A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat oral monotherapy in adult subjects with Fabry disease.

Published: 16-05-2018
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Primary objectiveThe primary objective of the study is to determine the effect of lucerastat on neuropathic pain in subjects with Fabry disease (FD).Secondary objectives* To determine the effects of lucerastat on gastro-intestinal (GI) symptoms (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50474

Source
ToetsingOnline

Brief title
MODIFY

Condition

- Congenital and hereditary disorders NEC

Synonym
alpha-galactosidase A deficiency, Fabry's disease

Research involving
Human

Sponsors and support

Primary sponsor: Idorsia Pharmaceuticals Ltd
Source(s) of monetary or material Support: Idorsia Pharmaceuticals Ltd

Intervention

Keyword: Adult, Fabry's disease, Lucerastat, Neuropathic pain

Outcome measures

Primary outcome

The primary efficacy endpoint is Change from baseline to Month 6 in the

modified BPI-SF3 score of *neuropathic pain at its worst in the last 24 hours

Secondary outcome

* Change from baseline to Month 6 in the 11-point Numerical Rating Scale

(NRS-11) score of *abdominal pain at its worst in the last 24 hours* in

subjects with GI symptoms at baseline.

The definition of a subject considered to have GI symptoms at baseline is

provided in Section 10.1.4 of the core protocol.

* Change from baseline to Month 6 in the number of days with at least one stool

of a Bristol Stool Scale (BSS) consistency Type 6 or 7 in subjects with GI

symptoms at baseline;

* Change from baseline to Month 6 in plasma globotriaosylceramide (Gb3).

Study description

Background summary

See protocol chapter 1 "Background" p. 39-48.

Study objective

Primary objective
The primary objective of the study is to determine the effect of lucerastat on neuropathic pain in subjects with Fabry disease (FD).
Secondary objectives
* To determine the effects of lucerastat on gastro-intestinal (GI) symptoms (abdominal pain and diarrhea) in subjects with FD and GI symptom(s) at baseline;
* To confirm the effect of lucerastat on biomarkers of FD;
* To determine the safety and tolerability of lucerastat in subjects with FD.
Other objectives
Other objectives are described in Section 2.3 of the core protocol.

Study design

This is a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study.
Approximately 99 adult subjects with FD exhibiting Fabry-associated pain of moderate to severe intensity will be randomized in a 2:1 ratio to either lucerastat (approximately 66 subjects) or placebo (approximately 33 subjects).
Treatment allocation will be stratified by sex and by specific background FD treatment at screening (subjects treated with Enzyme Replacement Therapy *ERT*, also called *switch* subjects, as they will have to stop ERT at screening visit, vs subjects not treated with ERT at screening).

Subjects not treated with ERT at screening include:
(i) *treatment-naïve* subjects who have never been treated with ERT.
(ii) *pseudo-naïve* subjects who stopped ERT at least 6 months prior to screening.
Once randomized, subjects will enter a 6-month double-blind treatment period.
The study comprises the following consecutive periods:
Screening period: Lasts approximately 6-7 weeks; starts with the signing of the informed consent form (ICF; at the screening visit) and ends the day before subject randomization.
Treatment period: Lasts approximately 6 months. Starts on the day of subject randomization (randomization visit) and ends at the End-of-Treatment (EOT) visit (Month 6).
Post-treatment observation period (PTOP): Subjects who discontinue study treatment prematurely will enter into the PTOP which starts on the day after the last dose of study treatment, and ends at latest at the Month 6PTOP visit.
Post-treatment safety follow-up (FU) period: The FU period is applicable to all subjects except those who enter the open-label extension (OLE) study. It starts on the day after the last dose of study treatment:
* For female and non-fertile male subjects: it includes 1 safety FU telephone call (FU1) taking place approximately 1 month after the last dose of study treatment;
* For fertile male subjects: it includes 2 safety FU telephone calls taking place approximately 1 month (FU1) and 3 months (FU2) after the last dose of study treatment.

Subjects who complete the 6-month double-blind treatment period will be proposed to enroll into an OLE study conducted under a separate protocol (provided the extension study protocol has been approved in the country/site by regulatory authorities and Ethics Committees (ECs) / Institutional Review Boards (IRBs).
Subjects who discontinue study treatment prematurely for any reason should be subsequently treated according to local standard-of-care at the investigator*s discretion and will be followed in the PTOP until the originally scheduled Month 6 visit.

Intervention

Study treatment: Lucerastat is currently available for clinical study use in hard gelatin capsules containing 250 mg of lucerastat and inactive excipients (lactose anhydrous and talc).
Placebo capsules will be identical in appearance to the lucerastat capsules, and will contain inactive excipients (lactose anhydrous and talc).
The starting dose of the study treatment (lucerastat or matching placebo) will be based on the subject*s eGFR value (as reported by the central laboratory) at the screening visit as shown in Table 1 of the core protocol.
During the study, the dose of the study treatment will be adjusted if the subject*s eGFR (as reported by the central laboratory during scheduled or unscheduled visits) decreases and crosses the next lower eGFR boundary as shown in Table 1 of the core protocol.
Study treatment must be discontinued if one of the study-treatment stopping criteria is met *see Section 5.1.10 of the core protocol*.

Study burden and risks

The following side effects have been seen with lucerastat in 2 or more subjects (out of 96 people110 subjects):
• StuffyHeadache (7 subjects 6.4%)
• Rash, stuffy nose and sore throat (4 people5 subjects 4.25%)
• Rash, headacheDiarrhea, increase of liver enzymes, diarrhea (2 side effects were not medically significant) (3 people 3.1subjects 2.7%)
• Constipation, flatulence (excess passing of gas), back pain, fatigue, cough, vertigo (feeling of spinning or whirling)), stomach pain (2 people 2.subjects 1.8%)

Blood tests: risk of discomfort when the needle is inserted. Blood with a needle can give sore and bruised arms.

Stool tests: If stool tests are done at home (at hospital is preferred) there is a risk that the fluids contained in the stool collection tubes are accidentally in contact with the eyes or your skin or are inhaled or ingested.

Extreme care should be used when opening and filling those tubes.

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

Screening visit criteria
1. Signed and dated ICF prior to any study-mandated procedure;
2. Male or female subjects; 18-years old and above;
3. FD diagnosis confirmed with local genetic test results (i.e., resence of at least 1 mutation in GLA, the gene coding for α-galactosidase A *α-GalA*);
4. Fabry-associated neuropathic pain, as defined by the subject, in the last 3 months prior to screening;
5. ERT treatment status:
a) Subject never treated with ERT; or

b) Subject has not received ERT for at least 6 months prior to screening; or
c) Subject treated with ERT at the time of the screening visit and meeting all of the following criteria at the time of screening:
i) ERT administration for the last 12 months;
ii) Stable ERT dose regimen during the last 3 months;
iii) Subject agrees to stop ERT administration at the screening visit for approximately 8 months (6-7 weeks screening + 6 months of double-blind treatment).
6. A woman of childbearing potential [see definition in Section 4.5.1 of the core protocol] is eligible only if the following applies:
- Negative serum pregnancy test at screening and a negative urine pregnancy test at randomization;
- Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation;
- Agreement to follow a highly effective contraception scheme as described in Section 4.5.2 of the core protocol from screening up to at least 30 days after study treatment discontinuation.
- Agreement not to donate ova from screening visit and up to 30 days after study treatment discontinuation.
7. A fertile male (physiologically capable of conceiving a child according to investigator judgment) who is sexually active with a woman of childbearing potential is eligible only if the following applies:
- Agreement to use a condom during the treatment period (starting at randomization) and for up to 3 months after study treatment discontinuation; and
- Agreement not to father a child during this period.
In addition, male subjects must agree not to donate sperm (except for study semen sampling) during the treatment period (starting at randomization) and for up to 3 months after study treatment discontinuation.
Randomization visit criteria
8. Adequate subject compliance with completion of an electronic diary (eDiary) during the screening period;
9. Subjects with moderate or severe neuropathic pain as determined from daily entries of the modified Brief Pain Inventory-Short Form item 3 (BPI-SF3) score of *neuropathic pain at its worst in the last 24 hours* in the eDiary during the screening period.

Exclusion criteria

Screening visit criteria:
Disease/condition:
1. Pregnant / planning to become pregnant up to 30 days after study treatment discontinuation or lactating subject;
2. Severe renal insufficiency defined as an estimated glomerular filtration rate (eGFR) per the Chronic Kidney Disease Epidemiology Collaboration creatinine equation < 30 mL/min/1.73 m2 at screening (as reported by the

central laboratory);
3. Subject on regular dialysis for the treatment of chronic kidney disease;
4. Subject has undergone, or is on a waiting list for, or is scheduled to undergo kidney or other organ transplantation.
5. Known and documented transient ischemic attack, stroke, unstable angina or myocardial infarction within 6 months prior to screening;
6. Clinically significant unstable cardiac disease in the opinion of the investigator (e.g., uncontrolled symptomatic arrhythmia, New York Heart Association class III or IV congestive heart failure);
7. Any other subject at high risk of developing clinical signs of organ involvement within the time period of the study, as per investigator judgment.
8. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as:
a) Other disease or condition associated with a pain component that could confound assessment of neuropathic pain (e.g., diabetic neuropathy, chemotherapy- or radiation-induced peripheral neuropathy, chronic inflammatory demyelinating polyneuropathy);
b) Other disease of the GI tract that could interfere with the assessment of GI symptoms in FD (e.g., inflammatory bowel disease);
c) Documented poorly controlled diabetes mellitus (i.e., HbA1c > 8.0% at screening as reported by the central laboratory);
d) Significant neurological disorder;
e) Significant psychiatric disease; suicidal ideation at screening or history of suicide attempt or behavior within 6 months prior to screening as per investigator judgment;
f) History of drug dependence (including opioids) or alcohol dependence;
g) Inability to complete an eDiary on a daily basis.
9. Known concomitant life-threatening disease with a life expectancy < 18 months;
Treatments:
10. Subject planned for imminent initiation of treatment with ERT;
11. Known hypersensitivity to lucerastat or drug of the same chemical class of iminosugars (e.g., miglitol, miglustat, migalastat), or any of their excipients;
12. Initiation or treatment at an unstable dose within 4 weeks prior to screening with any of the following medications:
a) Angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB);
b) Anti-epileptic;
c) Tricyclic antidepressant (TCA) and/or other antidepressants belonging to the serotonin-norepinephrine re-uptake inhibitor (SNRI) and selective serotonin re-uptake inhibitor (SSRI) classes.
13. Planned or current treatment with another investigational treatment within 3 months prior to screening;
14. Treatment with any inhibitor of the glucosylceramide synthase (GCS) (e.g., miglustat, lucerastat, eliglustat, ibiglustat/venglustat) or an α-GalA chaperone (e.g., migalastat) within 6 months prior to screening;, Randomization visit criteria:

15. Treatment with ERT (agalsidase alfa, agalsidase beta) during the screening period.

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):	18-09-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	lucerastat
Generic name:	lucerastat

Ethics review

Approved WMO

Date:	16-05-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-003369-85-NL
ClinicalTrials.gov	NCT03425539
CCMO	NL64566.018.18