Non-Interventional Study (NIS) Protocol	
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European, Observational, Prospective 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 (MTC)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

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

AstraZeneca

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

European, Observational, Prospective 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 (MTC)

National/International (*delete what is not applicable*) Co-ordinating Investigator of the Non-Interventional Study

<<Name, Qualification <<>>,
Position at the Site, <<>>
Address, <<>>
Telephone and Fax Numbers>>>>

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

It is estimated that 6 countries and 30 investigator sites from Europe shall participate in the study and will provide at least 40 Rearranged During Transfection (RET) positive and 40 RET 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 Rearranged During Transfection (RET) mutation negative but not prescribed vandetanib (CAPRELSA™) 300 mg will be allowed to enter the study.

Total planned Study period	
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

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

Vandetanib (CAPRELSA™) 300mg/once daily, film-coated tablets

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

Rationale for this Non-Interventional Study (NIS)

This study is being conducted to fulfil the specific obligation post-authorisation measure for the conditional marketing authorisation. It is carried on to confirm in real life conditions the benefit/risk of vandetanib (CAPRELSA™) 300 mg, both in RET negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. The clinical benefit of vandetanib (CAPRELSA™) 300 mg has previously been established in a clinical trial (Study 58) 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 Non-Interventional Study

(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) amongst RET mutation negative patients not treated with vandetanib

(e) To evaluate the incidence of 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 SAEs and AEs leading to discontinuation of vandetanib will be assessed.

(f) To compare Progression-Free Survival (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) and prospective study. European countries where vandetanib is on the market will participate in the study.

Target patient population

Patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib (CAPRELSA™) 300 mg/once daily and with a RET mutation positive or negative status. In addition, patients with symptomatic, aggressive, sporadic,

unresectable, locally advanced/metastatic MTC not prescribed vandetanib (CAPRELSA™) 300 mg but who are RET mutation negative will be allowed to enter the study.

Study variable(s):

Benefit/risk

- Objective response rate [using Response Evaluation Criteria In Solid Tumours (RECIST) 1.1]
- Disease control rate (using RECIST 1.1)
- Progression free survival derived (using RECIST 1.1)
- Duration of response and time to response
- Safety:
  - Adverse Events (AE): all relevant AEs, based on the safety profile outlined in the vandetanib SmPC, will be collected actively throughout the study
  - Electrocardiograms (ECGs): QTc prolongation
  - Vital signs: blood pressure, pulse
  - Laboratory data:
    - Electrolyte: serum potassium, calcium and magnesium
    - Thyroid stimulating hormone (TSH) at baseline
    - Renal function: creatinine clearance value (Cockroft Gault formula)
    - Hepatic function: serum bilirubin, aspartate aminotransferase (AST), alanine aminotranferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), 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, CTN, CEA doubling time, change of tumour 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 and at follow up visits (when performed).
- Date of measurements
- Symptoms at baseline and at every disease assessment timepoint (lump at the base of the neck, dysphagia, respiratory difficulty, hoarseness, diarrhoea, weight loss, lethargy, asthenia, anorexia and bone pain).
- Calcitonin (CTN) and carcinoembryonic antigen (CEA) doubling time at baseline.
- CTN and CEA at every disease assessment timepoint

Death

- Date and cause

Treatment information:

- Previous treatments received for the sporadic MTC (including non-pharmacologic)

- For 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 patients non treated with vandetanib at entry: current and subsequent treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: date of start and stop (if available).

- Dose adjustments / discontinuations during follow up (date of adjustment and dose)

- Opioid use: Date, Dose and Route by generic name

Statistical methods

The data cut off for the analysis will be 14 months after the last patient has been enrolled in the study and when at least 20 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. Twenty PFS events in each treated group will ensure that median PFS can be estimated for each group.

A hazard ratio for the comparison of PFS for vandetanib treated RET mutation positive patients versus vandetanib treated RET mutation negative patients will be derived using a Cox proportional hazards model adjusted for age, sex, CTN doubling time and CEA doubling time. A Kaplan-Meier plot of PFS split by RET mutation status will be presented. Median PFS will be presented, where possible, in the two groups. A parametric interval censored sensitivity analysis will be performed to assess the impact of any potential imbalance in the frequency of RECIST assessments in the two groups. If there are large differences in prognosis between the two groups, then a sensitivity analysis using propensity scores will be considered to assess the impact of this imbalance. Subgroup analyses will be performed for PFS by CTN doubling time and CEA doubling time at baseline.

The ORR and DCR will be summarized with corresponding exact 95% CIs amongst RET mutation positive patients treated with vandetanib and amongst RET mutation negative patients treat with vandetanib. Median duration of response and time to response will be summarized, where possible, for the two groups of patients. In addition, duration of response may be summarized graphically. 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.

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

The frequency and percentage of patients with symptoms at each time point will be summarised by RET mutation status. Opioid analgesic use will be summarised descriptively by RET mutation status.

Data for RET mutation negative patients not treated with vandetanib will be summarized with 95% CIs presented when appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse event
ARMS	Amplification Refractory Mutation System
Assessment	An observation made on a variable involving a subjective judgement (assessment)
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
ALT	Alanine aminotranferase
AZ	AstraZeneca
CEA	Carcinoembryonic antigen
CI	Confidence Interval
eCRF	Case Report Form (electronic)
CTN	Calcitonin
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HR	Hazard Ratio
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
MTC	Medullary Thyroid Cancer
National Coordinator	The National Coordinator is the main line of contact to coordinate the submissions and responses of the Leading Ethics Committee and of the Ethics Committees related to the other participating sites (Non-Leading Ethics Committees).
NIS	Non-Interventional Study

Abbreviation or special term	Explanation
NISA	Non-Interventional Study Agreement
NISP	Non-Interventional Study Protocol
ORR	Objective Response Rate
PCR	Polymerase chain reaction
PFS	Progression-free survival
QT	The interval between Q and T on ECG
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria In Solid Tumours
RET	Rearranged During Transfection
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
TCS	Tata Consulting Service
ULRR	Upper Limit of the Reference Range
Variable	A characteristic of a property of a patient that may vary eg, from time to time or between patients
WBDC	Web-based Data Capture

1. INTRODUCTION

1.1 Background

In Study 58 (the pivotal clinical trial in which the efficacy and safety of vandetanib 300mg were compared to placebo in patients with MTC), 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 tumour 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, 13-16. A RET mutation negative tumour was defined as having no M918T mutation by ARMS and a wild-type RET sequence in each of exons 10, 11, 13-16. The mutation status was considered to be unknown in tumours 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 tumour 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 58 (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 (CAPRELSA™) 300 mg in patients who were RET mutation negative, a post-hoc subgroup analysis of RET negative status based on absence of M918T mutation of the pivotal study 58 was performed. Based on a recent study with a data base consisting of 100 sporadic MTC tumours whose complete exon sequencing was done at all 6 RET exons where RET mutations have been described (Elisei 2008), 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 (Wohllk 1996). In study 58, 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) (Wells et al 2010).

Thus, patients with the sporadic form of MTC without the M918T mutation have nearly a 90% probability of being RET mutation negative. The table below summarises 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 1 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)***
Objective response rate (vandetanib arm)	52%	35%
Efficacy endpoint PFS Hazard Ratio (HR) (95%) confidence interval	0.45 (0.26, 0.78)	0.57 (0.29, 1.13)

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

1.2 Rationale for conducting this NIS

This study is being conducted to fulfil the specific obligation post-authorisation measure for the conditional marketing authorisation. It is carried on to confirm in real life conditions the benefit/risk of vandetanib (CAPRELSA™) 300 mg, both in RET negative and RET positive patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC. The clinical benefit of vandetanib (CAPRELSA™) 300 mg has previously been established in a clinical trial (Study 58) 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.

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

A non-interventional study 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, 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 in the EU.

A Non-Interventional Study (NIS) is a study in which no additional diagnostic or monitoring procedures shall be applied to the patients.

2. NIS 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) amongst RET mutation negative patients not treated with vandetanib

(e) To evaluate the incidence of 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 SAEs and AEs leading to discontinuation of vandetanib will be assessed.

(f) To compare Progression-Free Survival (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 Non-Interventional Study Protocol has been subject to an internal review according to AstraZeneca internal procedures.

3.1 Overall study design and flow chart

This is a multinational, multicenter, non-interventional, prospective study of patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, treated with vandetanib (CAPRELSA™) 300 mg/once daily and with a RET mutation positive or negative status. Forty vandetanib RET positive and forty vandetanib RET negative patients will be enrolled in the study.

In addition, patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC not prescribed vandetanib (CAPRELSA™) 300 mg but who are RET mutation negative will be allowed to enter the study.

Study visits will include a screening visit and/or enrolment visit, where the eligibility of the patient will be confirmed, plus additional follow up visits:

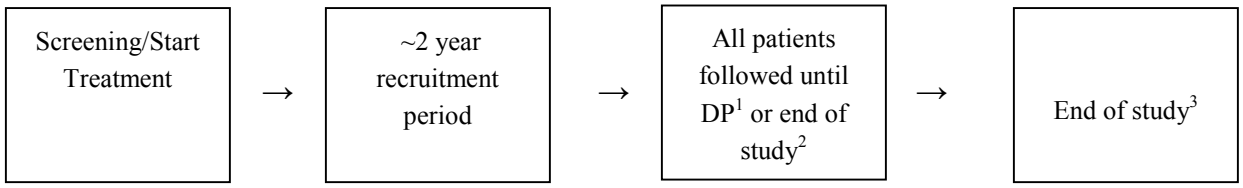
- For effectiveness measurement purposes, investigators are strongly recommended to perform a complete disease assessment (biomarkers, symptoms and imaging) at least every 6 months according to both site normal clinical practice and International MTC guidelines (Schlumberger et al 2012, Kloos et al 2009).RECIST 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 SmPC (see Appendix B).

Patients will be followed until objective progression or until the end of study (whichever occurs first). End of study is defined as 14 months after the last patient has been enrolled in the study and when at least 20 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 minimum follow up time period of 14 months 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 (Wells et al 2010). Twenty PFS events in each treated group will ensure that median PFS can be estimated for each group.

Figure 1 Study Flow Chart



1 DP = Disease progression
2 Whichever occurs first
3 End of study is defined as 14 months after the last patient has been enrolled in the study and when at least 20 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.

Detailed study assessments are described in Table 2.

Table 2 Study Plan

Time	Screening/Enrolment visit	Follow Up visits
Obtain Informed Consent	X	
Inclusion/exclusion criteria assessment	X	
Patient Characteristics, including RET status	X	
Disease assessment [a]	X	X
Treatment information	X	X
Safety information Laboratory [b]	X	X

(a) Patient disease assessment should be consistent (same time frequency and method) within a site across the study.
(b) 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

3.2 RET mutation analysis procedure

The assay to determine mutational status will be done in certified laboratories and must be based on one of these three tests:

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

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

(a) If mutation is present in M918T (exon 16) or any other additional exon tested where RET mutations have been described (10,11,13-16) then the patient is RET mutation positive.

(b) If mutation is absent in M918T (exon 16), or in any of the other additional exons where RET mutations have been described (10, 11, 13-16), 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 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 fulfil all the following criteria:

1. Signed informed consent

2. Male or female aged 18 years or above

3. Histological diagnosis of MTC

4. 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 CRF).

5. Measurable disease:

- assessment confirmed within the 12 weeks previous to start of treatment, and

- defined according to RECIST 1.1**:** at least one 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 CT or 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.

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

- for patients prescribed with vandetanib: positive or negative

- for patients not prescribed with vandetanib: negative

   RET mutation status must be determined from a tumour sample obtained within 18 months prior to enrollment. It is strongly recommended that a tissue sample obtained within 6 months prior to enrolment is used.

7. For patients newly prescribed vandetanib 300 mg, the prescription should be issued according to marketing authorisation and following the vandetanib Summary of

Product Characteristics (SmPC) (Appendix B). The starting dose could be reduced to 200 mg in patients with moderate renal impairment

Note: The **prescription of the medicinal product is clearly separated from the decision to include the patient** in the NIS.

4.3 Exclusion criteria

1. Current or planned inclusion/participation in a clinical trial

2. Patients already receiving vandetanib or who have received vandetanib for their MTC before the study first visit

3. Contraindications according to the vandetanib SmPC (not applicable for patients who do not receive vandetanib):

   (a) Patients with a QT interval corrected for heart rate (QTc) interval over 480 msec:

      (i) Congenital long QT syndrome

      (ii) Concomitant use of vandetanib with the following medicinal products known to also prolong the QT interval and / or induce Torsades de pointes: Arsenic, cisapride, erythromycine intravenous (IV), toremifene, mizolastine, moxifloxacine, Class IA and III antiarrhythmics

   (b) Currently pregnant or breast feeding

   (c) Hypersensitivity to the active substance or to any of the excipients

   (d) Severe renal impairment: creatinine clearance < 30 ml/minute calculated by Cockcroft-Gault formula. (See Appendix D).

   (e) Serum bilirubin greater than 1.5 x the upper limit of reference range (ULRR)

   (f) Potassium, magnesium or calcium outside the normal laboratory range

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

2. Incorrect enrolment (inclusion/exclusion criteria are not fulfilled)

3. Inclusion in a clinical trial at any time during the study

Discontinuation of the patient treatment is not a criterion for withdrawal from the study. In this case, the patient can continue in the study.

5.2 Procedures for withdrawal

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 clinical practice.

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

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.

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

Doses and treatment regimens of vandetanib (CAPRELSA™) 300 mg, and concomitant medication should be prescribed according to the instructions in the SmPC (see Appendix B) and current practice.

There is limited data with 300 mg in patients with moderate renal impairment. 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.

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.

7. STUDY CONDUCT

7.1 Patient Enrolment

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 fulfils all the study inclusion criteria and none of the exclusion criteria.

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient

2. Perform the RET determination in those patients where it is needed to confirm eligibility

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.

The aim is to have at least 40 vandetanib RET positive, 40 vandetanib RET negative and no more than 40 not treated with vandetanib RET negative patients recruited from across all sites. In order to achieve that, the enrolment of patients per group will be automatically stopped in the WBDC system to meet those requirements.

All the 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.

For the cases where the RET test needs to be done to confirm eligibility for the study, signed informed consent should be always obtained prior to that assessment.

The sponsor will reimburse the costs associated to the RET determination when the test is solely performed to confirm eligibility 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 electronic Case Report Form (eCRF) and record all the available information required for study purposes.

Follow up of each patient and collection of data for the study will cease at objective progression of the disease 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 (e.g., 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

- Objective response rate [using Response Evaluation Criteria In Solid Tumours (RECIST) 1.1]
- Disease control rate (using RECIST 1.1)
- Progression free survival derived (using RECIST 1.1)
- Duration of response and time to response
- Safety:
  - Adverse Events (AE): all relevant AEs, based on the safety profile outlined in the vandetanib SmPC, will be collected actively throughout the study
  - Electrocardiograms (ECGs): QTc prolongation
  - Vital signs: blood pressure, pulse
  - Laboratory data:
    - Electrolyte: serum potassium, calcium and magnesium
    - Thyroid stimulating hormone (TSH) at baseline
    - Renal function: creatinine clearance value (Cockroft Gault formula)

- Hepatic function: serum bilirubin, aspartate aminotransferase (AST), alanine aminotranferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), 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, CTN, CEA doubling time, change of tumour 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 and at follow up visits (when performed).
- Date of measurements

- Symptoms at baseline and at every disease assessment timepoint (lump at the base of the neck, dysphagia, respiratory difficulty, hoarseness, diarrhoea, weight loss, lethargy, asthenia, anorexia and bone pain).

- Calcitonin (CTN) and carcinoembryonic antigen (CEA) doubling time at baseline

- CTN and CEA at every disease assessment timepoint

Death

- Date and cause

Treatment information:

- Previous treatments received for the sporadic MTC (including non-pharmacologic)

- For 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 patients non treated with vandetanib at entry: current and subsequent treatments for symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC: date of start and stop (if available).

- Dose adjustments / discontinuations during follow up (date of adjustment and dose)

- Opioid use: Date, Dose and Route by generic name

The above information, the monitoring of which is specifically recommended in the SmPC, will be collected during the study visits 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 Adverse Event (AE)

An adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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 Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase and fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject 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 (ADR)

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing 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, from informed consent signature until the end of the study follow-up period. For patients who discontinue 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. SAEs occurring in the follow-up period should be reported to AstraZeneca 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 CRF. AstraZeneca 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 AstraZeneca.

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 hospitalisation
- 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 summarised in the clinical study report. Deterioration as compared to baseline in those laboratory values and vital signs should therefore only be reported as AEs if they fulfil 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 (e.g., anaemia versus low haemoglobin 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 greater than or equal to 3 times the upper limits of normal (ULN) **or** total bilirubin greater than or equal to 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.

9.2.8 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one 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 serious adverse events

All SAEs have to be reported, whether or not considered causally related to vandetanib, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca 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.

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 AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, i.e., immediately, or no later than 24 hours of when he or she becomes aware of it.

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 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.

9.3.2 Reporting of spontaneously mentioned adverse drug reactions

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 AZ (in case of an ADRs of an AZ-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 email alert is sent to the designated AstraZeneca representative and to the AstraZeneca Patient Safety data entry site (TCS).

<<Include information according to local regulations of every country. >>

9.3.3 Deaths

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.

10. ETHICAL CONDUCT OF THE NON-INTERVENTIONAL STUDY

The Non-Interventional Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation (ICH), Good Clinical Practices (GCPs), and the applicable legislation on Non-Interventional Studies.

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 Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable 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

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 Informed Consent Form. A copy of the signed Patient Informed Consent Form must be given to the patient.

10.3 Patient data protection

The Patient Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise 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 Informed Consent Form 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 Informed Consent Form will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ, will require direct access to the signed patient informed consent forms. In case source data verification will be planned as quality check, the Patient Informed Consent Form will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Non-Interventional Study.

11. STUDY MANAGEMENT BY ASTRAZENECA

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 select the sample
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca or its representatives. This will be documented in a NIS Agreement between AstraZeneca/delegate and the investigator.

During the study the local MC representative or delegate can implement different activities to assure compliance with AZ 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)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the case report forms (CRFs)
- Ensure that the patient informed consent forms are signed and stored at the investigator's site

- Ensure that the CRFs are completed properly and with adequate quality.

Monitoring activities for:

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

- Must ensure that the Patient Informed Consent Forms are properly signed, dated and stored at the site.

- Source Data Verification:

a) Patient Informed Consent Forms must be checked with the information in Medical Records to ensure the existence of the patients.

b) Some specific study data considered critical for study results validity (e.g 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 (e.g., high rejection rate in a site, continuous lack of availability, repetitive inconsistent answers in the CRF) should be used as potential identification of low protocol compliance by investigators.

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, 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 marketing company representative or delegate must ensure all applicable documents are properly filed at the marketing company 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 NIS 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 AstraZeneca and the Investigator/Institution is signed

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

- Estimated first subject in: 1Q2013

- Estimated last subject in: 2Q2014

- Estimated last subject last visit: 3Q2015

- Estimated date of database lock: 3Q2015

- Estimated date of final study report: 4Q2015

Should AstraZeneca 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 CD 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 patient has been enrolled in the study and when at least 20 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 includes 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, UK.

12.2 Reporting and publication of data

This study is being conducted to fulfil the specific obligation post-authorisation measure for the conditional marketing authorisation. There is a commitment to present the study results by the 4Q 2015.

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

AstraZeneca will communicate the study results to all participating investigators.

AstraZeneca seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals. In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. AstraZeneca endeavours to publish the results of NIS and is committed to ensure that the data are reported in a responsible and coherent manner.

AstraZeneca is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "Each author should have participated sufficiently in the work to take public responsibility for the content."

AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

Other contributors should be listed in the acknowledgments as appropriate.

AstraZeneca will manage the publication of the study results in partnership with the authors; the principle author will take a leading role in this process. AstraZeneca will propose a

suitable journal and/or meeting and timelines for publication production for agreement with the authors.

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.

13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

13.1 Statistical evaluation – general aspects

The data cut off for the analysis will be 14 months after the last patient has been enrolled in the study and when at least 20 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. Twenty PFS events in each treated group will ensure that median PFS can be estimated for each group.

A hazard ratio for the comparison of PFS for vandetanib treated RET mutation positive patients versus vandetanib treated RET mutation negative patients will be derived using a Cox proportional hazards model adjusted for age, sex, CTN doubling time and CEA doubling time. A Kaplan-Meier plot of PFS split by RET mutation status will be presented. Median PFS will be presented, where possible, in the two groups. A parametric interval censored sensitivity analysis will be performed to assess the impact of any potential imbalance in the frequency of RECIST assessments in the two groups. If there are large differences in prognosis between the two groups, then a sensitivity analysis using propensity scores will be considered to assess the impact of this imbalance. Subgroup analyses will be performed for PFS by CTN doubling time and CEA doubling time at baseline

The ORR and DCR will be summarized with corresponding exact 95% CIs amongst RET mutation positive patients treated with vandetanib and amongst RET mutation negative patients treat with vandetanib. Median duration of response and time to response will be summarized, where possible, for the two groups of patients. In addition, duration of response may be summarized graphically. 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.

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

The frequency and percentage of patients with symptoms at each time point will be summarised by RET mutation status. Opioid analgesic use will be summarised descriptively by RET mutation status.

Data for not treated with vandetanib RET mutation negative patients will be summarized with 95% CIs presented when appropriate.

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

A comprehensive Statistical Analysis Plan will be prepared before first subject in.

13.2 Determination of sample size

AstraZeneca and the EMA agreed that a sample size of 80 patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC receiving vandetanib: 40 RET mutation negative and 40 RET mutation positive would be appropriate. This would allow the ORR in each group to be estimated with adequate precision. For example, if 14/40 patients respond, the ORR would be 35% and the corresponding exact 95% confidence interval would be (20.6%, 51.7%).

RET negative patients with symptomatic, aggressive, sporadic, unresectable, locally advanced/metastatic MTC, who do not receive vandetanib but who fulfil all the inclusion criteria and none of the exclusion criteria, with the exception of the contraindications listed in exclusion criteria 3, will be invited to participate in the study as well. However, no more than 40 of these patients will be enrolled.

The aim is to have at least 40 vandetanib RET positive, 40 vandetanib RET negative and no more than 40 not treated with vandetanib RET negative patients recruited from across all sites. In order to achieve that, the enrolment of patients per group will be automatically stopped in the WBDC system to meet those requirements.

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