Phase IIa, open label, dose ascending study to determine the maximum tolerated dose, safety and tolerability, pharmacokinetics and pharmacodynamics of a single dose of lanreotide PRF in subjects with acromegaly previously treated and controlled with either ocreotide LAR or lanreotide Autogel.

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Primary:*To identify the maximum tolerated dose (MTD) and to investigate the pharmacokinetics (PK) of a single dose of lanreotide PRF in subjects with acromegalySecondary:*To investigate the safety and tolerability of a single dose of lanreotide PRF…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON45228

Source
ToetsingOnline

Brief title
IPSEN

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Acromegaly, Gigantism

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Pharmaceuticals
Source(s) of monetary or material Support: IPSEN Group

Intervention

Keyword: Acromegaly, Lanreotide, Octreotide, Somatostatin analogue

Outcome measures

Primary outcome

Safety variables:

* AEs, throughout the study.

* Vital signs (supine and standing blood pressure and heart rate, and body temperature) at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.

* Physical examination at Screening, Baseline (predose on Day 1), 6 and 24 hours postdose, and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.

* 12 lead ECG, QTc interval will be calculated using Fridericia methodology in all subjects at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, 24 hours postdose, and at Weeks 2, 5 and 13.

* Clinical laboratory assessments: haematology, coagulation, clinical

biochemistry, urinalysis at Screening, Baseline (predose on Day 1), 6 hours postdose on Day 1, Day 3, and Weeks 2, 3, 4, 5, 9 and 13 of the treatment period.

* HbA1c at Screening and Week 13.

* Estimated glomerular filtration rate (eGFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula [1], at Screening, Baseline (predose on Day 1), and Weeks 2, 5, 9 and 13 of the treatment period.

* Gallbladder echography at Screening, Week 5 and Week 13 of the treatment period.

* Putative antibodies to lanreotide at Baseline (predose on Day 1) and Week 13.

* Evaluation of injection site reactions (appearance, local symptoms). These will be evaluated on a specific form in the electronic case report form (eCRF) at 1 and 6 hours postdose on Day 1, 24 hours postdose and at Weeks 2, 3, 4, 5, 7, 9, 11 and 13 of the treatment period.

Pharmacokinetic variables:

Lanreotide serum concentration at the following timepoints after administration of lanreotide PRF:

* Baseline (predose on Day 1 of lanreotide PRF administration).

* At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1).

* At 24 hours postdose (Day 2).

* On Days 3 and 5, and at Weeks 2, 3, 5, 9 and 13 after lanreotide PRF administration (the Week 13 sample will be on Day 85 and will correspond to the concentration at the end of the dosing interval (Ctrough)).

* Noncompartmental analysis will be performed and the following PK parameters will be computed: Ctrough, maximum serum concentration (Cmax), time to maximum serum concentration (Tmax), area under the serum concentration time curve from time 0 to 85 days (AUC0 85), area under the concentration time curve extrapolated to infinity (AUC0 *), apparent terminal half life (t1/2), mean residence time (MRT), apparent clearance (CL/F) and apparent volume of distribution (V/F).

Excipient serum concentration at the following timepoints:

* Baseline (predose on Day 1 of lanreotide PRF administration).
* At 1, 2, 4, 6, 8 and 12 hours postdose on the day of dosing (Day 1), at 24 hours postdose (Day 2), and on Days 3 and 5 after lanreotide PRF administration.
* Noncompartmental analysis of the excipient time concentration data will be performed and the following PK parameters will be computed: Cmax, Tmax, area under the serum concentration time curve from time 0 to last quantifiable timepoint (AUCt), AUC0 *, t1/2, MRT, CL/F and V/F.

Secondary outcome

Pharmacodynamic variables:

The following PD variables will be assessed in all subjects:

* IGF 1 at Screening, Baseline (predose on Day 1), at 6 hours postdose on the day of dosing (Day 1) and at Weeks 5, 9 and 13.
* GH cycle (five sampling times with a sample every 30 minutes for 2 hours in the morning) at Screening, Baseline (predose on Day 1) and at Weeks 5 and 13.
* Random GH sample at 6 hours postdose on the day of dosing (Day 1) and at Week

9.

* Free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating

hormone (TSH) and prolactin (PRL) at Screening, Baseline (predose on Day 1),

and at Weeks 2, 5 and 13 of the treatment period.

Study description

Background summary

Acromegaly is a rare (incidence approximately 3 cases per million persons per year; prevalence approximately 60 per million), chronic disease caused by excessive secretion of growth hormone (GH) from a pituitary tumour. Increased plasma levels of GH cause the symptoms and pathology of the disease, either directly through actions on target tissues, or indirectly by stimulating excessive secretion of insulin like growth factor 1 (IGF 1).

Disease control of acromegaly consists of different components: biochemical control, tumour volume reduction and improvement of clinical symptoms. GH and IGF 1 concentrations are the main biochemical markers used to measure the response to treatment and represent the most frequent primary endpoints in clinical trials that evaluate efficacy. Both GH and IGF 1 responses have been associated with improved prognosis and mortality decrease.

The treatment of choice is trans sphenoidal surgery, sometimes in association with radiotherapy. However, despite these measures acromegaly remains active in many patients, as defined by increased systemic levels of GH and IGF 1, the persistence of clinical symptoms, and increased morbidity and mortality. For example, between 40% and 60% of macroadenomas are unlikely to be controlled with surgery alone. Primary medical therapy or surgical debulking followed by medical therapy and/or radiation therapy are options for treatment of such tumours.

Somatostatin analogues (SSTa) successfully reduce GH and IGF 1 secretion in approximately 70% of patients. They alleviate many symptoms of acromegaly, improve related comorbid complications, and may reduce or stabilise tumour size in a subset of patients.

Compared to short acting SSTa, long acting formulations have been shown to provide equivalent or better control of acromegaly. The main adverse events (AEs) associated with SSTa are gastrointestinal disorders, including abdominal

cramps and an increased incidence of gallbladder sludge and/or stones.

Study objective

Primary:
*To identify the maximum tolerated dose (MTD) and to investigate the pharmacokinetics (PK) of a single dose of lanreotide PRF in subjects with acromegaly

Secondary:
*To investigate the safety and tolerability of a single dose of lanreotide PRF
*To investigate the pharmacodynamics (PD) of a single dose of lanreotide PRF
*To investigate the PK of the excipient

Exploratory:
Biobanking of blood samples for further biomarkers analysis in subjects who consent to the exploratory part of the study

Study design

This is an open label, dose ascending study to assess the PK, PD, safety and tolerability of a single dose of lanreotide PRF. Doses of 180 mg, 270 mg and 360 mg will be investigated in adults with acromegaly previously treated and controlled with a stable dose of either octreotide LAR or lanreotide Autogel. The study consists of a 4 week run in period, followed by a 12 week treatment period, and then a 12 week follow up period.

Intervention

Eligible subjects will enter a 4 week screening period, during which they will receive the same single dose of either octreotide LAR or lanreotide Autogel as their previous treatment (Day *28). A 12 week treatment period will then commence, during which subjects will receive one deep subcutaneous injection of lanreotide PRF on Day 1 (4 weeks after the last octreotide LAR administration). It is planned to include three cohorts of subjects; Cohort 1 will receive lanreotide PRF 180 mg, Cohort 2 will receive 270 mg and Cohort 3 will receive 360 mg.

Study burden and risks

The study overall has more frequent clinic visits and more comprehensive monitoring compared with normal clinical practice. Screening (Visit 1) involves patient interview, a physical exam, a 12 lead ECG, venepuncture (fasting), urine collection and Gallbladder echography The main burden falls on the day of study drug administration (Visit 2) where hospitalization for 24 hours and serial venepuncture is required. Procedures at subsequent clinic visits

(treatment and follow-up) will be of less burden for the patients. The side effects associated with the study medication are well characterized, and patients will be monitored carefully for injection site reactions. The study burden and risks are balanced by the potential for extended (up to 12 weeks) relief from or lessening of the signs and symptoms of acromegaly.

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

All subjects must fulfil all of the following criteria to be included in the study:
- Documented diagnosis of acromegaly.
- Provided written informed consent prior to any study related procedures.
- Between 18 and 75 years of age inclusive.
- Female of nonchildbearing potential or male. Nonchildbearing potential is defined as being

postmenopausal for at least 1 year, or women with documented infertility (natural or acquired).
- Male subjects must agree that, if their partner is at risk of becoming pregnant, they will use a medically accepted, effective method of contraception (i.e. condom) for the duration of the study (up to 7.5 months).
- Treatment with a stable dose of either octreotide LAR or lanreotide Autogel for at least 3 months immediately prior to study entry, with confirmation of disease control during this treatment period (documentation of age adjusted IGF-1 < 1.3 x upper limit of normal (ULN), based on local lab results, during Screening period).
- If the subject is receiving treatment for hypertension, the dose has been stable for at least 1 month prior to study entry.
- Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow up evaluation as specified in the protocol.

Exclusion criteria

Subjects will not be included in the study if the subject:
- Has undergone radiotherapy within 2 years prior to study entry.
- Has been treated with a dopamine agonist and/or GH receptor antagonist or has undergone pituitary surgery within 3 months prior to study entry.
- Is anticipated to require pituitary surgery or radiotherapy during the study.
- Has clinically significant hepatic abnormalities and/or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) *3 x ULN and/or alkaline phosphatase (AP) *2.5 x ULN and/or total bilirubin *1.5 x ULN and/or gamma-glutamyl transpeptidase (GGT) *2.5 x ULN during the Screening period (central laboratory results) or a history of these findings when on somatostatin analogue (SSTa) treatment.
- Has clinically significant pancreatic abnormalities and/or amylase and/or lipase *1.5 x ULN during the Screening period (central laboratory results).
- Has any significant renal abnormalities and/or creatinine *1.5 x ULN during the Screening period (central lab results).
- Has uncontrolled diabetes (glycosylated haemoglobin (HbA1c) *9%, centrally assessed during the Screening period), or has diabetes treated with insulin for less than 6 months prior to study entry.
- Has any known uncontrolled cardiovascular disease or had any of the following within 6 months of Screening: ventricular or atrial dysrhythmia *grade 2, bradycardia *grade 2, electrocardiogram (ECG) QT interval corrected (QTc) prolonged *grade 2, myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, hypertension not adequately controlled by current medications.
- Use of any hormone replacement therapy (HRT) with oestrogens.
- Has symptomatic gallstones/sludge at the Screening Visit echography (local assessment) OR is asymptomatic but has echography showing clear evidence of impending inflammation such as localized mucosal thickening suggesting the subject is at high risk of developing acute disease. Subjects with asymptomatic gallstones/sludge and otherwise normal

echography may be entered at the discretion of the investigator.
- Has abnormal findings during the Screening period, any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject*s safety.
- Has been treated with any other investigational medicinal product (IMP) prior to the first study visit without undergoing a washout period of seven times the elimination half life of the investigational compound.
- Has a known hypersensitivity to any of the test materials or related compounds.
- Is likely to require treatment during the study with drugs that are not permitted by the study protocol.
- Has a history of, or known current, problems with alcohol or drug abuse.
- Has any mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

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):	24-06-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lanreotide PRF
Generic name:	Lanreotide acetate

Ethics review

Approved WMO Date:	11-12-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2017
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	EUCTR2014-002389-62-NL
CCMO	NL51243.078.14