A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy and Safety of Octreotide Capsules in Patients Who Previously Tolerated and Demonstrated Biochemical Control on Injectable Somatostatin Receptor Ligands (SRL) Treatment

Published: 17-07-2017
Last updated: 13-04-2024

- To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on SRLs.- To assess maintenance of biochemical control, based on GH, with…

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

Summary

ID

NL-OMON48842

Source
ToetsingOnline

Brief title
Optimal

Condition

- Hypothalamus and pituitary gland disorders
- Endocrine neoplasms benign

- Nervous system neoplasms benign

Synonym
Acromegaly, pituitary tumor

Research involving
Human

Sponsors and support

Primary sponsor: Chiasma, Inc.
Source(s) of monetary or material Support: Sponsor is Chiasma Inc.

Intervention

Keyword: acromegaly, capsules, ocreotide, placebo-controlled

Outcome measures

Primary outcome

The proportion of patients who maintain their biochemical response at the end of the DPC period.

Maintenance of response will be defined by using the average IGF-1 level of the last 2 available assessments between weeks 34 and 36 in the DPC period. If the average IGF-1 is * 1 × ULN, a patient will be classified as a responder (i.e., maintained their biochemical response). If the average IGF-1 is > 1 × ULN, a patient will be classified as a non-responder. Patients who discontinue study medication during the DPC period for any reason will be classified as nonresponders for the primary analysis, regardless of their IGF-1 values.

Secondary outcome

- Proportion of patients who maintain GH response (i.e., GH < 2.5 ng/mL) at week 36, out of those who were responders (i.e., GH < 2.5 ng/mL) on SRL injections at Screening. GH response will be defined using the mean integrated GH value, based on 5 assessments, 30 minutes apart.

- Time to loss of response: Loss of response is defined as the earliest time

when the IGF-1 of 2 consecutive visits is > 1×ULN, after the patient is treated

for at least 2 weeks with 4 capsules per day.

- Time to loss of response: Loss of response is defined as the earliest time

when the IGF-1 of 2 consecutive visits is > 1.3×ULN, after the patient is

treated for at least 2 weeks with 4 capsules per day.

- Proportion of patients who begin rescue treatment prior to and including week

36.

Study description

Background summary

Acromegaly is a rare disorder of disproportionate skeletal, tissue, and organ growth arising from hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The elevated GH and IGF-1 levels lead also to a wide range of cardiovascular, respiratory, endocrine, and metabolic co-morbidities. In over 95% of cases the etiology is attributed to GH-producing benign pituitary adenoma (Ben-Shlomo and Melmed, 2008; Melmed, 2009; Melmed et al., 2009).
Treatment options for acromegaly include surgical resection of the pituitary adenoma, radiotherapy, and drug therapy to reduce GH and IGF-1 levels to normal values. Currently, there are three drug classes available for the treatment of acromegaly: somatostatin receptor ligands (SRLs) or somatostatin analogs (octreotide, lanreotide and pasireotide), dopamine agonists (bromocriptine and cabergoline), and a GH receptor antagonist (pegvisomant) (Melmed et al., 2009; Melmed et al., 2014). SRLs are, at present, the most widely used drugs to control acromegaly. Chiasma has developed octreotide capsules, a new formulation of octreotide for oral delivery. It is an enteric coated capsule filled with an oily suspension of unmodified octreotide formulated with transient permeability enhancer (TPE®)1 excipients. The enteric coating allows the intact capsule to pass through the stomach and disintegrate when it reaches the higher pH of the small intestine to discharge octreotide capsules suspension.
In the complete response letter, to Chiasma NDA, the FDA noted that in order to address the deficiency listed, Chiasma needs to provide substantial evidence that treatment with octreotide capsules has the effect it purports to have

under the conditions of use recommended in the labeling for patients with acromegaly in a new clinical trial. The study design, conduct of the study and primary analysis should minimize biases to the extent possible to ensure the effect size captured is attributable to octreotide capsules and not to a confounder. The study should enroll patients from the United States and be of sufficiently long duration to ensure that control of disease activity is stable. The FDA strongly recommended that the study be a randomized, double-blind, placebo-controlled study.

Study objective

- To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on SRLs.
- To assess maintenance of biochemical control, based on GH, with octreotide capsules compared to placebo;
- To evaluate the safety profile of octreotide capsules compared to placebo.

Open Label Extension objectives:
- To assess the long-term efficacy and safety of octreotide capsules in acromegaly patients

Study design

This will be a phase 3, randomized, dubbel-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL).
The core study will consist of three phases: a Screening phase of maximal 8 weeks, a double-blind treatment phase (DBP) of 36 weeks and Follow-Up phase of maximal im 12 weeks.
For suitable patients there is a Study Extension treatment phase of minimal 1 year which will continue until the date when the study medication becomes commercially available in the applicable region or country or when the Sponsor decides to terminate the study.
A Steering Committee (SC) will act in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion.
An Independent Data Monitoring Committee (IDMC) will act in an advisory capacity to the Sponsor to monitor patient safety during the study.
For a more explicit explanation of the study design see 'Intervention' section.

Intervention

After the Screeningphase of maximal 8 weeks, suitable patients who are biochemically controlled (defined as IGF-1 * 1.0 × ULN) are randomised to a group that will be treated for a maximum of 36 weeks (DPC) with either

octreotide capsules or placebo capsules. Patients who showed a detoriation in symptoms or IGF-1 values during these 36 weeks, will be put back on SRL injections and be asked by the treating physician to complete the 36 week period according protocol.
Patients that completed the main study (Screening and DPC), either on capsules or with SRL injections and fulfil certain criteria, will be requested to participate in the Study Extension Phase. During this phase they will receive octreotide capsules for a minumum of one year, and possibly longer until the product is registered and available in that particular country or until the sponsore decides to end the study.
Patients who have not completed the 36 weeks treatment period according protocol and patients who do not want to participate in the Study Extension phase, will complete 2 follow-up visits. They will return also to their pre-study treatment.

Study burden and risks

Side effects with octreotide capsules are consistent with the known safety profile of octreotide but with no injection site reactions. No new AEs related to the new formulation or change in route of administration were identified in the clinical (and non-clinical) development program.
The most common body systems (system organ class) associated with the reported AEs were gastrointestinal disorders, nervous system disorders, and musculoskeletal and connective tissue disorders, consistent with the known safety profile of octreotide.
The following side effects, according to how common or rare they are, may be caused by oral octreotide in this study: Common (occurs in more than 10 out of 100 patients): nausea, diarrhea, headache, pain in your joints, weakness, swollen feet and ankles, excessive sweating.
Less Common (occurs in 5-10 out of 100 patients): indigestion, excessive gases in your stomach, abdominal pain, abdominal distension, vomiting, feeling faint, back pain, fatigue, common cold, influenza, upper respiratory tract infection, hypertension, biliary stones.
Common adverse drug reactions reported with octreotide injections also include increased blood glucose, decreased blood glucose, decreased thyroid hormone and potential effect on heart rhythm and rate (conduction abnormalities).
In completed studies with octreotide capsules, side effects related to the digestive system usually started within 8 weeks of start of treatment, and lasted for a short time.
Four patients had serious side effects (requiring hospitalization) that were assessed as possibly related to octreotide capsules. 3 had bile stones and one patient had jaundice (yellowing of the skin) and increased liver enzymes (indicative of damage to liver cells). These side effects have also been reported with octreotide injections. It is not known if these side effects are more or less frequent with octreotide capsules compared to octreotide injections.
The risk/side effects that have been observed with the use of cabergoline

include: Occurs in more than 1 out of 100 patients: nausea, headache, dizziness, constipation, weakness/lack of energy, fatigue, abdominal pain, drowsiness/sleepiness, head rush/dizzy spell, depression, intense or unusual urges.

POSSIBLE RISKS AND DISCOMFORT ASSOCIATED WITH DRAWING BLOOD
During this study, small amounts of blood will be drawn from a vein and used for tests that allow study doctors to see how patients are doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.

REPRODUCTIVE (ABILITY TO HAVE CHILDREN) RISKS
Men able to father a child must agree to use birth control methods. Women who can become pregnant must have a blood test that shows they are not pregnant before they can be enrolled in this study. They will also have pregnancy blood tests when they come to the clinic for their study visit at the end of each study part. If they can become pregnant, they must agree to use birth control methods.

Contacts

Public
Chiasma, Inc.

460 Totten Pond Road Suite 530
Waltham MA 02451
US
Scientific
Chiasma, Inc.

460 Totten Pond Road Suite 530
Waltham MA 02451
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Adult subjects, aged *18 years old at the first Screening visit.
2. Patients with active acromegaly, defined as documented evidence of GH-secreting pituitary tumor based on MRI/Pathology report and documented evidence of IGF-1 levels *1.3 × ULN. This needs to be at least 3 months following pituitary surgery in those patients who had prior pituitary surgery.
3. Received parenteral SRL monotherapy (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last three months of therapy.
4. Average IGF-1 of 2 assessments obtained during the Screening period is *1xULN.
5. Patients able and willing to comply with the requirements of the protocol at the time of Screening.
6. Women who are of childbearing potential should use an acceptable method for birth control. Acceptable methods include hormonal contraception (oral contraceptives * as long as on stable dose, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence1 or a vasectomized partner. Women may be surgically sterile or at least 1-year post-last menstrual period. Women taking oral contraception containing levonorgestrel should either change treatment (at least one month prior to first study medication dose) or use a mechanical barrier method.
7. Patients able to understand and sign written informed consent to participate in the study.

Exclusion criteria

1. Patients taking injections of long-acting SRLs off label (unlabeled doses or dosing interval. e.g. 60 or 90 mg lanreotide every 8 weeks or 30 mg octreotide every 6 or 8 weeks).
2. Patients who previously participated in CH-ACM-01 or OOC-ACM-302 (MPOWERED).
3. Symptomatic cholelithiasis.
4. Conventional or stereotactic Radiotherapy any time in the past.
5. Undergone pituitary surgery within six months prior to screening or have elective pituitary surgery (or other elective surgery that may affect compliance with protocol or confound study outcomes), planned within the course of the core study.
6. High-risk pattern1 of pituitary tumor location on pituitary magnetic resonance imaging (MRI)/Computed tomography (CT) as per medical history or most recent MRI/CT.
7. History of unstable angina or acute myocardial infarction within the 12 weeks preceding the screening visit or other clinically significant cardiac disease at the time of screening as judged by the Principal Investigator.

8. Any clinically significant uncontrolled nervous system, gastrointestinal (GI), renal, pulmonary, or hepatic concomitant disease that in the Investigator*s opinion would preclude patient participation.
9. Evidence of active malignant disease or malignancies diagnosed within the previous one year (except for basal cell carcinoma and uncomplicated * up to stage 1 squamous cell carcinoma that has been excised and cured).
10. Known allergy or hypersensitivity to any of the test compounds or materials.
11. Known uncontrolled diabetes defined as having a fasting glucose > 150 mg/dL (8.3 mmol/L) or glycosylated hemoglobin (HbA1c) > 8% (patients can be rescreened after diabetes is brought under adequate control, or in case HbA1c < 8%).
12. Known defects in visual fields due to optic chiasmal compression or other neurological signs, related to the pituitary tumor mass. Patients with long-standing (>12 months), fixed, minor defects may be considered on a case-by-case basis after consultation with the medical monitor.
13. Female patients who are pregnant or lactating or intending to become pregnant during the study.
14. Known history of immunodeficiency (e.g., HIV positive).
15. ALT, AST or ALP > 3 xULN or Total Bilirubin >1.5 x ULN.
16. Undergone major surgery/surgical therapy for any cause within four weeks prior to enrollment or planned procedure during the study.
17. Known hypothyroidism or hypocortisolism not adequately treated with a stable dose of thyroid or steroid hormone replacement therapy for >12 weeks.
18. Any condition that may jeopardize study participation (e.g., clinically significant abnormal screening clinical or laboratory finding during screening), the interpretation of study results or may impede the ability to obtain informed consent (e.g., mental condition).
19. History of illicit drug or alcohol abuse within five years.
20. Intake of an investigational drug within 30 days prior to initiation of study treatment.
21. Treatment with pegvisomant within 24 weeks before the screening visit.
22. Treatment with dopamine agonists within 12 weeks before the screening visit.
23. Treatment with pasireotide within 24 weeks before the screening visit.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-08-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MYCAPSSA
Generic name:	Ocreotide capsules

Ethics review

Approved WMO

Date:	17-07-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	25-06-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-09-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	12-11-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2017-000737-31-NL
ClinicalTrials.gov	NCT03252353
CCMO	NL61526.058.17