An International, Randomised, Double-Blind, Two-Arm Study to Evaluate the Safety and Efficacy of Vandetanib 150 and 300 mg/day in Patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma with Progressive or Symptomatic Disease.

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The primary objective of this study is to assess the objective response rates (ORR) for two starting doses of vandetanib, 150 mg and 300 mg in patients with unresectable locally advanced or metastatic MTC having progressive or symptomatic disease....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON37338

Source
ToetsingOnline

Brief title
D4200C00097 - MTC Vandetanib study

Condition

- Thyroid gland disorders
- Endocrine neoplasms malignant and unspecified

Synonym
Unresectable or medullary thyroid carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Medullary Thyroid Carcinoma, Phase IV, Vandetanib

Outcome measures

Primary outcome

1. To assess the ORR for two starting doses of vandetanib, 150 mg and 300 mg, in patients with unresectable locally advanced or metastatic MTC having progressive or symptomatic disease. (OR defined as complete response [CR] + partial response [PR]) as per Response Evaluation Criteria in Solid Tumours (RECIST Version 1.1.) criteria. The ORR is defined as the percentage of patients with a best response of complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 at the end of the 14 month blinded phase (Part A) or before objective progression, whichever comes first.

2. To provide additional information to prescribers of the likely range of response rates with a starting dose of 150 mg/day or a starting dose of 300 mg/day

Study variable: tumour assessments

Secondary outcome

1. To evaluate the safety and tolerability of 150 mg and 300 mg vandetanib: To provide additional information to prescribers of the safety and tolerability profile with a starting dose of 150 mg/day or a starting dose of 300 mg/day. Vortex keratopathy was observed in approximately 30% of vandetanib patients receiving ophthalmology exams on Study 58. The exams in this study, Study 97, will provide further data with 300 mg on the incidence of vortex keratopathy, and allow for photographic documentation of the changes. The effect of vandetanib 150 mg on the cornea has not been evaluated. The effect of vandetanib on the left ventricular ejection fraction has not been studied in previous clinical studies. Provide further data on vandetanib*s effect on QT prolongation with 300 mg. The effect of vandetanib 150 mg on QT prolongation has not been evaluated.
2. To evaluate the time to objective response, duration of objective response, and the best percentage change in TL size: To fully characterize the efficacy profile based on objective response of 150 mg and 300 mg
3. To evaluate the pharmacokinetics (PK) of vandetanib at 150 mg and 300 mg in this patient population: To provide additional information on PK at 150 mg and 300 mg
4. To examine the relationship between PK and QTcF: To provide additional information on PK and QTcF relationship

Study variables:

Safety: recording of adverse events/serious adverse events, Laboratory safety assessments, physical examination, ECG, Echocardiogram, vital signs, ophthalmologic examination.

Pharmacockinetics: Blood samples for the determination of plasma levels of vandetanib during part A only.

Study description

Background summary

On 06 April 2011, vandetanib 300 mg received New Drug Application (NDA) approval from the US Food and Drug Administration (FDA) with the indication for treatment of symptomatic or progressive medullary thyroid carcinoma (MTC) in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic, or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.
As part of the NDA approval process, AstraZeneca committed to conduct a Post-Marketing Requirement (PMR) randomized study in which patients with progressive or symptomatic MTC will be randomized to vandetanib 150 mg or 300 mg daily.

The results of this PMR study will provide data on 150 mg as a starting dose and additional information on the 300 mg dose regarding the likely range of response rates, tolerability, and pharmacokinetics (PK). This information may be helpful to inform decisions about starting dose in certain patient subgroups, accepting that 300 mg is the only dose with a demonstrated clinical benefit in terms of progression free survival (PFS).

Study objective

The primary objective of this study is to assess the objective response rates (ORR) for two starting doses of vandetanib, 150 mg and 300 mg in patients with unresectable locally advanced or metastatic MTC having progressive or symptomatic disease.
The secondary objectives of this study are:
1. To evaluate the safety and tolerability of vandetanib 150 mg and 300 mg
2. To evaluate the time to objective response, duration of objective response, and the best percentage change in target lesion (TL) size while in Part A of the study

3. To evaluate the pharmacokinetics (PK) of vandetanib at 150 mg and 300 mg in this patient population
4. To examine the relationship between PK and QTcF (QT interval corrected for heart rate according to Fridericia)

Study design

This is a randomised, double-blind, international study to evaluate the safety and efficacy of vandetanib 150 and 300 mg/day. The study will consist of a double-blind randomised phase (Part A) and an unblinded phase (Part B). Patients will be followed for efficacy only during the double-blind randomised phase (Part A) of the study that will continue for a maximum of 14 months. No further efficacy data will be collected in Part B, but safety evaluations will continue in Part B until each patient has received vandetanib for a total (Parts A and B) of 2 years, or for 60 days following permanent discontinuation of vandetanib if prior to 2 years.

Intervention

Vandetanib 150 mg or 300 mg will be administered once daily. There will be 3 vandetanib tablet strengths: 50 mg, 100 mg, and 300 mg and 3 placebo tablet sizes: 50 mg, 100 mg, and 300 mg to mimic the respective vandetanib tablets.

Study burden and risks

There may be risks involved in taking this medication, including possible life threatening reactions that have not been identified in the studies done so far. There is always a risk involved in taking a medication but every precaution will be taken and patients are encouraged to report anything that is troubling them.

Patients may experience none, some, or all of the following:
Very Common (experienced by more than 10% of patients taking vandetanib)
Diarrhoea, fatigue, nausea, vomiting, loss of appetite, indigestion, abdominal pain, headache, elevated blood pressure, weight loss, rash, asymptomatic changes in the electrical activity of the heart, anxiety, and trouble sleeping.
Patients taking vandetanib may develop a skin rash, which may become severe, but is manageable with proper treatment. Vandetanib may also make the skin more sensitive to the sun. It is recommended that patients take preventative action to prevent the rash from occurring whilst receiving study medication and for 3 to 4 weeks after stopping treatment by using the following guidelines:
•Avoiding direct sunlight, •Covering sun exposed skin with clothing (long trousers, long sleeve shirts, and hats), •Using a sun protection factor (SPF) 45 or higher sun protection cream, •Notifying the Study Doctor when the first sign of a rash occurs so he/she may take the appropriate steps in preventing the rash from becoming severe.

AstraZeneca has observed changes in ECGs in some patients being treated with vandetanib. These changes in the ECG may be drug-related and usually occur without symptoms; accordingly, frequent safety follow-up visits have been built into all studies. Similar changes in the ECGs of patients receiving other medications have led to heart rhythm changes, some of which have been life threatening. However, it is estimated that between 0.1% to 1% of patients receiving vandetanib 300 mg have developed heart rhythm changes linked to life-threatening arrhythmia called Torsades de Pointes. Torsades de Pointes has been associated with sudden death. If any such changes are noted on your ECGs, you may need to attend additional visits for further safety assessments. The risk of developing changes in the ECG and serious heart rhythm changes will be greater if a patient has diarrhoea, blood electrolyte imbalance (imbalance of minerals in your blood), vomiting, high fever, faintness or dizzy spells, or are unable to maintain a normal diet. A patient should report any of these symptoms to their Study Doctor immediately. A patient should review his/her medications and diet with the Study Doctor at each visit while continue receiving study medication.
Changes in the heart rhythm may cause rapid or irregular heart beat, dizziness, light-headedness, chest discomfort, shortness of breath, or losing consciousness. These or other new symptoms or possible side effects should be reported immediately to the Study Doctor.

In addition, anxiety, depressed mood, and trouble sleeping have been seen in some patients. These events may not be directly related to vandetanib, but rather to symptoms associated with cancer or other effects related to vandetanib such as skin rash.

Common (Experienced by 1% to 10% of patients taking vandetanib):
Weakness, dehydration, abnormalities in tests of blood or urine (generally mild), stroke, cough, mild nose bleeding, feeling depressed, abnormal taste in mouth, dry mouth, blurry vision, dry or irritated eyes, and kidney stones have been reported.

Uncommon (Experienced by fewer than 1% of patients taking vandetanib):
Small bluish/purple spots on the skin are uncommon. Heart failure, which is the weakening of the heart's ability to pump blood, has also been reported and may be related to vandetanib. The heart function will be monitored with an echocardiogram. If significant changes occur, the therapy may need to stop. Some patients have had seizures while taking vandetanib, and in one case a patient with seizures also had swelling in the brain that was found on an MRI scan, which got better after vandetanib was stopped. If a patient develops seizures, dizziness, headache, changes in vision, or confusion, the Study Doctor will need to know as soon as possible. These may be symptoms of reversible posterior leukoencephalopathy syndrome (RPLS).
A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough because of an inflammation of scar tissue formation in the lungs, although this symptom could also be due to the

underlying lung cancer.
A few patients have developed an inflammation of the pancreas.

Additional Risk (not associated with vandetanib, but may be associated with participation in the study):
Drawing Blood - The taking of a blood sample may cause some discomfort. Risks associated with drawing blood include pain, bruising, light-headedness, and on rare occasions, infection.
Imaging - CT Scan - A CT examination involves having a dye injected into a vein. As a result, a patient may experience a slight burning feeling at the injection site, a metallic taste in your mouth, and hot flushes. Very rarely an allergic reaction can appear as a result of a contrast dye injected during the scan. Such allergic reaction can involve itching, rash, or in severe cases, difficulty in breathing and lowering of blood pressure. Additionally, these CT scans are associated with exposure to a very small amount of radiation.
Imaging - MRI Scan - Those who suffer from claustrophobia (fear of enclosed spaces) will probably find an MRI scan uncomfortable. The MRI scanner is very noisy. MRI scans do not involve the use of radiation. When needed, a special type of contrast dye will be injected into a vein to improve the quality of images. MRI contrast dye reactions are rare and usually no more severe than a headache.

Women of Childbearing Potential and Men with Partners of Childbearing Potential
There might be unknown risks to the unborn baby if a patient is pregnant or if a patient becomes pregnant during the study; or if a patient is a man with a partner who becomes pregnant during the study. Due to these risks, a patient must not take part in this study if she is pregnant, plans to become pregnant, or is breast-feeding a baby during the research study period; or if his partner plans to become pregnant during the research study period.

It is hoped that the study treatments will help patients. However, this cannot be guaranteed. The information that becomes available from this study may help treating future subjects with medullary thyroid cancer better.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of informed consent prior to any study specific procedures being performed.
2. Female or male aged 18 years and over.
3. Previously confirmed histological diagnosis of unresectable, locally advanced or metastatic, hereditary or sporadic MTC.
4. Objective disease progression within the previous 14 months prior to enrolment, and/or have one or more symptoms that the Investigator believes to be related to the patient*s MTC.
5. World Health Organisation (WHO) or Eastern Cooperative Oncology Group (ECOG) Performance status 0-2.
6. Negative pregnancy test (urine or serum) for female patients of childbearing potential.
7. Measurable disease defined as at least one lesion, not irradiated within 12 weeks of the date of randomisation, 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 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.

Exclusion criteria

1. Unstable brain metastases or spinal cord compression that requires treatment, unless the treatment ended at least 4 weeks before randomisation and the condition has been stable without steroid treatment for at least 10 days prior to randomisation.
2. Major surgery (includes any surgery that carries significant risk of blood loss, extended

periods of general anaesthesia, or requires at least an overnight hospital admission) within 28 days before randomisation.
3. The last dose of prior chemotherapy received less than 28 days prior to randomisation.
4. Radiation therapy if not completed 28 days prior to randomisation.
5. Any unresolved chronic toxicity greater than CTCAE Grade 2 from previous anticancer therapy (this criterion does not apply to alopecia).
6. Serum bilirubin greater than 1.5 x the upper limit of reference range (ULRR), this criterion does not apply to patients with Gilbert*s Disease.
7. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 x ULRR, or greater than 5.0 x ULRR if judged by the Investigator to be related to liver metastases.
8. Creatinine clearance <50 mL/min
9. Potassium <4.0 mmol/L despite supplementation, or above the CTCAE Grade 1 upper limit. Magnesium below the normal range despite supplementation, or above the CTCAE Grade 1 upper limit.
10. Significant cardiac event (e.g., myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease >=2 within 12 weeks before randomisation or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.
11. Cardiac ejection fraction <40% as measured by echocardiogram.
12. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.
13. Congenital long QT syndrome.
14. Any concomitant medications that are known to be associated with Torsades de Pointes or potent inducers of cytochrome P450 3A4 (CYP3A4) function and/or any prohibited medications.
15. History of QT prolongation associated with other medications that required discontinuation of that medication.
16. QTcF correction unmeasurable or >450 ms on screening ECG
17. Participation in a clinical study and/or receipt of an investigational drug within 28 days prior to randomisation (participation in the survival follow-up period of a study is not an exclusion).
18. Previous exposure to vandetanib.
19. Previous randomisation in the present study.
20. For women only - currently pregnant or breast feeding.
21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, its agents, and/or staff at the study site).
22. Previous or current malignancies of other histologies within the last 5 years, with the exception of tumours associated with MEN2a and MEN2b, in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-08-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caprelsa
Generic name:	Vandetanib

Ethics review

Approved WMO Date:	05-03-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-08-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-08-2012

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-004701-24-NL
ClinicalTrials.gov	NCT01496313
CCMO	NL39592.058.12