A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE CONTROLLED, MULTICENTER STUDY TO EVALUATE MAINTENANCE OF RESPONSE, SAFETY AND PATIENT REPORTED OUTCOMES IN ACROMEGALY PATIENTS TREATED WITH OCTREOTIDE CAPSULES, AND IN PATIENTS TREATED WITH STANDARD OF CARE PARENTERAL SOMATOSTATIN RECEPTOR LIGANDS WHO PREVIOUSLY TOLERATED AND DEMONSTRATED A BIOCHEMICAL CONTROL ON BOTH TREATMENTS

Published: 14-03-2016
Last updated: 17-04-2024

* To assess maintenance of biochemical control of octreotide capsules compared to parenteral SRLs in patients with acromegaly, who previouslydemonstrated biochemical control on both treatments.* To assess symptomatic response to octreotide capsules...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON43570

Source
ToetsingOnline

Brief title
MPOWERED

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, Injections, Octreotide

Outcome measures

Primary outcome

The proportion of patients who are biochemically controlled throughout the RCT

phase. A patient will be considered biochemically controlled if their IGF-1

Time Weighted Average (TWA), during the RCT phase is < 1.3 x ULN.

Secondary outcome

* Proportion of patients with clinical and biochemical response at the end of

the RCT phase (week 62/End of Treatment; EOT). Patients will be considered

controlled if they meet both of the following criteria:

- Biochemically controlled if their IGF-1 TWA during the RCT phase is < 1.3 x

ULN;

- Clinical control defined as maintained or reduced Acromegaly Symptoms - Index of Severity (AIS) score at week 62/EOT as compared to week 26 (start of RCT).

* Proportion of patients who maintain or reduce the overall number of active acromegaly symptoms, at the end of the RCT phase (week 62/EOT), compared to week 26 (start of RCT).

* Proportion of patients who maintain or improve their overall AIS score at the end of the RCT phase (improvement defined as a reduction of at least one point in the AIS score), compared to week 26 (start of RCT)

* Acromegaly treatment satisfaction questionnaire (ACRO-TSQ) at the end of the RCT phase.

* Proportion of patients of those completing the RCT phase (at a time octreotide capsules were not commercially available at the specific country), who enter the Study Extension phase, overall and by treatment group.

* Change from the start of the randomized phase of the study (week 26) through the end of the RCT (week 62) for IGF-1.

* Change from the start of the randomized phase of the study (week 26) to end of the RCT (week 62) in mean integrated GH.

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.

Study objective

* To assess maintenance of biochemical control of octreotide capsules compared to parenteral SRLs in patients with acromegaly, who previously demonstrated biochemical control on both treatments.
* To assess symptomatic response to octreotide capsules compared to parenteral SRLs.
* To assess patient reported outcome (PRO) in patients treated with octreotide capsules compared to parenteral SRLs.
* To evaluate the safety profile of octreotide capsules compared to parenteral SRLs.

Combination phase sub-study (in selected sites) objective:
* To assess the efficacy of octreotide capsules co-administered with cabergoline in the treatment of acromegaly patients with modestly elevated IGF-1 levels (defined as 1.3 * IGF-1 <2 × ULN).

Study design

This will be a phase 3, randomized, open-label, active controlled, multicenter study to evaluate maintenance of response, safety and patient reported outcomes (PROs) in acromegaly patients treated with octreotide capsules and in patients treated with SOC parenteral SRLs, who previously tolerated and demonstrated biochemical control on both treatments.

The core study will consist of three phases: a Screening phase, Run-in phase and an RCT phase.

Suitable patients enter the Study Extension treatment phase 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

Following up to 4-weeks Screening phase, eligible patients who are biochemically controlled (defined as IGF-1 < 1.3 × ULN and mean integrated GH <2.5 ng/mL), on parenteral SRLs will be switched to octreotide capsules for a 26-week Run-in phase. During this phase the effective dose for each patient will be determined through dose titration (see Run-in phase below).

Patients whose acromegaly is been controlled biochemically on octreotide capsules at the end of the Run-in Phase will enter a 36-week open-label RCT phase where they will be randomized to continue on octreotide capsules or switch back to their injectable SRL treatment (as received prior to Screening) or other treatment as determined by their physician. Following the completion of the core study (Screening, Run-in and RCT phases), eligible patients will be offered to enter the Study Extension phase and receive octreotide capsules until product marketing or study termination.

Patients who fail to respond to octreotide capsules 80 mg for at least two weeks therapy during the course of the Run-in phase, or patients ineligible to enter the RCT phase on octreotide capsules 80 mg, due to in-adequate biochemical control, with IGF-1 * 1.3 × ULN to IGF-1 <2 × ULN), will be eligible to enter the Combination phase sub-study (in selected sites). These patients will receive co-administration of octreotide capsules (80 mg/day) with cabergoline (up to 3.5 mg/week) for a total of 24 weeks. At the end of the Combination phase sub-study eligible patients will be offered to enter the Study Extension phase and continue the same combined treatment regimen.

Patients discontinuing early from the Combination phase sub-study (not executed in NL) or all other patients not meeting the criteria for randomization into the RCT phase or Combination phase sub-study will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician, and be followed for 12 weeks after last dose.

Patients who early terminate the Run-in phase for any reason in sites who do not participate in the Combination phase sub-study (in selected sites) will

revert back to their injectable SRL treatment (prior to Screening) or other treatment as determined by their physician and will be followed up for 12 weeks after last dose of study medication.

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 1-10 out of 100 patients): iIndigestion, excessive gases in your stomach, abdominal pain, abdominal distension, vomiting, feeling faint,* fatigue, common cold, influenza, upper respiratory tract infection.

In completed studies, 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

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Scientific
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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. Adult subjects, aged 18 to 75 years old, inclusive, at the Screening visit.;2. Patients with

acromegaly, defined as documented evidence of GH-secreting pituitary tumor that is abnormally responsive to an oral glucose tolerance test or abnormal IGF-1 levels (>1 x ULN), any time in the past, who are currently receiving parenteral SRLs (octreotide or lanreotide but not pasireotide) for at least 6 months with a stable dose for at least the last four months.;3. Documented biochemical control of their acromegaly on the current dose of SRL (IGF 1 < 1.3 x ULN and mean integrated GH < 2.5 ng/mL over two hours) based on Screening assessment.;4. Patients able and willing to comply with the requirements of the protocol at the time of Screening.;5. Women who are of childbearing potential should use an acceptable method for birth control. Acceptable methods include hormonal contraception (oral contraceptives, patch, implant, and injection), intrauterine devices, or double barrier methods (e.g. vaginal diaphragm/ vaginal sponge plus condom, or condom plus spermicidal jelly), sexual abstinence 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.;6.Patients able to understand and sign written informed consent to participate in the study.

Exclusion criteria

1. Patients taking injections of long-acting SRLs less frequently than once every eight weeks (dosing interval > 8 weeks).;2. Patients who previously participated in CH-ACM-01.;3.Symptomatic cholelithiasis.;4. Received pituitary radiotherapy within five years prior to screening (including total body, head and neck or stereotactic radiotherapy).;5. Undergone pituitary surgery within six months prior to screening or have elected surgery planned within the course of the core study.;6. High-risk pattern of pituitary tumor location on pituitary magnetic resonance imaging (MRI)/Computed tomography (CT) as per medical history or most recent MRI.;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, ALP or GGT > 3 * ULN 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 12 weeks before the screening visit.;22.Treatment with dopamine agonists within 6 weeks before the screening visit.;23.Treatment with pasireotide within 12 weeks before the screening visit.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Somatuline Autogel
Generic name:	Lanreotide - injectable
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MYCAPSSA
Generic name:	Octreotide Capsule

Product type:	Medicine
Brand name:	Sandostatin LAR
Generic name:	Octreotide LAR - injectable
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-03-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-11-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-12-2016
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	EUCTR2015-002854-11-NL
CCMO	NL55250.058.16