Efficacy and safety of lanreotide Autogel® 120 mg administered every 14 days in well differentiated, metastatic or locally advanced, unresectable pancreatic or midgut neuroendocrine tumours having progressed radiologically while previously treated with lanreotide Autogel® 120 mg administered every 28 days.

Published: 02-09-2015
Last updated: 20-04-2024

Objectives:Primary:• To assess progression free survival (PFS) when treated with lanreotide Autogel® 120 mg administered every 14 days based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.0, and according to central review.Secondary:•...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43877

Source
ToetsingOnline

Brief title
Clarinet Forte

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
kanker, neuro-endocriene tumoren

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Innovation
Source(s) of monetary or material Support: Ipsen Innovation

Intervention

Keyword: 14 days, injection, Lanreotide Autogel, Neuroendocrine tumours

Outcome measures

Primary outcome

The primary endpoint is median PFS (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression or death). Disease progression will be assessed by tumour response evaluation according to RECIST v1.0, every 12 weeks, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review to ensure intra and intersubject consistency and reliability.

Secondary outcome

Secondary endpoints and evaluations:

- Median time to progression (defined as time from first injection of lanreotide Autogel® 120 mg every 14 days to progression).

- Proportion of subjects alive and without progression every 12 weeks.

- Overall survival at Week 48 and at the end of the study for each cohort.

- ORR every 12 weeks as per RECIST v1.0. ORR is defined as the proportion of subjects who achieve either complete response (CR) or partial response (PR).
- DCR evaluated according to RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort. The DCR is defined as the rate of CR plus PR plus SD.
- Best overall response according to RECIST v1.0 (defined as the best response recorded from the initiation of treatment until disease progression).
- Median duration of SD according to RECIST v1.0 (defined as the time from first injection of lanreotide Autogel® 120 mg every 14 days until the first occurrence of progressive disease by central assessment).
- Factors associated with PFS will include but will not be limited to: hepatic tumour olume <=25% versus >25%, grade 1 versus grade 2, previous surgery of the primary tumour (yes/no), Ki67 <10% versus >=10%, duration of treatment with lanreotide Autogel® 120 mg every 28 days, time from diagnosis to progressive disease during the study.
- Symptom control (diarrhoea, flushing) at Baseline, Weeks 8 and 12 and every 12 weeks thereafter, and at the End of Study visit, as measured by the total number of stools and flushing episodes during the 7 days prior to the visit reported orally by the subject to the investigator.
- Quality of life measured at Baseline, Week 12 and every 12 weeks thereafter, and at the End of Study visit, after diagnosis of progression, using European Organisation into the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) v3.0 and Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumour 21 (QLQ-GI.NET21; 2006), and the EuroQoL

5 dimensions, 5 levels (EQ-5D-5L) v1.0 questionnaires.

- pNET cohort:

• nonspecific tumour biomarkers (CgA, NSE and 5 HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5 HIAA at all scheduled visits; urinary 5 HIAA at Baseline, Week 12 and at the End of Study visit only). Note: at all scheduled visits, except Baseline, plasma/urinary 5 HIAA should only be performed in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above ULN) at Baseline.

• pNET specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, SST, *) at Baseline, every 12 weeks thereafter and at the End of Study visit: only for the tumour biomarkers above normal range at Baseline.

- Midgut cohort:

• nonspecific tumour biomarkers (CgA, NSE and 5 HIAA) at Baseline, every 12 weeks thereafter and at the End of Study visit (plasma 5 HIAA at all scheduled visits; urinary 5 HIAA at Baseline, Week 12 and at the End of Study visit only).

Tertiary endpoints and evaluations:

- Variation in TGR across *retrospective* (lanreotide Autogel® 120 mg every 28 days) and *prospective* (reduced dosing interval) treatment periods. The TGR is calculated from tumour size (sum of the longest diameters of target lesions as per RECIST criteria) and tumour volume. Tumour size will be measured from MRI

(optimal) or CT scans collected during lanreotide Autogel® 120 mg every 28 day

treatment period

(i.e. the scan used for disease progression evaluation), and using MRI every 12

weeks during the reduced dosing interval period.

- Tumour response as per exture analysis on CT or MRI.

Study description

Background summary

Neuroendocrine tumors (NETs) are rare tumors that originate in the neuroendocrine system . Neuroendocrine cells are located in many tissues in the body. In NET these cells grow uninhibited and they produce hormones and hormone-like substances. Pancreatic neuroendocrine and Midgut Tumors are two types of gastro- intestinal neuroendocrine Tumors.

Initial treatment, when possible, is the surgical removal of the tumour. The study drug, lanreotide Autogel, is a manmade form of a natural hormone called somatostatin. Lanreotide Autogel® 120 mg every 28 days is used for the treatment and control of the growth of some advanced tumors of the intestine and the pancreas called gastro-enteropancreatic neuroendocrine tumors or GEP-NETS.

Previous research studies have shown that lanreotide and similar drugs may decrease and stabilise the size of tumours. They also showed the activity of Lanreotide Autogel® 120 mg every 28 days on tumour control and their positive effect relief of clinical symptoms.

This study is designed to assess whether the study drug Lanreotide Autogel® 120 mg, given every 14 days can stop your tumour growing after treatment with Lanreotide Autogel® (120 mg every 28 days).

Study objective

Objectives:
Primary:
• To assess progression free survival (PFS) when treated with lanreotide Autogel® 120 mg administered every 14 days based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.0, and according to central review.

Secondary:
• To evaluate the clinical and biological safety profile.
• To evaluate time to progression.
• To evaluate PFS rate every 12 weeks.
• To evaluate overall survival at Week 48 and at the end of the study period in each cohort.
• To evaluate the objective response rate (ORR) as per RECIST v1.0 every 12 weeks.
• To evaluate the disease control rate (DCR) as per RECIST v1.0 at Weeks 24 and 48 and at the end of study period in each cohort.
• To evaluate the best overall response as per RECIST v1.0.
• To evaluate the duration of stable disease (SD) as per RECIST v1.0.
• To detect predictive factors of PFS.
• To evaluate the effect on symptoms (diarrhoea, flushing).
• To evaluate quality of life.
• To evaluate the changes in tumour biomarkers:
- pNET cohort: nonspecific tumour biomarkers (Chromogranin A (CgA), neuron specific enolase (NSE) and 5 hydroxyindoleacetic acid (5 HIAA); 5-HIAA only in subjects with symptoms of carcinoid syndrome (diarrhoea and/or flushing) or if urinary 5-HIAA was elevated (above upper limit of normal (ULN)) at Baseline) and pancreatic neuroendocrine tumours (pNET) specific tumour biomarkers (e.g. pancreatic polypeptide, gastrin, glucagon, somatostatin (SST), *; only for the tumour biomarkers above normal range at Baseline).
- Midgut cohort: nonspecific tumour biomarkers (CgA, NSE and 5 HIAA).
• To evaluate the appearance of antilanreotide antibodies.
• To evaluate the pharmacokinetic (PK) profile of lanreotide and to evaluate, if any, the relationship between PK and pharmacodynamics (PD; PFS, tumour response or CgA).
• To evaluate, if any, the relationships between PK parameters and the safety outcomes.

Tertiary:
• To evaluate the effect on tumour growth rate (TGR) prior to and during reduced dosing interval administrations.
• To evaluate changes in texture analysis on computed tomography (CT) or magnetic resonance imaging (MRI).

Study design

This is a phase II, multicentre, prospective, open label, noncomparative, exploratory study.

Intervention

Following the Screening visit (Visit 1) and a Screening period of up to 28 days, where eligibility tests and assessments will be performed, eligible

subjects will be treated with lanreotide Autogel® at a reduced dosing interval (i.e. 120 mg every 14 days) beginning at Baseline (Visit 2).

Study visits will be performed at Weeks 2, 4, 8, 12, 24, 36 and 48 (both cohorts), and Weeks 60, 72, 84 and 96 (midgut cohort only). An End of Study visit is scheduled approximately 2 weeks after the study visit at which progression is confirmed or after Weeks 48 (pNET cohort) or 96 (midgut cohort) for nonprogressive subjects, once central review of the radiological imaging is available.

As long as 25 events have not been observed in the respective cohorts, subjects who have not progressed at Week 48 (pNET cohort) or Week 96 (midgut cohort) will continue study treatment with lanreotide Autogel® 120 mg every 14 days and additional visits will be performed every 12 weeks until disease progression, death or unacceptable toxicity or tolerability.

Tumour response will be assessed every 12 weeks by tumour response evaluation according to RECIST v1.0, measured using the same imaging technique (CT scan or MRI) for each subject throughout the study, and by independent central review. Additional efficacy assessments include symptom control (diarrhoea and flushing) and quality of life, as well as factors associated with PFS, and nonspecific (both cohorts) and pNET-specific (pNET cohort only) tumour biomarker concentrations. Safety evaluations will be performed throughout the study and will include the collection of clinical and biological safety data, including adverse events (AEs), vital signs, physical examination findings, serum haematology and biochemistry panels, urinalysis, and liver and pancreatic enzyme concentrations, as well as electrocardiogram (ECG) and gallbladder echography. PK evaluations will consist of lanreotide concentrations at selected timepoints throughout the study. The presence of lanreotide antibodies will be measured and blood samples for biobanking may also be taken from subjects who consent to the optional biobanking programme. The overall duration of the study will be approximately 102 weeks assuming at least 25 subjects progress within 48 and 96 weeks in the 2 cohorts respectively.

Study burden and risks

The study overall has more frequent clinic visits (e.g. PK sampling) and more comprehensive monitoring compared with normal clinical practice.

Possible side effects and other undesirable effects
- Blood sampling: painful or may cause some bruising
- CT or MRI-scan: exposure to radiation
- Adverse Events of the study medication (as described in the Investigator's Brochure)

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) Male or female subjects aged 18 years old or older.;2) Histopathologically confirmed well differentiated (grade 1 or grade 2 according to the WHO 2010 classification), metastatic or locally advanced, unresectable pNET (pNET cohort) or midgut NET (midgut cohort) with or without hormone related syndromes, with a proliferation index (Ki67) <=20%.;3) Positive somatostatin receptors type 2 (SSTR2) as assessed by imaging (scintigraphy or positron emission tomography (PET) scan) in the organs of target lesions.;4) Progression as assessed by an independent central reviewer according to RECIST v1.0 from radiological imaging (CT scan or MRI) while receiving first line treatment with lanreotide Autogel® at a standard dose of 120 mg every 28 days for at least 24 weeks (6 injections). Progression must be radiologically documented using the same technique of images (CT scan or MRI) within 24 months prior to enrolment. Inclusion into the study must be within 28 days of the radiological imaging that is performed to document progression.;5) Eastern Cooperative Oncology Group

(ECOG) Performance Status (PS) of 0 to 2.;6) Provision of written informed consent prior to any study related procedures. ;7) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must provide a negative urine pregnancy test at Screening, and use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 2 months after participation in the study. Acceptable methods of contraception include double barrier method, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted and injected).;8) Subjects must be willing and able to comply with study restrictions and willing to return to the clinic for the follow up evaluation as specified in the protocol.

Exclusion criteria

1) Has poorly differentiated grade 3 NET or rapidly progressive NET (within 12 weeks of initiation of lanreotide Autogel® 120 mg every 28 days) as per RECIST v1.0. ;2) Has been diagnosed with VIPoma (i.e. Verner Morrison syndrome), insulinoma, foregut (except for pNET), hindgut NET, unknown primary NET or multiple endocrine neoplasms (MEN).;3) Has progressed during treatment with somatostatin analogues (SSAs) other than lanreotide Autogel® 120 mg.;4) Has been previously treated with any antitumour agent for NET other than lanreotide Autogel® 120 mg every 28 days: chemotherapy, molecular targeted therapy, peptide receptor radionuclide therapy (PRRT) or interferon.;5) Has had major surgery related to the studied disease within 3 months prior to entering the study. Previous debulking surgery and liver-directed therapies are acceptable as long as tumour burden is measurable (other target lesions).;6) Has gallbladder lithiasis at Screening echography or a history of cholelithiasis with no cholecystectomy since then.;7) Has had previous cancer, except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus and/or subjects treated with curative intent and free from disease for more than 5 years.;8) Was treated with any other investigational medicinal product (IMP) within the last 30 days before study entry.;9) Is pregnant or lactating. ;10) Has abnormal findings at Screening, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety.;11) Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.;12) Has been previously screened in this study.;13) Has a history of hypersensitivity to lanreotide Autogel® or drugs with a similar chemical structure, or any excipient used in the formulation.;14) Is likely to require treatment during the study with drugs that are not permitted by the study protocol. ;15) Has a history of, or known current, problems with substance or alcohol abuse.;16) Vulnerable subjects (i.e. subjects who are under legal protection, who are interned due to a mental disease and who are kept in detention).;17) Subjects who have a link with the sponsor, the clinical trial site or the investigator (medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the sponsor).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lanreotide Autogel
Generic name:	Lanreotide acetate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	02-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	10-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	19-02-2016
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-005607-24-NL
CCMO	NL54223.078.15
Other	The trial will be registered in http://www.ClinicalTrials.gov but registration is not yet complete

Study results