will be followed on treatment for at least 14 months provided it is considered appropriate for a patient to remain on treatment in the opinion of the Investigator. In any case, all included patients (prospective and retrospective) will be followed until death, loss of follow-up, or end of the study.

7 STUDY CONDUCT

7.1 PATIENT ENROLLMENT

For prospective patients, once vandetanib is launched in the country and the participant site has the appropriate local approvals, the Investigator will systematically identify and invite to participate in the study every patient who fulfills all the study inclusion criteria and none of the exclusion criteria.

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient (except for retrospective patients).
2. Perform the RET determination in those patients where it is needed to confirm eligibility for prospective patients, provided that a biopsy sample is available and provided that no intervention is needed that would not have been done otherwise to obtain this sample. Verify the RET mutation negative status for retrospective patients.
3. Register the patient in the Web-based Data Capture (WBDC) system when the patient is entered into screening and/or is enrolled.

The recruitment of patients will be centrally controlled by the study team through the WBDC system. Therefore, in order to achieve the appropriate study sample target, it is of great importance that the Investigator registers in the study WBDC system**, immediately after known,** the information related to eligibility of the patient, even if some of these information are incomplete in the beginning.

All the prospective patients who sign the consent form will be allocated an E-code by the WBDC system. For patients who enter into screening period, but are not finally eligible, they will be registered in the WBDC as screening failure and withdrawn. All the screened patients will be registered in the site screening log and reason for withdrawal documented.

Applicable for retrospective patients: the site will search the databases for the prevalent MTC patients and review the records to consider recruitment using 2010 as a cutoff without any limitation for the date of diagnosis and identify among these patients all those who were RET mutation negative, all of whom should be included into the study (unless if there is a contract with another company for a clinical trial that precludes this).

For the cases where the RET test needs to be done on an available biopsy sample to confirm eligibility for the study, without any intervention that would not have been done otherwise, a signed informed consent should be always obtained prior to performing the laboratory analyses on the available sample (except for retrospective patients). An informed consent is never needed for the intervention itself, since this intervention should never be related to the study.

The Sponsor will reimburse the costs associated to the RET determination when the test is solely performed to confirm eligibility for the study, provided that the intervention allowing to collect the sample (biopsy) was not done specifically for the study.

7.2 PATIENT FOLLOW-UP

Once the patient is enrolled in the study, every time he/she attends the office/clinic/hospital for routine visits (see follow-up visits description in Section 3.1), the Investigator will create a visit in the eCRF and record all the available information required for study purposes, together with the dates of these routine visits. Follow-up (labelled as "time points" for retrospective patients) of each patient and collection of data for the study will cease at the death of the patient, loss to follow-up, or at the end of study (whichever occurs first). For safety data collection period, please refer to Section 9.2. For special warnings and precautions for use of vandetanib during the follow-up period (eg, QTc prolongation), please refer to SmPC (Appendix B).

7.3 RESTRICTIONS DURING THE STUDY

There are no specific restrictions in this study.

8 MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

8.1 BENEFIT/RISK

- ORR (using RECIST 1.1)
- DCR (using RECIST 1.1)
- PFS derived (using RECIST 1.1)
- Duration of response and time to response
- Safety:

  All efforts will be made to collect the following safety data, for prospective (RET mutation positive or negative) and retrospective RET mutation negative patients:
  - AE: All AEs, (for patients treated with vandetanib) will be collected actively throughout the study, and retrospectively for retrospective RET mutation negative patients
  - ECGs: QTc prolongation
  - Vital signs: blood pressure, heart rate
  - Laboratory data:
    - Electrolyte: serum potassium, calcium and magnesium
    - Thyroid stimulating hormone (TSH) at baseline
    - Renal function: creatinine clearance value (Cockcroft Gault formula)
    - Hepatic function: serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and albumin.

8.2 PATIENTS CHARACTERISTICS

Patient demographics and medical history

- Age
- Sex
- Co-morbidities
- Chronic drug therapy related to relevant medical conditions at baseline

Disease characteristics

- First diagnosis of sporadic MTC date
- Date of diagnosis of sporadic, unresectable, locally advanced/metastatic MTC
- Investigator´s assessment of symptomatic and aggressive (clinical deterioration, calcitonin [CTN], carcinoembryonic antigen [CEA] doubling time, change of tumor volume, other)

- Date of last determination of disease progression
- RET determination (if more than 1 determination has been done, information from all will be collected):
    - Date of RET assay
    - Mutational status
    - Assay type
    - Tissue type used for assay
    - Date of tissue biopsy
    - Exons analyzed
- Disease assessment (including number/sites of disease locations): at baseline (for all patients and before treatment with vandetanib for the patients who received vandetanib) and at follow-up visits for prospective patients or at any time point for retrospective patients (whenever performed)
- Date of measurements
- Symptoms at baseline (before treatment with vandetanib for the patients who received vandetanib) and at every disease assessment time point (lump at the base of the neck, dysphagia, respiratory difficulty, hoarseness, diarrhea, weight loss, lethargy, asthenia, anorexia and bone pain)
- CTN and CEA doubling time at baseline
- CTN and CEA at every disease assessment time point

Death/Lost to follow-up

- Date and cause

Treatment information:

- Previous treatments received for the sporadic MTC (including non-pharmacologic)
- For prospective (RET mutation negative and positive status) patients prescribed vandetanib at entry: current and any subsequent treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: date of treatment start and stop (if available)
- For retrospective (RET mutation negative status) patients diagnosed with MTC, and prescribed vandetanib at any time or never prescribed vandetanib: previous, current and any further treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: dates of treatments start and stop (if available)
- For RET mutation negative patients not treated with vandetanib at entry: previous, current and further treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: dates of start and stop (if available)
- Dose adjustments/discontinuations during follow-up (dates of adjustments and doses)
- Opioid use: Dates, doses and routes by generic name

The above information, the monitoring of which is specifically recommended in the SmPC, will be collected during the study visits/reporting time points when available in medical records.

9 SAFETY REPORTING

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

9.1 DEFINITIONS

9.1.1 Definition of AE

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term adverse event is used generally to include any AE whether serious or non-serious.

Refer to Section 9.2.1 for further details of the study safety reporting requirements.

9.1.2 Definition of SAE

A SAE is an AE occurring during any study phase and fulfills 1 or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the ~~subject~~ patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix E.

9.1.3 Definition of Adverse Drug Reactions

An (adverse drug reaction) ADR is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

9.2 RECORDING OF ADVERSE EVENTS

9.2.1 Time period for collection of adverse events

The AEs listed below will be collected throughout the study for prospective patients and retrospectively for retrospective RET mutation negative patients (based on data available in the patient charts), from informed consent form (ICF) signature (or start of vandetanib for retrospective patients where no ICF is required) until the end of the study follow-up period. For patients who discontinue or have discontinued (retrospective patients) the treatment with vandetanib before the end of the study follow-up period, AEs will be collected up to 60 days after the last dose received. Serious AEs occurring in the follow-up period should be reported to the Sponsor in the usual manner (see Section 9.3.1).

1. All SAEs
2. All AEs that led to discontinuation, interruption or modification of vandetanib dose
3. All events of diarrhea or dehydration, regardless of seriousness and severity
4. Abnormal results in ECG data, including heart rate and QT when clinically significant

9.2.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to vandetanib, the Investigator should notify the Sponsor.

9.2.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the vandetanib (yes or no)
- Action taken with regard to vandetanib
- AE caused volunteer's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for an SAE
- Date Investigator became aware of SAE
- AE is serious due to (specify reason)
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to any medication
- Description of AE

The following intensity ratings will be used:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.1.2. An AE of severe intensity needs not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

9.2.4 Causality collection

The Investigator will assess causal relationship between vandetanib and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by vandetanib?’

For SAEs, causal relationship will also be assessed for other medication.

Adverse events and SAEs will be considered associated with the last dose of vandetanib given prior to onset, as judged by the Investigator.

A guide to the interpretation of the causality question is located in Appendix E.

9.2.5 Adverse events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.2.6 Adverse events based on examinations and tests

The results from laboratory tests and vital signs described in this protocol (see study variables, Section 8.1) will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in those laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the following criteria:

- SAE criteria is fulfilled.
- The abnormality causes the patient to discontinue the treatment with vandetanib.
- The abnormality causes the patient to interrupt the treatment with the vandetanib.
- The abnormality causes the patient to modify the dose of the treatment with the vandetanib.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE. Any clinically significant prolongation of the QT interval or other clinically significant abnormal findings on ECG should be reported as an AE.

Cases where a patient shows an AST **or** ALT≥3 times the upper limits of normal (ULN) **or** total bilirubin ≥2 times the ULN may need to be reported as SAEs, please refer to Appendix F for further instructions.

9.2.7 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which vandetanib is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. However, all events of disease progression that meet seriousness criteria must be reported using the SAE reporting procedure in Section 9.3.1.

9.2.8 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the serious criteria. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be disease progression.

9.3 REPORTING

9.3.1 Reporting of adverse events

The AEs defined in Section 9.1.2 will be collected throughout the study for prospective patients and retrospectively for retrospective RET mutation negative patients. All AE's defined in Section 9.1.2 will be recorded in the eCRF. If any SAE occurs in the course of the study, then Investigators or other site personnel will inform appropriate Sponsor representatives within 24 hours, ie, immediately, from awareness and if any non-SAE occurs, no later than 30 calendar days from awareness.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to Global Pharmacovigilance (GPV) **within 24 hours** for SAE and **within 5 calendar days** for non-SAE.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately, or no later than 24 hours of when he or she becomes aware of it.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the Sponsor within the timelines described above.

If the WBDC system is not available, then the Investigator or other study site personnel reports the SAE to the appropriate Sponsor representative by telephone. The Sponsor representative will advise the Investigator/study site personnel how to proceed. If the system will not be available within the time frames for SAE reporting, the SAE report form in the Investigator study file shall be used. The eCRF must be completed with SAE information as soon as the WBDC system is available again.

In case of paper or fax CRF, or eCRF back-up:

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) from the CRF to the representative of the monitoring team whose name, fax number and e-mail address appear in the clinical trial protocol.
- ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further documentation should be sent to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

9.3.2 Reporting of spontaneously mentioned ADRs

With regards to the reporting of ADRs observed in patients participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the Investigator considers it appropriate, to the Sponsor (in case of an ADRs of a Sponsor product) or the corresponding marketing authorization holder of the drug.

Once the Investigators or other site personnel indicate an ADR in the WBDC system, an automated e-mail alert is sent to the Sponsor.

9.3.3 Deaths

All deaths (both cancer-related and other) that occur during the study up to 60 days after the last dose received must be reported as a SAE. In the event of death, the patient will be considered as having completed the study.

All dead patients will be considered for the retrospective data collection, with no exception.

10 ETHICAL CONDUCT OF THE NIS

The NIS will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonization (ICH), Good Clinical Practices (GCPs), and the applicable legislation on NISs.

The Investigator will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

10.1 ETHICS REVIEW

The final protocol of the NIS, including the final version of the patient ICF, must be approved or given a favorable opinion in writing by the Ethics Committee.

The Ethics Committee must also approve any amendment to the protocol and all advertising used to recruit patients for the study, according to local regulations.

10.2 PATIENT INFORMED CONSENT

For prospective patients: The Investigator at each site will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the NIS. Patients must also be notified that they are free to discontinue from the NIS at any time. The patients should be given the opportunity to ask questions and allowed time to consider the information provided.
The signed and dated patient informed consent must be obtained before any specific procedure for the NIS is performed, including:

- Interview with the Investigator
- CRFs completion
- RET test, when is done to confirm eligibility in the study.

The Investigator must store the original, signed patient ICF. A copy of the signed patient ICF must be given to the patient.

For retrospective patients a waiver of informed consent is requested due to the retrospective, and Non-Interventional nature of this study, and also because most retrospective patients may either have already died, or not be followed anymore by the study site.

10.3 PATIENT DATA PROTECTION

Prospective patients:

The patient ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorize the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the NIS. The patient ICF will explain that NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for data protection. The patient ICF will also explain that for quality check purposes, a monitor of the Sponsor or a monitor of company representing the Sponsor, will require direct access to the signed patient ICFs. In case source data verification will be planned as quality check, the patient ICF will explain that for data verification purposes, monitor of the Sponsor or a monitor of company representing the Sponsor may require direct access to source documents that are part of the hospital or practice records relevant to the NIS.

Retrospective patients:

Patient confidentiality will be strictly maintained. Access to the WBDC system will be controlled via a hierarchical user-name and password control. Patient data will be pseudonymized through design of data entry fields that do not permit the entry of identifying information such as initials, date of birth, or center-assigned patient identifiers. Only trained site staff will enter data into the eCRFs. Patient's ages in range of 5 years, but not date of birth, will be entered. Patient identifiers used by sites will not be entered; rather the WBDC program will automatically assign a study ID to each patient. The pseudonymized data as entered into the WBDC system will be visible to the Clinical Research Organization (CRO) and the Sponsor, but only center staff will be able to trace a study ID number back to a patient identity, a necessary measure to allow center staff to respond to data queries raised by the CRO later. Eventually, once the database will be frozen, the sites will destroy this correspondence between study ID and their own identifiers.

11 STUDY MANAGEMENT BY SPONSOR

11.1 MONITORING, QUALITY CONTROL AND ARCHIVING

Before the first patient is recruited into the study, the local Marketing Company (MC) representative or delegate will:

- Establish the adequacy of the facilities and the Investigator's capability to appropriately collect the sample, which should always be done in the frame of an intervention that was already planned independently from the study.
- Discuss with the Investigator(s) (and other personnel involved with the study), their responsibilities with regards to protocol compliance, and the responsibilities of the Sponsor or its representatives. This will be documented in a NIS Agreement between the Sponsor/delegate and the Investigator.

During the study the local MC representative or delegate can implement different activities to assure compliance with Sponsor standards of quality. These activities will be described in the study source data verification (SDV) and monitoring plan and could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the Investigator(s).
- Ensure that the screening is performed properly and thoroughly, so that no patient who may be eligible is missed from the systematic screening process.
- Confirm that the research team is complying with the protocol of this NIS and that data are being accurately recorded in the eCRFs.
- Ensure that the patient ICFs are signed and stored at the Investigator's site, for prospective patients.
- Ensure that the eCRFs are completed properly and with adequate quality.

Monitoring activities for:

A qualified and trained Sponsor representative or delegate should perform the following tasks:

- Must ensure that the screening is performed properly and thoroughly, so that no patient who may be eligible is missed from the systematic screening process.
- Must ensure that the patient ICFs are properly signed, dated and stored at the site, for prospective patients.

- SDV:
  - Screening log must be checked thoroughly against the information from any sources of data available at the site, including admission logs, discharge logs, hospital databases, laboratory databases, etc.
  - Patient ICFs must be checked with the information in medical records to ensure the existence of the patients.
  - Some specific study data considered critical for study results validity (eg, RET result, safety data), will be verified against the information in the medical record.
- Ensure that at the study site the NIS documents are archived in accordance with the NIS Investigator's Study File Index by the Investigator.

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of patients, number of sites, etc., and is detailed in the study source data verification and monitoring plan provided by the coordinating country.

Different signals (eg, low enrollment rate, high rejection rate in a site, continuous lack of availability, repetitive inconsistent answers in the eCRF) should be used as potential identification of low protocol compliance by Investigators, or any other reason for this. If these or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site Investigator, especially with respect to the Non-Interventional nature of this study, specific measures should be adopted to evaluate the situation, identify the issue, and implement specific action plans to correct the situation.
All NIS documents must be archived by the site for 15 years after last data collected except if local or regional legislation requires longer archiving time. Before final archiving the local MC representative or delegate must ensure all applicable documents are properly filed at the MC and at the study sites.

11.2 TRAINING OF STUDY SITE PERSONNEL

The Principal Investigator will ensure that appropriate training relevant to the NIS is given to investigational staff, and that any new information relevant to the performance of this NIS is forwarded to the staff involved.

11.3 NON-INTERVENTIONAL STUDY TIMETABLE AND END OF STUDY

Before the first patient is enrolled in the NIS and any NIS- related procedures are undertaken the following should be fulfilled:

- Written approval of the NIS by the Ethics Committee and/or Regulatory Authorities, according to local regulations
- Proper agreements between the Sponsor and the Investigator/Institution is signed

The planned timetable for the NIS is estimated to be as follows:

- Estimated first patient in: 1Q2013
- Estimated last patient in: 3Q2019
- Estimated last patient last visit: 4Q2020
- Estimated date of database lock: 2Q2020
- Estimated date of CSR: 3Q2020
- Estimated date of CSR addendum: Q32021

Should the Sponsor decide to discontinue the study prior to what was established in this protocol, the Investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date. The Investigator will immediately notify the patients taking part in the study; they will continue to receive their treatment according to usual clinical practice.

12 DATA MANAGEMENT

12.1 COLLECTION, MONITORING, PROCESSING OF DATA AND ARCHIVING

Data will be entered in the WBDC system at the Investigator's site. The Investigator will be responsible for entering data into the WBDC system in a regular manner and according to the Investigator Instructions Manual and Non-Interventional Study Agreement (NISA) specifications. The Investigator Instructions Manual will also provide the site with data entry instructions.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, and edited, the Investigator will be notified to sign the eCRF electronically and data will be locked to prevent further editing. A compact disk with a copy of the eCRF(s) will be distributed to the Investigator after clean file. Clean file for the final database will be declared when all data have been signed off and all queries have been resolved. The database will be locked after clean file has been declared. After clean file, editing in the database will only be allowed with the proper documentation.

Following clean file, all data will be extracted to a separate dataset and the statistical analysis will be performed. The final analysis of the study will be performed 14 months after the last prospective patient has been enrolled in the study and when at least 10 events in both treatment groups have been observed. If all patients have progressed prior to 14 months after the last patient is recruited, the study will stop.

The data management plan will include the detailed information.

The Company responsible for the WBDC and the whole data management process is Worldwide Clinical Trials: Isaac Newton Centre, Nottingham Science Park, Nottingham NG7 2RH, United Kingdom.

12.2 REPORTING AND PUBLICATION OF DATA

This study is being conducted to fulfill the specific obligation post-authorization measure for the conditional marketing authorization. There is a commitment to present the study results by the 3Q 2020.

The Sponsor is obliged to analyze and report all NIS data as described in the protocol. In collaboration with the International Coordinating Investigator (when applicable), the Sponsor will prepare a NIS Report within 12 months after completion of the last patient. The Medical Science Director, the Study Scientific Leader and or Study Physician in the Sponsor is the appointed signatory, along with the appointed International Coordinating Investigator (when applicable).

The Sponsor will communicate the study results to all participating Investigators. Publications based on this trial will be subject to current Sponsor policies and applicable regulations.
The NIS should be registered on Clinical Trials.gov, public website before first ~~subject~~ patient in, with study status updates and final results reporting performed in compliance with applicable regulations.

13 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 STATISTICAL EVALUATION – GENERAL ASPECTS

All statistical analysis will be performed by Worldwide Clinical Trials Limited (WCT), 172 Tottenham Court Road, London W1T7NS, United Kingdom under the supervision of the Sponsor Study Scientific leader.

A comprehensive Statistical Analysis Plan (SAP) will be prepared before first patient in.

13.2 DETERMINATION OF SAMPLE SIZE

The Sponsor and the EMA agreed that a sample size between 40 and 50 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC receiving vandetanib: 20 to 25 RET mutation negative and 20 to 25 RET mutation positive would be appropriate. If the ORR is 35% with a standard deviation (SD) of 0.4770, then Table 1 shows the 95% confidence interval (CI) for different sample sizes.

13.3 STATISTICAL ANALYSIS

The changes implemented in the protocol amendment define, in addition to the original study population, 2 other groups of patients: a retrospective group and a group of patients from the Study DC4200C00058 whose RET data were re-analyzed with new classifications as positive and negative. The criteria for selecting these data, described elsewhere in this amended protocol, are intended to assure that the populations are comparable, and hence, may be pooled. In order to confirm comparability, all analyses will report the descriptive statistics for each of these groups as well as the pooled data both for RET mutation positive and RET mutation negative subjects, as presented in Table 2.

Table content will adapt to the type of variable as defined below:
Qualitative variables will be described by number of observed values, percentage and number of missing values (patients with missing data will not be included in the percentage calculation).

Quantitative variables will be described by number of observed values, mean, standard deviation, median, first quartile, third quartile, minimum and maximum.
For time-to-event, the median time to event and, number and percentage of each group remaining at risk at the last point of observation will be provided.

Statistical analyses will be conducted with SAS Software version 9.3 or upper.

13.3.1 Analysis of primary criteria

Estimate ORR, DCR rates for RET positive and negative
The ORR and DCR will be summarized as qualitative variables.

Time to response and Duration of response for RET positive and negative
The time to response and duration of response will be summarized as time-to-event data.

Kaplan-Meier curves will be produced. A waterfall plot of the best percentage change in the sum of the longest diameters of the target lesions from baseline will be produced split by RET mutation status.

13.3.2 Analysis of secondary criteria

PFS and ORR exploration for RET positive and negative

A Kaplan-Meier plot of PFS split by RET mutation status will be presented. Median PFS will be presented, where possible, in the 2 groups.

Subgroup analyses will be performed for PFS by CTN doubling time and CEA doubling time at baseline.

QTc prolongation under vandetanib for RET positive and negative

QTc will be treated as a continuous variable.

The following will be executed without formal testing:

- The frequency and percentage of patients with symptoms at each time point will be summarized by RET mutation status. Opioid analgesic use will be summarized descriptively by RET mutation status.
- Data for RET mutation negative patients not treated with vandetanib will be summarized with 95% CIs presented when appropriate.

13.3.3 Safety evaluation

Serious AE and AE leading to discontinuation – summary by RET mutation positive and RET mutation negative

Safety data will be presented by RET mutation status. Caution will be used when interpreting safety data in RET negative patients who are not treated with vandetanib, that cannot be compared with safety data from the RET mutation negative patients who are treated with vandetanib.

14 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1 COUNTRY-SPECIFIC REQUIREMENTS

Not Applicable

14.2 PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amended protocol 01: (29 February 2016**)**

REASON FOR AMENDMENT:

Genzyme assumption of responsibility for trial from AstraZeneca

In sections: cover page, headers, appendices, and all sections of the protocol.

Rationale: In 2015, territory rights for the clinical development and commercialization of vandetanib were granted from AstraZeneca to Genzyme Corporation and Genzyme will be assuming responsibility of the current clinical program. Therefore, the AstraZeneca logo and reference to AstraZeneca within the confidentiality statement were deleted from the title page. Throughout all sections of the protocol including headers and appendices, AstraZeneca has been changed to “Genzyme” or “Sponsor.” The Sanofi-Genzyme study code OBS14778 has been added. Sections regarding IMP and pharmacovigilance have been updated to reflect the Genzyme environment.

Correction of minor typographical errors or inconstancies.

DESCRIPTION OF CHANGE AND WHAT IS BEING CHANGED:

In section(s):

Cover page

The following text:

AstraZeneca AB, 151 85 Södertälje, Sweden

Is replaced with:

~~AstraZeneca AB, 151 85 Södertälje, Sweden~~ Genzyme Corporation, 500 Kendall Street, Cambridge, MA USA

In section(s):

Cover page and subsequent page headers

The following text:

Study Code D4200C00104

Is replaced with:

Study Code D4200C00104 (Sanofi-Genzyme OBS14778)

In section(s):

Study Synopsis

11.3 NIS timetable and end of study

The following text:

Estimated date of first subject in	1Q2013
Estimated date of last subject in	2Q2014
Estimated date of last subject last visit	3Q2015
Estimated date of data base lock	3Q2015
Estimated date of final study report	4Q2015

Is replaced with:

Estimated date of first subject in	1Q2013
Estimated date of last subject in	~~2Q2014~~ 2Q2018
Estimated date of last subject last visit	~~3Q2015~~ 3Q2019
Estimated date of data base lock	~~3Q2015~~ 4Q2019
Estimated date of final study report	~~4Q2015~~ 3Q2020

In section(s):

List of abbreviations and definition terms

The following text is deleted:

AZ AstraZeneca

TCS Tata Consulting Service

In section(s):

3 STUDY PLAN AND PROCEDURES

9.2.1 Time period for collection of adverse events

9.2.2 Follow-up of unresolved adverse events

9.3.1 Reporting of serious adverse events

9.3.2 Reporting of spontaneously mentioned adverse drug reactions

10.3 Patient data protection

11 STUDY MANAGEMENT BY ASTRAZENECA

11.1 Monitoring, Quality Control and Archiving

11.3 NIS timetable and end of study

12.2 Reporting and publication of data

13.1 Statistical evaluation – general aspects

13.2 Determination of sample size

Appendix E

Appendix F

The following text:

AstraZeneca or AZ

Is replaced with:

~~AstraZeneca~~ the Sponsor

In section(s):

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following text is added:

WHO-DD World Health Organization Drug Dictionary

Insection(s):

3.1 Overall study design and flow chart

Figure 1 Study Flow Chart

The following text:

~2 year recruitment period

Is replaced with:

~~2~~ ~5 year recruitment period

In section(s):

9.2.7 Disease progression

The following text has been added:

However, all events of disease progression that meet seriousness criteria must be reported using the SAE reporting procedure in Section 9.3.1.

In section(s):

9.3.1 Reporting of serious adverse events

The following text:

If any SAE occurs in the course of the study, then Investigators or other site personnel inform appropriate Sponsor representatives within 1 day, ie, immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor Patient Safety data entry site (TCS) **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

…

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated AstraZeneca representative and to the AstraZeneca Patient Safety data entry site (TCS).

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. If the system will not be available within the timeframes for SAE reporting, the SAE report form in the

Investigator study file shall be used. The eCRF must be completed with SAE information as soon as the WBDC system is available again.

Is replaced with:

If any SAE occurs in the course of the study, then Investigators or other site personnel inform appropriate Sponsor representatives within ~~1 day~~ **24 hours**, ie, immediately~~, or no later than 24 hours of when he or she becomes aware of it~~.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor ~~Patient Safety data entry site (TCS)~~ **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

…

~~Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative and to the AstraZeneca Patient Safety data entry site (TCS).~~

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the Sponsor within the timelines described above.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate Sponsor representative by telephone. The Sponsor representative will advise the Investigator/study site personnel how to proceed. If the system will not be available within the timeframes for SAE reporting, the SAE report form in the Investigator study file shall be used. The eCRF must be completed with SAE information as soon as the WBDC system is available again.

In case of paper or fax CRF, or eCRF back-up:

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) from the CRF to the representative of the monitoring team whose name, fax number and e-mail address appear in the clinical trial protocol
- ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges
- All further documentation should be sent to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

In section(s):

9.3.2 Reporting of spontaneously mentioned adverse drug reactions

The following text:

With regards to the reporting of ADRs observed in subjects participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the Investigator considers it appropriate, to the Sponsor (in case of an ADRs of a Sponsor product) or the corresponding marketing authorization holder of the drug.

Once the Investigators or other site personnel indicate an ADR in the WBDC system, an automated e-mail alert is sent to the designated Sponsor representative and to the Sponsor Patient Safety data entry site (TCS).

Is replaced with:

With regards to the reporting of ADRs observed in subjects participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the Investigator considers it appropriate, to the Sponsor (in case of an ADRs of a Sponsor product) or the corresponding marketing authorization holder of the drug.

Once the Investigators or other site personnel indicate an ADR in the WBDC system, an automated e-mail alert is sent to the ~~designated~~ Sponsor ~~representative and to the Sponsor Patient Safety data entry site (TCS)~~.

In section(s):

9.3.3 Deaths

The following text:

All deaths (both cancer-related and other) that occur during the study must be reported as follows:

- Death clearly resulting from unequivocal disease progression should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF but should not be reported as an AE or SAE.
- When death is not due to progression of disease under study, the AE causing death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

In the event of death, the patient will be considered as having completed the study.

Is replaced with:

All deaths (both cancer-related and other) that occur during the study up to 60 days after the last dose received must be reported as a SAE. ~~follows:~~

- ~~Death clearly resulting from unequivocal disease progression should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF but should not be reported as an AE or SAE.~~
- ~~When death is not due to progression of disease under study, the AE causing death must be reported to the study monitor as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.~~

In the event of death, the patient will be considered as having completed the study.

In section(s):

12.2 Reporting and publication of data

The following text:

There is a commitment to present the study results by the 4Q 2015.

Is replaced with:

There is a commitment to present the study results by the ~~4Q 2015~~ 3Q 2020.

In section(s):

The following text:

AstraZeneca will communicate the study results to all participating Investigators.

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The results of the NIS will be posted at AstraZeneca Clinical Trials portal not later than 12 months after completion of the last patient. The NIS should be registered on Clinical Trials.gov, public website before first subject in.

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~~Publication of data subsets from individual institutions participating in multicentre studies should not precede the primary manuscript, and when developed should always reference the primary publication of the entire study.~~

~~The results of the NIS will be posted at AstraZeneca Clinical Trials portal not later than 12 months after completion of the last patient.~~ The NIS should be registered on Clinical Trials.gov, public website before first subject in, with study status updates and final results reporting performed in compliance with applicable regulations.

In section(s)

Appendix A Astra Zeneca signatures

The content of appendix A is deleted since this appendix is no longer relevant.

And is replaced with:

This appendix is no longer relevant.

In section(s):

All Headers and first pages

The following text:

Non-Interventional Study (NIS) Protocol Appendix

Drug Substance Vandetanib

Study Code D4200C00104

Edition Number 1.0
Date 11 March 2013

Is replaced with:

Non-Interventional Study (NIS) Protocol Appendix

Drug Substance Vandetanib

Study Code OBS14778 (Formerly AstraZeneca D4200C00104)

Edition Number ~~1.0~~ 2.0

Date ~~11 March 2013~~ 29 February 2016

In section(s):

Appendix C

The following text:

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D4200C00104 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

Is replaced with:

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the OBS14778 study (Formerly AstraZeneca study code D4200C00104) with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

In section(s):

Appendix C

The following text:

D4200C00104

Is replaced with:

~~D4200C00104~~ OBS14778

In section(s):

The following page has been added as Page 2:

NAMES AND ADRESSES OF:

MONITORING TEAM'S REPRESENTATIVE

Name: Address: Tel: Fax: E-mail	

SPONSOR

Name: Address:	Genzyme Corporation 500 Kendall Street Cambridge, MA 02142

15 LIST OF REFERENCES

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APPENDICES

Appendix A Signatures

This appendix is no longer relevant.

Appendix B Summary of product characteristics

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg film-coated tablets

Caprelsa 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caprelsa 100 mg tablets

Each film-coated tablet contains 100 mg of vandetanib.

Caprelsa 300 mg tablets

Each film-coated tablet contains 300 mg of vandetanib.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Caprelsa 100 mg tablets

The Caprelsa 100 mg tablet is a round, biconvex, white film-coated tablet with 'Z100' impressed on one side.

Caprelsa 300 mg tablets

The Caprelsa 300 mg tablet is an oval-shaped, biconvex, white film-coated tablet with 'Z300' impressed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Caprelsa is indicated in adults, children and adolescents aged 5 years and older.

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).

4.2 Posology and method of administration

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 prescription is required.

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 (see also package leaflet).

Posology for MTC in adult patients

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

Dose adjustments in adult patients with MTC

QTc interval should be carefully assessed 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 (see section 4.4). 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 (see section 4.4).

Posology in paediatric patients with MTC

Dosing for paediatric patients should be on the basis of BSA in mg/m^2. Paediatric patients treated with Caprelsa and patients' caregivers must be given the dosing guide and be informed on the correct dose to be taken with the initial prescription and each subsequent dose adjustment. Recommended dosing regimens and dose modifications are presented in **Error! Reference source not found.**.

Table 5 - Dosing nomogram for paediatric patients with MTC

BSA (m^2)	Start dose (mg)[a]	Dose increase (mg)[b] when tolerated well after 8 weeks at starting dose	Dose reduction (mg)[c]
0.7 - <0.9	100 every other day	100 daily	-
0.9 -<1.2	100 daily	7 day schedule: 100-200-100-200-100-200-100	100 every other day
1.2 -<1.6	7 day schedule: 100-200-100-200-100-200-100	200 daily	100 daily
≥1.6	200 daily	300 daily	7 day schedule: 100-200-100-200-100-200-100

a The starting dose is the dose at which treatment should be initiated.
b Higher vandetanib doses than 150 mg/m2 have not been used in clinical studies in paediatric patients.
c Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions.

Dose adjustments in paediatric patients with MTC

- In the event of 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.
- Patients who are on the starting dose ([a] in Table 5), should be recommenced at the reduced dose ([c] in Table 5).
- Patients who are on the increased dose ([b] in Table 5), should be recommenced at the starting dose ([a] in Table 5). If another event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with Caprelsa should be at least temporarily stopped and resumed at a reduced dose ([c] in Table 5) when toxicity has resolved or improved to CTCAE grade 1.
- If a further event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be permanently stopped.

The patient must be monitored appropriately. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly (see section 4.4).

Duration

Vandetanib may be administered until disease progression or until the benefits of treatment continuation do no longer outweigh its risk, thereby considering the severity of adverse events (see sections 4.8) in relation to the degree of clinical stabilization of the tumour status.

Special patient populations

Paediatric population

Caprelsa should not be given to children below 5 years of age. The safety and efficacy of Caprelsa in children below 5 years of age have not been established. No data are available.

There is no experience in paediatric patients with hereditary MTC below 9 years of age (see section 5.1). Patients aged 5-18 years should be dosed according to the nomogram in Table 1. vandetanib doses higher than 150 mg/m² have not been used in clinical studies in paediatric patients.

Elderly

No adjustment in starting dose is required for elderly patients. There is limited clinical data with vandetanib in patients with MTC aged over 75.

Renal impairment in adult patients with MTC

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 mL/min) renal impairment at baseline (see section 5.2). 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 renal impairment; safety and efficacy have however not been established with 200 mg (see section 4.4). 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.

Renal impairment in paediatric patients with MTC

There is no experience with the use of vandetanib in paediatric patients with renal impairment. Considering the data available in adult patients with renal impairment:

- No change in starting dose is recommended in paediatric patients with mild renal impairment
- The reduced dose as specified in Table 5 could be used in paediatric patients with moderate renal impairment. Individual patient management will be required by the physician, especially in paediatric patients with low BSA.
- Vandetanib is not recommended in paediatric patients with severe renal impairment

Hepatic impairment

Vandetanib is not recommended for use in adult and paediatric patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of reference range (ULRR), this criterion does not apply to patients with Gilbert's Disease-and alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 times

ULRR, or greater than 5.0 times ULRR if judged by the physician to be related to liver metastases), since there is limited data in patients with hepatic impairment, and safety and efficacy have not been established (see section 4.4).

Pharmacokinetic data from volunteers, suggests that no change in starting dose is required in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Method of administration

For patients who have difficulty swallowing, vandetanib tablets may be dispersed in half a glass of non-carbonated drinking water. No other liquids should be used. The tablet is to be dropped in water, without crushing, stirred until dispersed (approximately 10 minutes) and the resultant dispersion swallowed immediately. Any residues in the glass are to be mixed with half a glass of water and swallowed. The liquid can also be administered through nasogastric or gastrostomy tubes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Congenital long QTc syndrome.
- Patients with a QTc interval over 480 msec.
- Concomitant use of vandetanib with the following medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes: Arsenic, cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, Class IA and III antiarrhythmics (see section 4.5).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (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 treatment with vandetanib.

QTc prolongation and Torsades de Pointes

Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec). First QTc prolongations occurred most often in the first 3 months of treatment but continued to first occur after this time. The half-life of vandetanib (19 days) renders this prolongation in QTc interval particularly problematic (see section 4.8). At a dose of 300 mg per day in MTC, ECG QTc prolongation to above 500 msec was observed in a phase III study in 11% of patients. ECG QTc prolongation appears to be dose-dependent. 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 (see section 4.8).

Vandetanib treatment must not be started in patients whose ECG QTc interval is greater than 480 msec. Vandetanib should not be given to patients who have a history of Torsades de pointes**.** Vandetanib has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

An ECG, and levels of serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. This schedule should apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than two weeks. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. Frequent ECG monitoring of the QTc interval should be continued.

Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhea, increase in diarrhea/dehydration, electrolyte imbalance and/or impaired renal function. If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought.

The administration of vandetanib with substances known to prolong the ECG QTc interval is contraindicated or not recommended (see section 4.3 and 4.5).

The concomitant use of vandetanib with ondansetron is not recommended (see section 4.5)

Patients who develop a single value of a QTc interval of ≥500 msec should stop taking vandetanib. Dosing can be resumed at a reduced dose after return of the QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made.

Posterior reversible encephalopathy syndrome, PRES (Reversible posterior leukoencephalopathy syndrome-RPLS)

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.

Rearranged during transfection (RET) status

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).

Skin reactions

Rash and other skin reactions including photosensitivity reactions and palmar-plantar erythrodysaesthesia syndrome have been observed in patients who have received vandetanib.

Mild to moderate skin reactions can be managed by symptomatic treatment, or by dose reduction or interruption. For more severe skin reactions (such as Stevens-Johnson syndrome), referral of the patient to seek urgent medical advice is recommended.

Care should be taken with sun exposure by wearing protective clothing and/or sunscreen due to the potential risk of phototoxicity reactions associated with vandetanib treatment.

Diarrhea

Diarrhea is a disease related symptom as well as a known undesirable effect of vandetanib. Routine anti-diarrheal agents are recommended for the treatment of diarrhea. QTc and serum electrolytes should be monitored more frequently. If severe diarrhea (CTCAE grade 3-4) develops, vandetanib should be stopped until diarrhea improves. Upon improvement, treatment should be resumed at a reduced dose (see Sections 4.2 and 4.8).

Hemorrhage

Caution should be used when administering vandetanib to patients with brain metastases, as intracranial haemorrhage has been reported.

Heart failure

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.

Hypertension

Hypertension, including hypertensive crisis, has been observed in patients treated with vandetanib. Patients should be monitored for hypertension and controlled as appropriate. If high blood pressure cannot be controlled with medical management, vandetanib should not be restarted until the blood pressure is controlled medically. Reduction in dose may be necessary (see section 4.8).

Patients with renal impairment

Vandetanib is not recommended for use in adult and paediatric patients with moderate or severe renal impairment since there is limited data, and safety and efficacy have not been established (see sections 4.2, 5.1, and 5.2).

Patients with hepatic impairment

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 (see sections 4.2 and 5.2).

Alanine aminotransferase elevations

Alanine aminotransferase elevations occur commonly in patients treated with vandetanib. The majority of elevations resolve while continuing treatment, others usually resolve after a 1-2 week interruption in therapy. Periodic monitoring of alanine aminotransferase is recommended.

Interstitial lung disease

Interstitial Lung Disease (ILD) has been observed in patients receiving vandetanib and some cases have been fatal. If a patient presents with respiratory symptoms such as dyspnoea, cough and fever, vandetanib treatment should be interrupted and prompt investigation initiated. If ILD is confirmed, vandetanib should be permanently discontinued and the patient treated appropriately.

CYP3A4 inducers

The concomitant use of vandetanib with strong CYP3A4 inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) should be avoided (see section 4.5).

CTN less than 500 pg/ml

The benefit of vandetanib in patients with CTN less than 500 pg/ml has not been determined, therefore use in patients with CTN < 500 pg/ml should be carefully considered because of the treatment related risks of vandetanib.

Patient Alert Card

All prescribers of Caprelsa must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Caprelsa therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

Paediatric population

Based on height measurements at all visits, all children and adolescents in a paediatric study demonstrated linear growth while receiving vandetanib. However, long term safety data in paediatric patients are not available.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Effect of vandetanib on other medicinal products

In healthy subjects, the exposure for midazolam (CYP3A4 substrate) was not affected when given together with a single dose of vandetanib at 800 mg.

Vandetanib is an inhibitor of the organic cation 2 (OCT2) transporter. In healthy subjects with wild type for OCT2, the $AUC_{(0-t)}$ and C_{max} for metformin (OCT2 substrate) were increased by 74% and 50%, respectively and CL_R of metformin was decreased by 52% when given together with vandetanib. Appropriate clinical and/or laboratory monitoring is recommended for patients receiving concomitant metformin and vandetanib, and such patients may require a lower dose of metformin.

In healthy subjects, the $AUC_{(0-t)}$ and C_{max} for digoxin (P-gp substrate) were increased by 23% and 29% respectively, when given together due to P-gp inhibition by vandetanib. Furthermore, the bradycardiac effect of digoxin may increase the risk of vandetanib QTc interval prolongation and Torsade de Pointes. Therefore, an appropriate clinical (e.g. ECG) and/or laboratory monitoring is recommended for patients receiving concomitant digoxin and vandetanib, and such patients may require a lower dose of digoxin. (For vandetanib monitoring, see section 4.2 Posology and Method of administration and section 4.4 Special warnings and precautions for use).

As regards other P-gp substrates such as dabigatran, a clinical monitoring is recommended in case of combination with vandetanib.

Effect of other medicinal products on vandetanib

In healthy subjects, no clinically significant interaction was shown between vandetanib (a single dose of 300 mg) and the potent CYP3A4 inhibitor, itraconazole (repeated doses of 200 mg once daily). In healthy male subjects, the exposure to vandetanib was reduced by 40% when given together with the potent CYP3A4 inducer, rifampicin. Administration of vandetanib with potent CYP3A4 inducers should be avoided.

In healthy subjects, the C_{max} for vandetanib was decreased by 15% while the $AUC_{(0-t)}$ for vandetanib was not affected when given together with omeprazole. Neither the C_{max} nor the $AUC_{(0-t)}$ for vandetanib was affected when given together with ranitidine. Therefore, no change in dose of vandetanib is required when vandetanib is given with either omeprazole or ranitidine.

Pharmacodynamic interactions

Biliary excretion of unchanged vandetanib is one of the excretion pathways for vandetanib. Vandetanib is not a substrate of multidrug resistance protein 2 (MRP2), p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Medicinal products known to prolong QTc interval

Vandetanib has been shown to prolong the ECG QTc interval; Torsades de pointes have 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.

- Combinations contraindicated (see section 4.3): Cisapride, erythromycin intravenous (IV), toremifene, mizolastine, moxifloxacin, arsenic, Class IA and III antiarrhythmics
- Combinations not recommended: Methadone, haloperidol, amisulpride, chlorpromazine, sulpiride, zuclopenthixol, halofantrine, pentamidine and lumefantrine.

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

Results of a pharmacodynamic and pharmacokinetic interaction study indicated that co-administration with ondansetron in healthy patients appeared to have little effect on the pharmacokinetics of vandetanib but had a small additive effect on the prolongation of the QTc interval of approximately 10 ms. Therefore, the concomitant use of ondansetron with vandetanib is not recommended. If ondansetron is administered with vandetanib, closer monitoring of serum electrolytes and ECGs and aggressive management of any abnormalities is required.

Vitamin K antagonists

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation is frequent. In consideration of the high intra-individual variability of the response to anticoagulation, and the possibility of interaction between vitamin K antagonists and chemotherapy, an increased frequency of the INR (International Normalised Ratio) monitoring is recommended, if it is decided to treat the patient with vitamin K antagonists.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during therapy and for at least four months following the last dose.

Pregnancy

There is a limited amount of data on the use of vandetanib during pregnancy. As expected from its pharmacological actions, vandetanib has shown significant effects on all stages of female reproduction in rats (see section 5.3).

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.

Breast-feeding

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 (see section 5.3).

Breast-feeding is contraindicated while receiving vandetanib therapy.

Fertility

In rats, vandetanib had no effect on male fertility but impaired female fertility (see section 5.3).

Effects on reproduction in paediatric patients treated with vandetanib are not known.

4.7 Effects on ability to drive and use machines

No studies to establish the effects of vandetanib on ability to drive and use machines have been conducted. However, fatigue and blurred vision have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions have been diarrhea, rash, nausea, hypertension, and headache.

Tabulated list of adverse reactions

The following adverse reactions have been identified in clinical studies with patients-receiving vandetanib as treatment for MTC. Their frequency is presented in Table 6, adverse reactions using Council for International Organizations of Medical Sciences (CIOMS III), listed by MedDRA System Organ Class (SOC) and at the preferred term level and then by frequency classification. Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). This section includes only data derived from completed studies where patient exposure is known.

Table 6 - Adverse reactions and system organ class

Adverse reactions and system organ class			
System Organ Class	Very common	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, staphylococcal 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 system disorders	Headache, paraesthesia, 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, accommodation disorders
Cardiac disorders	Prolongation of ECG QTc interval[a b]		Heart failure, acute heart failure, rate and rhythm disorders, cardiac conduction disorders, ventricular arrhythmia and cardiac arrest
Vascular disorders	Hypertension	Hypertensive crisis, ischaemic cerebrovascular conditions	

Adverse reactions and system organ class			
Respiratory, thoracic and mediastinal disorders		Epistaxis, haemoptysis, pneumonitis	Respiratory failure, pneumonia aspiration
Gastrointestinal disorders	Abdominal pain, diarrhea, 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 reactions (including acne, dry skin, dermatitis, pruritus), 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 QTc interval prolonged	Increase of serum ALT and AST, weight decreased blood creatinine increased	Increased haemoglobin, serum amylase increased

a 13.4% vandetanib patients had QTc (Bazett's) ≥ 500 ms compared with 1.0% placebo patients. QTcF prolongation was > 20 ms in over 91% of patients, > 60 ms in 35%, > 100 ms in 1.7%. Eight percent of patients had a dose reduction due to QTc prolongation.

b Including two deaths in patients with QTc > 550 ms (one due to sepsis and one due to heart failure).

Description of selected adverse reactions

Events such as Torsades de pointes, Stevens-Johnson syndrome, erythema multiforme, interstitial lung disease (sometimes fatal) and PRES (RPLS) have occurred in patients treated with vandetanib monotherapy. It is expected that these would be uncommon adverse reactions in patients receiving vandetanib for MTC.

Ocular events such as blurred vision are common in patients who received vandetanib for MTC. Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients; however, routine slit lamp examinations are not required for patients receiving vandetanib.

At various exposure durations, median haemoglobin levels in patients treated with vandetanib were increased by 0.5-1.5 g/dl compared to baseline.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Paediatric population

Paediatric clinical trial data with vandetanib in MTC (see section 5.1) obtained during drug development is limited to 16 patients aged 9 years to 17 years with hereditary medullary thyroid carcinoma (Study IRUSZACT0098). Whilst the study size is small owing to the rarity of MTC in children, it is considered representative of the target population. The safety findings in this study are consistent with the safety profile of vandetanib in adult patients with MTC. Long term safety data in paediatric patients are not available.

4.9 Overdose

There is no specific treatment in the event of overdose with vandetanib and possible symptoms of overdose have not been established. An increase in the frequency and severity of some adverse reactions, like rash, diarrhea and hypertension was observed at multiple doses at and above 300 mg in healthy volunteer studies and in patients. In addition, the possibility of QTc prolongation and Torsades de pointes should be considered. Vandetanib doses higher than 150 mg/m2 have not been used in clinical studies in paediatric patients.

Adverse reactions associated with overdose are to be treated symptomatically; in particular, severe diarrhea must be managed appropriately. In the event of an overdose, further doses must be interrupted, and appropriate measures taken to assure that an adverse event has not occurred ie, ECG within 24 hours to determine QTc prolongation. Adverse reactions associated with overdose may be prolonged due to the long half-life of vandetanib (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: antineoplastic agent, protein kinase inhibitor

ATC Code: L01XE12

Mechanism of action and pharmacodynamic effects

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 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, 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 majority of mutated, activated forms of RET, and significantly inhibits the proliferation of 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 tumor 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.

Clinical efficacy in adults

Clinical data from MTC

A randomied, double-blind, placebo-controlled study (Study 58) was conducted to demonstrate safety and efficacy of vandetanib 300 mg versus placebo. This study included 331 patients with unresectable locally advanced or metastatic MTC. Only patients with CTN ≥500 pg/mL (conventional units) or ≥ 146.3 pmol/L (international standard units) were enrolled. Of the patients enrolled in the study 10 patients on vandetanib and 4 on placebo (4% of all patients) had a World Health Organization performance status (WHO PS) score of ≥2 and 28 (12.1%) patients on vandetanib and 10 (10.1%) on placebo had cardiac impairment. Cardiac impairment was defined as patients with previous cardiovascular abnormality.

The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib compared to placebo. The secondary endpoints were evaluation of overall objective response rate (ORR), disease control rate (DCR) defined as, partial response (PR) or complete response (CR) or stable disease (SD) lasting at least 24 weeks, duration of response (DOR), time to worsening of pain based on Brief Pain Inventory (BPI) worst pain scale, and overall survival (OS). The PFS primary endpoint, ORR and DCR were based on centralized, independent blinded review of the imaging data. Biochemical response with vandetanib as compared to placebo as measured by CTN and CEA was also assessed as secondary endpoints.

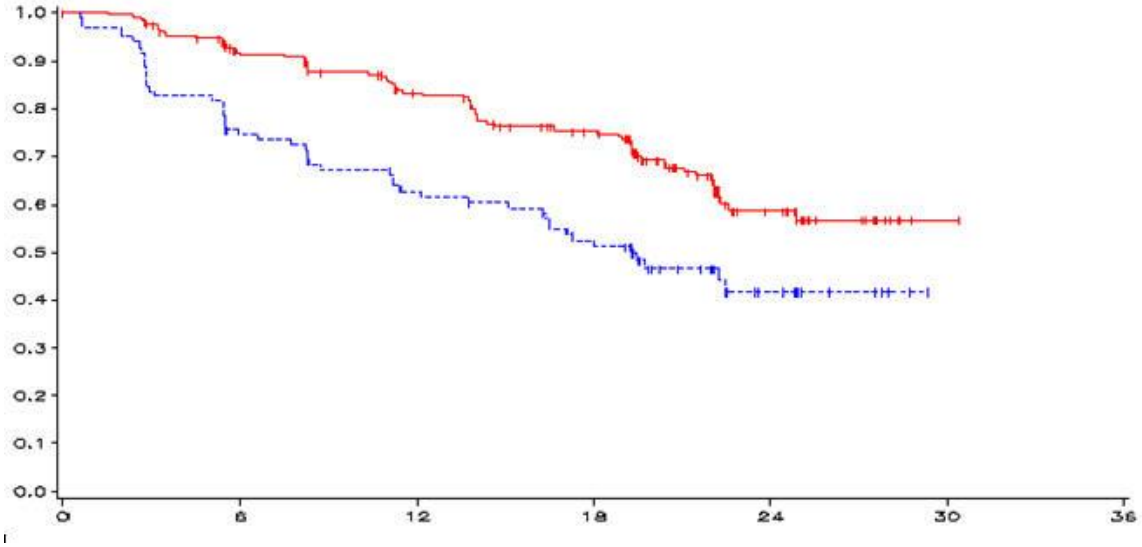
Patients were treated with vandetanib or placebo until they reached objective disease progression. Upon objective disease progression based on the investigator's assessment, patients were discontinued from blinded study treatment and given the option to receive open-label vandetanib. Twenty-eight of the 231 patients (12.1%) on vandetanib and 3 of the 99 (3.0%) on placebo discontinued treatment because of an adverse event. Fourteen of the 28 patients (50%) who stopped vandetanib for an adverse event discontinued without a dose reduction. Five out of 6 patients (83%) with moderate renal failure who were treated with vandetanib had a dose reduction to 200 mg for adverse reaction; 1 patient required a further reduction to 100 mg.

The result of the primary analysis of PFS showed a statistically significant improvement in PFS for patients randomised to vandetanib compared to placebo (Hazard Ratio (HR) = 0.46; 95% Confidence Interval (CI) = 0.31-0.69; p=0.0001).

The median PFS for patients randomised to vandetanib has not been reached; however, based on statistical modelling of data observed up to the 43rd percentile, the median PFS is predicted

to be 30.5 months with 95% confidence interval 25.5 to 36.5 months. The median PFS for patients randomised to placebo was 19.3 months. At 12 months, the proportion of patients alive and progression-free was 192 (83%) for patients randomised to vandetanib and 63 (63%) for patients randomised to placebo. In the vandetanib arm, a total of 73 (32%) patients progressed: 64 (28%) by response evaluation criteria in solid tumours (RECIST) progression and 9 (4%) by death in the absence of progression. The remaining 158 patients (68%) were censored in the analysis of PFS. In the placebo arm, a total of 51 (51%) of patients had progressed: 46 (46%) by RECIST progression and 5 (5%) by death in the absence of progression. The remaining 49 patients (49%) were censored in the analysis of PFS.

Figure 2 - Kaplan Meier plot of PFS



months	0	6	12	18	24	30	36
n-vandetanib	231	196	169	140	40	1	0
n-placebo	100	71	57	45	13	0	0

____ vandetanib 300 mg, ------ placebo, y-axis=PFS, x-axis=time in months, n-vandetanib=number of patients at risk-vandetanib, n-placebo=number of patients at risk-placebo

HR = 0.46, 95% CI (0.31-0.69), p = 0.0001

PFS	N	Median PFS	HR	95% CI	p-value
Vandetanib 300 mg	73/231 (32%)	Not reached (predicted 30.5 months)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			

Survival status and the median final overall survival (81.6 months in the vandetanib arm and 80.4 months in the placebo arm) were similar across both treatment arms. There was no statistically significant difference in final OS (HR 0.99, 95.002% CI 0.72, 1.38, p=0.9750). Results should be interpreted with caution due to the high percentage of patients in the placebo arm switching to open-label vandetanib (79.0% [79/100] of patients).

Most (95% of the patients) had metastatic disease. Fourteen patients treated with vandetanib, and 3 with placebo had unresectable locally advanced disease only. There is limited clinical experience with vandetanib in patients with unresectable locally advanced disease and without metastasis.

Statistically significant advantages were seen for vandetanib for the secondary endpoints of response rate, disease control rate, and biochemical response.

Table 7 - Summary of other efficacy findings in study D4200C00058

ORR[a]	**N**	**Response rate**	**OR**[b]	**95% CI**	**p-value**
Vandetanib 300 mg	104/231	45%	5.48	2.99, 10.79	< 0.0001
Placebo	13/100	13%			
DCR[a]	N	Response rate	OR[b]	95% CI	p-value
Vandetanib 300 mg	200/231	87%	2.64	1.48, 4.69	0.001
Placebo	71/100	71%			
CTN Response	N	Response rate	OR[b]	95% CI	p-value
Vandetanib 300 mg	160/231	69%	72.9	26.2, 303.2	< 0.0001
Placebo	3/100	3%			
CEA Response	N	Response rate	OR[b]	95% CI	p-value
Vandetanib 300 mg	119/231	52%	52.0	16.0, 320.3	< 0.0001
Placebo	2/100	2%			
OVERALL SURVIVAL	N	Median OS	HR[c]	95% CI	p-value
Vandetanib 300 mg	116/231	81.6 months	0.99	0.72, 1.38	0.9750
Placebo	52/100	80.4 months			

a Overall response rate = complete + partial responses. Disease control rate = response rate + stable disease at 24 weeks. Intent-to-treat (ITT) analysis includes patients who received open-label vandetanib before progression according to the central read.

b OR=Odds Ratio. A value >1 favors vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.

c HR= Hazard Ratio. A value <1 favors vandetanib. The analysis was performed using a log rank test with treatment as the only factor.

N=Number of events/number of randomised patients

A statistically significant advantage was seen for vandetanib for the secondary endpoint of time to worsening of pain (derived as a composite endpoint using the worst pain score from BPI and patient reported opioid analgesic use) (vandetanib 49%, placebo 57%, HR 0.61, 97.5% CI 0.43-0.87, p <0.006: 8 vs. 3 months). There were no statistically significant differences observed for the exploratory endpoint of diarrhea (reported as stool frequency).

RET mutation status in Study D4200C00058

In Study 58, RET mutation testing was performed by using the PCR) based 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 in patients 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 8.

Table 8 - Summary of efficacy findings in a segment of patients according to RET mutation status

	Patients with documented RET mutation (n=187)	**Patients with no M918T mutation and other mutations not tested or negative (n=79)[a]**
Objective response rate (vandetanib arm)	52%	35%
Efficacy endpoint PFS HR (95%) confidence interval	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)

a RET mutation status was obtained at the time of diagnosis in a majority of patients and could have changed since.

Clinical efficacy in paediatric patients:

A Phase I/II single-center open-label, single-arm study (Study IRUSZACT0098) assessed the activity of vandetanib in 16 patients with unresectable locally advanced or metastatic hereditary MTC. Characteristics of the patients at study entry were the following: mean age 14.2 years (range 9-17 years), 50% female, 50% male, 93.8% White, 26.7% Hispanic and 6.3% were Black. Most patients (81.3%) had undergone partial or total thyroidectomy prior to study entry. Starting vandetanib dose was 100mg/m^2/day for all patients except for one who started at 150mg/m^2/day. After having well tolerated the first 1 or 2 cycles of therapy (1 cycle = 28 days), the remaining patients continued on 100 mg/m^2 of treatment. The primary efficacy outcome was ORR according to RECIST v 1.0. The objective response rate observed was 43.8%, all of which were partial responses. 31.3% of patients had stable disease for at least 8 weeks. Disease Control Rate including best response or Stable Disease $\geq$24 weeks was 75.0%. There is no experience with Caprelsa in patients 5-8 years of age in this study.

This medicinal product has been authorized under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on the product every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of vandetanib absorption is slow with peak plasma concentrations typically achieved at a median of 6 hours, range 4-10 hours, after dosing. Vandetanib accumulates approximately 8-fold on multiple dosing with steady state achieved from approximately 2 months.

Distribution

Vandetanib binds to human serum albumin and alpha-1-acid-glycoprotein with *in vitro* protein binding being approximately 90%. In *ex vivo,* plasma samples from colorectal cancer patients at steady state exposure after 300 mg once daily, the mean percentage protein binding was 93.7% (range 92.2 to 95.7%). The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterised by a volume of distribution of approximately 7450 l.

Biotransformation

Following oral dosing of ^{14}C- vandetanib, unchanged vandetanib and metabolites vandetanib N-oxide and N-desmethyl vandetanib were detected in plasma, urine and feces. A glucuronide conjugate was seen as a minor metabolite in excreta only. N-desmethyl-vandetanib is primarily produced by CYP3A4, and vandetanib-N-oxide by flavin-containing monooxygenase enzymes (FM01 and FMO3). N-desmethyl-vandetanib and vandetanib-N-oxide circulate at concentrations of approximately 11% and 1.4% of those of vandetanib.

Elimination

The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterised by a clearance of approximately 13.2 l/h. and plasma half-life of approximately 19 days. Within a 21 day collection period after a single dose of ^{14}C-vandetanib, approximately 69% was recovered with 44% in faeces and 25% in urine. Excretion of the dose was slow and further excretion beyond 21 days would be expected based on the plasma half-life.

Special populations

Renal impairment

A single dose pharmacokinetic study in volunteers indicated that exposure to vandetanib is enhanced (up to 1.5, 1.6 and 2-fold) in mild, moderate and severe renal impaired subjects respectively compared to subjects with normal renal function (see sections 4.2, 4.4 and 4.5).

Hepatic impairment

A single dose pharmacokinetic study in volunteers indicated that hepatic impairment did not affect exposure to vandetanib. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal (see sections 4.2 and 4.4).

Food effect

Exposure to vandetanib is not affected by food.

Pharmacokinetics in paediatric population

The pharmacokinetic parameters of vandetanib in paediatrics MTC patients aged 9-17 years were similar to those in adults. Vandetanib exposure in children between 5-8 years old with glioma-related indications was comparable to MTC patients aged 9-18 years. Dosing at 100mg/m^2/day of the indicated posology (function of BSA) in paediatrics delivers similar exposure to that achieved in adults at 300 mg daily.

5.3 Preclinical safety data

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 diarrhea 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-à-go-go related gene (hERG) current and prolongation of QTc interval in dogs. Elevation of systolic and diastolic blood

pressure was 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.

Reproductive toxicology

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.

Carcinogenicity

Vandetanib has shown no carcinogenic potential effect in a 6 month carcinogenicity study in rasH2 transgenic mice. A 2-year carcinogenicity study in rats was impaired by low survival in the high dose female group and limited exposure of the animals to vandetanib; however, no carcinogenic effects were observed in the remaining animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium hydrogen phosphate dihydrate

Microcrystalline cellulose

Crospovidone (type A)

Povidone (K 29-32)

Magnesium stearate

Film-coating

Hypromellose

Macrogol (300)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/ PVDC/Alu blisters, sealed with aluminium foil, each containing 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/001

EU/1/11/749/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 February 2012

Date of latest renewal: 15 January 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca UK Ltd.

Silk Road Business Park

Macclesfield, Cheshire SK10 2NA

United Kingdom

Or

Genzyme Ltd.

37 Hollands Road

Haverhill

Suffolk, CB9 8PU

United Kingdom

Or

Genzyme Ireland Ltd.

IDA Industrial Park,

Old Kilmeaden Road,

Waterford

Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed risk management plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of CAPRELSA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where CAPRELSA is marketed, all healthcare professionals (HCPs) and patients / caregivers who are expected to prescribe, dispense and use CAPRELSA have access to/are provided with an **educational package** containing:

HCPs

- The summary of Product Characteristics (SmPC);
- The educational material, including:
  - Information about the risks associated with CAPRELSA:
    - QTc prolongation and Torsades de pointes
    - Posterior reversible encephalopathy syndrome (PRES);
    - Teeth and bone development abnormalities in pediatric patients

        - Medication errors in the pediatric population
    - The Physicians' dosing and monitoring guide for paediatric patients;
- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

Patients/caregivers

- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

The **HCPs educational materials** should include the following key elements:

QTc prolongation and Torsades de pointes

- Caprelsa prolongs the QTc interval and can cause Torsades de pointes and sudden death
- Caprelsa 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 de pointes have been corrected;
- The need for an ECG, and serum levels of potassium, calcium and magnesium and 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 Caprelsa. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pre-treatment 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 Caprelsa is either contraindicated or not recommended;
- The role and use of the Patient Alert Card.

Posterior reversible encephalopathy syndrome also known as reversible posterior leukoencephalopathy syndrome

- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. A 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.

Teeth and bone development abnormalities in pediatric patients

- Vandetanib was found not to impair linear growth in clinical trials conducted in children and adolescents;
- Vandetanib has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in non-clinical studies;
- The need to closely monitor teeth and bone abnormalities in the paediatric population;

Medication errors in the paediatric population

The **Physicians' dosing and monitoring guide for paediatric patients** should contain the following key elements:

- How Caprelsa dose for infants and adolescents is calculated;
- The posology regimens according to patient's body surface area (BSA), including a visual representation of the two-week posology regimen per BSA;
- How Caprelsa is used/administered;
- Instructions on how to use the dosing and monitoring guide and the daily tracker for paediatric patients and caregivers.

The **dosing and monitoring guide for patients and patient's caregivers** should contain the following key elements:

- What Caprelsa is, what it treats, how it is administered;
- How Caprelsa dose is calculated;
- What are the side effects associated with Caprelsa and which monitoring is requested;
- How to use the daily tracker table (including examples of a completed daily tracker);
- The general daily tracker for 14 days and blank copies of the daily tracker.

The **Patient Alert Card** should include the following key elements:

- Information about the risks of QTc prolongation and Torsades de pointes, and PRES;
- Signs or symptoms of the safety concerns and when to seek attention from a HCP;
- Not to stop taking Caprelsa, or change the dose, without consulting the prescriber;
- Contact details of the Caprelsa prescriber.

E. 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
In order to confirm the efficacy and safety of Caprelsa in RET-negative patients, the MAH should submit: - the clinical study report of study D4200C00104, an observational study including a retrospective arm to evaluate the Benefit/Risk of vandetanib (Caprelsa) 300 mg in RET mutation negative and RET mutation positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic thyroid cancer (MTC). - The re-evaluation of treatment efficacy in RET-negative patients based on the re-analysis of archived tumour samples from the pivotal study D4200C00058.	3Q 2020

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF CAPRELSA 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg film-coated tablets

vandetanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg vandetanib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.,

Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caprelsa 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER OF CAPRELSA 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 100 mg tablets

vandet anib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF CAPRELSA 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 300 mg film-coated tablets

vandetanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg vandetanib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.,

Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/749/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Caprelsa 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF CAPRELSA 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Caprelsa 300 mg tablets

vandetanib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Genzyme Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Caprelsa 100 mg film-coated tablets

Caprelsa 300 mg film-coated tablets

vandetanib

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

In addition to this leaflet you will be given the Patient Alert Card, which contains important safety information that you need to know before you are given Caprelsa and during treatment with Caprelsa.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet and the patient alert card. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Caprelsa is and what it is used for

Caprelsa is a treatment for adults and children aged 5 years and above with:

Medullary thyroid cancer that cannot be removed by surgery or has spread to other parts of the body.

Caprelsa works by slowing down the growth of new blood vessels in tumours (cancers). This cuts off the supply of food and oxygen to the tumour. Caprelsa may also act directly on cancer cells to kill them or slow down their growth.

2. What you need to know before you take Caprelsa

Do not take Caprelsa:

- if you are allergic to vandetanib or any of the other ingredients of this medicine (listed in section 6).
- if you have a heart problem that you were born with called 'congenital long QTc syndrome'. This is seen on an ECG.
- if you are breast-feeding.
- if you are taking any of the following medicines: arsenic, cisapride (used to treat heartburn), erythromycin intravenous and moxifloxacin (used to treat infection), toremifene (used to treat breast cancer), mizolastine (used to treat allergies), Class IA and III antiarrhythmics (used to control heart rhythm).

Do not take Caprelsa if any of the above applies to you. If you are not sure, talk to your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Caprelsa if you are sensitive to the sun. Some people who are taking Caprelsa become more sensitive to the sun. This can cause sunburn. While you are taking Caprelsa, protect yourself when you go outside by always using sunscreen and wearing clothes to avoid exposure to the sun.

Monitoring of your blood and your heart:

Your doctor or nurse should perform tests to check the levels of your blood potassium, calcium, magnesium, and TSH as well as the electrical activity of your heart with a test called an ECG. You should have these tests:

- Before starting Caprelsa
- Regularly during Caprelsa treatment
- 1, 3 and 6 weeks after starting Caprelsa
- 12 weeks after starting Caprelsa
- Every 3 months thereafter

- If your doctor or pharmacist changes your dose of Caprelsa
- If you start taking medicines that affect your heart
- As instructed by your doctor or pharmacist

Children

Caprelsa should not be given to children below 5 years of age.

Other medicines and Caprelsa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines that you buy without a prescription and herbal medicines. This is because Caprelsa can affect the way some medicines work and some medicines can have an effect on Caprelsa.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- itraconazole, ketoconazole, ritonavir, clarithromycin, rifampicin and moxifloxacin (medicines used to treat infections)
- carbamazepine and phenobarbital (used to control seizures)
- ondansetron (used to treat nausea and vomiting)
- cisapride (used to treat heart burn), pimozide (used to treat uncontrolled repeated movements of the body and verbal outbursts) and halofantrine and lumefantrine (used to treat malaria)
- methadone (used to treat addiction), haloperidol, chlorpromazine, sulpiride, amisulpride, and zuclopenthixol, (used to treat mental illness)
- pentamidine (used to treat infection)
- vitamin K antagonists and dabigatran often referred to as ‘blood thinners’
- cyclosporine and tacrolimus (used to treat transplant rejection), digoxin (used to treat irregular heart rate), and metformin (used to control your blood sugar)
- proton pump inhibitors (used to treat heartburn)

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. This is because Caprelsa may harm an unborn child. Your doctor will discuss with you the benefits and risks of taking Caprelsa during this time.

- If you may become pregnant you must use effective contraception when you are taking Caprelsa and for at least four months after the last dose of Caprelsa.

You must not breast-feed during treatment with Caprelsa for the safety of your baby.

Driving and using machines

Use caution before driving or using machines. Keep in mind Caprelsa may make you feel tired, weak, or cause blurred vision.

3. How to take Caprelsa

Use in adults

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is 300 mg each day.
- Take Caprelsa about the same time each day.
- Caprelsa may be taken with or without food.

Use in children

The doctor will tell you how many tablets of Caprelsa to give to your child. The amount of Caprelsa given will depend on your child's body weight and height. The total daily dose in children must not exceed 300 mg. The treatment may either be given to your child as a once-daily dose, an every other day dosing or a repeating 7-day schedule as indicated in the dosing guide that has been given to you by your doctor. It is important that you keep this dosing guide and show it to your caregiver.

If you have trouble swallowing the tablet

If you have trouble swallowing the tablet, you can mix it with water as follows:

- Take half a glass of still (non-carbonated) water. Only use water, do not use any other liquids.
- Put the tablet into the water.
- Stir the tablet until it has dispersed into the water. This may take about 10 minutes.
- Then drink it straight away.

To make sure there is no medicine left, refill the glass halfway with water and drink it.

If you get side effects

If you get side effects always tell your doctor. Your doctor may tell you to take Caprelsa at a lower or increased dose (such as two 100 mg tablets or one 100 mg tablet). Your doctor may also prescribe other medicines to help control your side effects. The side effects of Caprelsa are listed in section 4.

If you take more Caprelsa than you should

If you take more Caprelsa than you have been prescribed, talk to a doctor or go to a hospital straight away.

If you forget to take Caprelsa

What to do if you forget to take a tablet depends on how long it is until your next dose.

- **If it is 12 hours or more until your next dose**: Take the missed tablet as soon as you remember. Then take the next dose at the normal time.
- **If it is less than 12 hours until your next dose**: Skip the missed dose. Then take the next dose at the normal time.

Do not take a double dose (two doses at the same time) to make up for a forgotten tablet.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get side effects, your doctor may tell you to take Caprelsa at a lower dose. Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

- Fainting, dizziness or heart rhythm changes. These may be signs of a change in the electrical activitiy of your heart. They are seen in 8% of people taking Caprelsa for medullary thyroid cancer. Your doctor may recommend you take Caprelsa at a lower dose or stop taking Caprelsa. Caprelsa has uncommonly been associated with life-threatening changes in heart rhythm.
- Severe skin reactions affecting large areas of your body. The signs may include redness, pain, ulcers, blisters and shedding of the skin. The lips, nose, eyes and genitals may also be affected. These may be common (affecting less than 1 in 10 people) or uncommon (affects less than 1 in 100 people) depending on the type of skin reaction.
- Severe diarrhea.
- Serious breathlessness, or sudden worsening breathlessness, possibly with a cough or a high temperature (fever). This may mean that you have an inflammation of the lungs called ‘interstitial lung disease’. This is uncommon (affects less than 1 in 100 people) but can be life-threatening.
- Seizures, headache, confusion or finding it difficult to concentrate. These may be signs of a condition called RPLS (Reversible Posterior Leukoencephalopathy Syndrome). These usually go away when Caprelsa is stopped. RPLS is uncommon (affects less than 1 in 100 people).

Tell your doctor straight away if you notice any of the side effects above.

Other side effects include:

Very common (affects more than 1 in 10 people):

- Diarrhoea. Your doctor may prescribe a medicine to treat this. If it gets severe, tell your doctor straight away.
- Abdominal pain.
- Skin rash or acne.
- Depression.
- Tiredness.
- Feeling sick (nausea).
- Upset stomach (dyspepsia).
- Nail disorders.
- Being sick (vomiting).
- Loss of appetite (anorexia).
- Weakness (asthenia).
- High blood pressure.Your doctor may prescribe a medicine to treat this.
- Headache.
- Fatigue.
- Trouble sleeping (insomnia).
- Inflammation of the nasal passages.
- Inflammation of the main air passages to the lungs.
- Upper respiratory tract infections.
- Urinary tract infections.
- Numbness or tingling of the skin.
- Abnormal sensation of the skin.
- Dizziness.
- Pain.
- Swelling caused by excess fluid (edema).
- Stones or calcium deposits in the urinary tract (nephrolithiasis).
- Blurred vision, including mild changes in the eye which can lead to blurred vision (corneal opacity).
- Sensitivity of the skin to sunlight. While you are taking Caprelsa, protect yourself when you go outside by always using sun cream and wearing clothes to avoid exposure to the sun.

Common (affects less than 1 in 10 people)

- Dehydration.
- Severe high blood pressure.
- Weight loss.
- Stroke or other conditions where the brain may not get enough blood.
- A type of rash that affects the hands and feet (hand foot syndrome).
- Sore mouth (stomatitis).
- Dry mouth.
- Pneumonia.

- Toxins in the blood as a complication of infection.
- Flu.
- Inflammation of the urinary bladder.
- Inflammation of the sinuses.
- Inflammation of the voice box (larynx).
- Inflammation of a follicle, especially a hair follicle.
- Boil.
- Fungal infection.
- Kidney infection.
- Loss of body fluid (dehydration).
- Anxiety.
- Tremor.
- Drowsiness.
- Fainting.
- Feeling unsteady.
- Increased pressure in the eye (glaucoma).
- Coughing up of blood.
- Inflammation of the lung tissue.
- Difficulty swallowing.
- Constipation.
- Inflammation of the lining of the stomach (gastritis).
- Gastrointestinal bleeding.
- Gallstones (cholelithiasis).
- Painful urination.
- Kidney failure.
- Frequent urination.
- Urgent desire to urinate.
- Fever.
- Nose bleed (epistaxis).
- Dry eye.
- An irritation of the eyes (conjunctivitis).
- Visual impairment.
- Halo vision.
- Seeing flashes of light (photopsia).
- Disorder of the cornea of the eye (keratopathy).
- A type of diarrhea (colitis).
- Loss of hair from the head or body (alopecia).
- Changes in taste of foods (dysgeusia).

Uncommon (affects less than 1 in 100 people)

- Heart failure.
- Inflammation of the appendix (appendicitis).
- Bacterial infection.
- Inflammation of the diverticula (small bulging pouches that can form in your digestive system).
- Bacterial skin infection.
- Abdominal wall abscess.
- Malnutrition.
- Involuntary muscle contraction (convulsions).
- Rapidly alternating muscular contraction and relaxation (clonus).
- Swelling of the brain.
- Clouding of the lens of the eye.
- Heart rate and rhythm disorders.
- Loss of heart function.
- Failure of the lungs to function properly.
- Pneumonia that happens when you breathe in foreign matter into your lungs.
- Bowel obstruction.
- Hole in your bowel.
- Inability to control your bowel movements.
- Abnormal color of urine.
- Lack of urine.
- Inability to heal properly.
- Inflammation of the pancreas (pancreatitis).
- Blistering of skin (bullous dermatitis).

The following side effects may be shown in tests that may be carried out by your doctor:

- Protein or blood in your urine (shown in a urine test).
- Heart rhythm changes (shown in an ECG). Your doctor may tell you to stop taking Caprelsa or take Caprelsa at a lower dose.
- Abnormalities in your liver or pancreas (shown in blood tests). These do not usually cause symptoms but your doctor may want to monitor them.
- Decreased levels of calcium in your blood. Your doctor may need to prescribe or change your thyroid hormone treatment.
- Decreased levels of potassium in your blood.
- Increased levels of calcium in your blood.
- Increased levels of glucose in your blood.
- Decreased levels of sodium in your blood.
- Decrease in thyroid function.
- Increased levels of red cells in your blood.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist **straight away**.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Caprelsa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Caprelsa contains

- The active substance is vandetanib. Each tablet contains 100 or 300 mg of vandetanib.
- The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, crospovidone (type A), povidone (K29-32), magnesium stearate, hypromellose, macrogol and titanium dioxide (E171).

What Caprelsa looks like and contents of the pack

Caprelsa 100 mg is a white round film-coated tablet with “Z100” imprinted on one side.

Caprelsa 300 mg is a white oval-shaped film-coated tablet with “Z300” imprinted on one side.

Caprelsa comes in blister packs of 30 tablets.

Marketing Authorisation Holder

Genzyme Europe B.V.,

Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

Manufacturer

AstraZeneca UK Limited, Macclesfield, Cheshire, SK10 2NA, United Kingdom

Or

Genzyme Ltd., 37 Hollands Road, Haverhill, Suffolk, CB9 8PU, United Kingdom

Or

Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien/ Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: + 32 (0)2 710 54 00

Magyarország
SANOFI-AVENTIS Zrt.
Tel: +36 1 505 0050

България
SANOFI BULGARIA EOOD
Тел: +359 (0)2 970 53 00

Malta
Sanofi Malta Ltd
Tel: +356 21493022

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Nederland
Genzyme Europe B.V.
Tel: +31 20 245 4000

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Norge
sanofi-aventis Norge AS
Tlf: + 47 67 10 71 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel.: 0800 04 36 996
Tel. aus dem Ausland: +49 69 305 70 13

Österreich
sanofi-aventis GmbH
Tel: + 43 1 80 185 - 0

Eesti
Sanofi-aventis Estonia OÜ
Tel. +372 627 34 88

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Ελλάδα
sanofi-aventis AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
sanofi-aventis France
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 3 4 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.p.A.
Tel: +39 059 349 811

Κύπρος
Sanofi-aventis Cyprus Ltd.
Τηλ: +357 22 871600

Latvija
Sanofi-aventis Latvia SIA
Tel: +371 67 33 24 51

Lietuva
UAB „SANOFI-AVENTIS LIETUVA"
Tel. +370 5 2755224

Portugal
Sanofi – Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Romania
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
sanofi-aventis d.o.o.
Tel: +386 1 560 48 00

Slovenská republika
sanofi-aventis Pharma Slovakia s.r.o.
Tel.: +421 2 33 100 100

Suomi/Finland
Sanofi Oy
Puh/Tel: + 358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom
Sanofi
Tel: +44 (0)845 372 7101

This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on the medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Appendix C Guidelines for evaluation of objective tumor response using response evaluation criteria in solid tumors (RECIST) 1.1 criteria

1 Introduction

This appendix details the implementation of RECIST 1.1 Guidelines (6) for the D4200C00104 (Sanofi-Genzyme OBS14778) study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

2 Definition of measurable, non-Measurable, target and non-target lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least 1 measurable lesion which has not been previously irradiated.

Measurable: A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline*).

Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

Previously irradiated lesions**

Skin lesions assessed by clinical examination Brain metastasis

* Nodes with <10 mm short axis are considered non-pathological and should not be recorded

or followed as non-target lesions (NTL).

**Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

Special Cases:

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TL).

Target lesions: A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified TL at baseline.

Non-target lesions: All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumor assessments for this study are highlighted, with the rationale provided.

Table 9 - Summary of methods of assessment

Target lesions	Non-target Lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

CT= Computed tomography, FDG-PET= Fluorodeoxyglucose-positron emission tomography, MRI = Magnetic resonance imaging

3.1 Computed tomography and magnetic resonance imaging

Computed Tomography and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the OBS14778 study, it is recommended that CT examinations of the abdomen, pelvis and other areas as clinically indicated will be used to assess tumor burden at baseline and follow-

up visits. Computed tomography examination with intravenous contrast media administration is the preferred method. Magnetic Resonance Imaging should be used where CT is not feasible, or it is medically contraindicated. For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the OBS14778 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

In OBS14778, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In OBS14778, plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In OBS14778, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the OBS14778 study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

3.6 Tumor markers

In the OBS14778 study tumor markers will not be used for tumor response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the OBS14778 study, histology will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during the study is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the OBS14778 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI, and X-ray is recommended where bone scan findings are equivocal.

3.9 Fluorodeoxyglucose-positron emission tomography scan

In the OBS14778 study, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: new lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. Tumor response evaluation

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed according to the usual clinical practice. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

4.2 Target lesions

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

If the CT/MRI slice thickness used is >5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.

If 2 or more TL merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided, where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL.

Table 10 - Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD)
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
Not evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides not evaluable as a target lesion response

4.3 Non-target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 11 - Evaluation of non-target lesions

Complete response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in 1 lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when 1 or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTL, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TL, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTL is usually not sufficient to qualify for unequivocal progression status.

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of 1 or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, eg, because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response, as per RECIST 1.1, will be derived using the algorithm shown in Table 12.

Table 12 - Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR

Target lesions	Non-target lesions	New lesions	Overall response
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response, NA = Not applicable (only relevant if there were no NTLs at baseline), NE = Not evaluable, PD = Progressive disease, PR = Partial response, SD = Stable disease

5. Specifications for radiological imaging

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 Computed tomography scan

Computed Tomography scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI

(enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TL on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed, then CT without intravenous contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

5.2 Magnetic resonance imaging scan

Magnetic resonance imaging has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impacts image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 Fluorodeoxyglucose-positron emission tomography scans

Fluorodeoxyglucose-positron emission tomography has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 minutes prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 minutes post injection. Positron-emission tomography camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the study.

5.3.1 Positron-emission tomography/computed tomography scans

At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET-CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may introduce bias in an Investigator if it is not routinely or serially performed.

Appendix D Cockcroft-Gault formula

1. Cockcroft-Gault formula

Creatinine clearance should be calculated for this study using the modified Cockcroft-Gault formula.

Modified Cockcroft-Gault formula is calculated by the following formula:

([140 – age{years}] × [actual weight{kg}]) / (72 × serum creatinine[mg/dL])

Multiply by another factor of 0.85 if female.

Intended for ages 18 to 110, serum creatinine 0.6-7 mg/dL.

Appendix E Additional safety information

Further guidance on the definition of a serious adverse event

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.

Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N--acetylcysteine.

Intensive treatment in an emergency room or at home for allergic bronchospasm.

Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.), or convulsions that do not result in hospitalization

Development of drug dependency or drug abuse.

A guide to interpreting the causality question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

Time course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The Sponsor would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

Is this a recognised feature of overdose of the drug?

Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix F Actions required in cases of combined increase of aminotransferase and total bilirubin - Hy's Law

1. Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) decisive factors are fulfilled, indicating a drug induced liver injury (DILI) caused by the Medicinal Product (MP). Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than the MP.

The Investigator fulfills requirements for the recording of data pertaining to PHL/HL cases and adverse event (AE)/serious AE (SAE) reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

For the purpose of this process definitions are as follows

Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)≥3 times the upper limit of normal (ULN) and total bilirubin (TBL)≥2 times the ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law

Aspartate aminotransferase or ALT greater than or equal to 3 times ULN and TBL greater than or equal to 2 times the ULN, where no other reason, other than the MP, can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, or another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. Actions required in cases of alanine aminotranferase≥3 times the upper limits of normal, aspartate aminotransferase≥3 times the upper limits of normal, or total bilirubin ≥2 times the upper limits of normal

3.1 Identification and determination

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following criteria in isolation or in combination:

ALT≥3 times the ULN

AST≥3 times the ULN

TBL≥2 times the ULN

When a patient meets the criteria above, in isolation or in combination, the laboratory will immediately send an alert to the Investigator (also sent to Sponsor representative).

When this alert is received follow the instructions below without delay:

- Review laboratory reports from all previous visits
- Review any available local laboratory reports and if a patient has ALT greater than or equal to 3 times the ULN, AST greater than or equal to 3 times the ULN or TBL greater than or equal to 2 times the ULN at any time
- Repeat test
- Complete the appropriate laboratory case report form (CRF) modules with the original local laboratory test result
- Determine whether the patient meets PHL criteria (see section 2 of this Appendix) Note: Applicable for both central laboratory and additional local laboratory reports

3.2 Follow-up

3.2.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria (see section 2 of this Appendix):

- Inform the Sponsor representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

3.2.2 Potential Hy's Law Criteria met

If the patient meets PHL criteria (see section 2 of this Appendix):

- Notify the Sponsor representative who will then inform the central study team.
- The study physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patient's follow-up and the continuous review of data.

The Investigator:

- Follows the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the study physician
- If at any time (in consultation with the study physician) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

3.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the study physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than DILI caused by the MP. The Sponsor Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate. According to outcome of the review and assessment, please follow the instructions below:

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate electronic case report form (eCRF).
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Sponsor standard processes.
- If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the MP:
    - Report an SAE (report term 'Hy's Law') according to Sponsor standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
    - As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

- If there is an unavoidable delay of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.
- Report a SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above. (7)

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