A Randomized, Placebo-Controlled, Double-Blind, Parallel Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Oral Doses of LTI-291 in Patients with Parkinson*s Disease and a GBA1 Mutation

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON44216

Source
ToetsingOnline

Brief title
Phase 1b study for LTI-291

Condition

- Movement disorders (incl parkinsonism)

Synonym
GBA-Associated Parkinson's Disease, movement disorder

Research involving
Human

Sponsors and support

Primary sponsor: Lysosomal Therapeutics Incorperated
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: GBA-Associated Parkinson's Disease, GCase activation, Glucocerebrosidase, Movement Disorder

Outcome measures

Primary outcome

Safety and tolerability endpoints

Secondary outcome

Functional outcome measures

Pharmacokinetic endpoints

Pharmacodynamic endpoints

Study description

Background summary

Approximately 10% of patients with clinically diagnosed Parkinson*s disease, Lewy Body Dementia, or Diffuse Lewy Body disease have a GBA1 mutation. More recently, it has become clear that even carrying one mutated allele of GBA1 significantly increases the lifetime risk of developing parkinsonism. Existing treatments are symptomatic in nature, and do not modify the underlying disease progression. For patients with GBA-associated parkinsonism (GBA-AP), some approaches eg DBS and anti-cholinergic agents may be contra-indicated due to the risk of worsened cognitive decline (Sasagasako et al., 1994; Thaler et al., 2017). Therapies targeting underlying pathogenesis could slow disease progression in this population. Preclinical studies demonstrate that LTI-291

penetrates the blood brain barrier, to access the GCase within the brain and central nervous system (CNS). Activation of GCase in the periphery or CNS may be measured by a reduction in the levels of the GCase substates GluCer or GluSph. Several lines of evidence suggest that activation of GCase enzymatic activity could provide therapeutic benefit to patients carrying a heterozygous mutation in the GBA1 gene, and that activation of enzyme via allosteric modulation, as with LTI-291, represents a novel, first-in-class potential treatment for patients with GBA-AP.

Study objective

The main objectives of this study are:
To evaluate the safety and tolerability of three oral dose levels of LTI-291 following 28 days of LTI-291 treatment in patients with GBA-PD
To characterize the plasma and CSF pharmacokinetics (PK) of LTI-291 following 28 days of LTI-291 treatment in patients with GBA-PD
To evaluate the pharmacodynamics of LTI-291 following 28 days of treatment in patients with GBA-PD using the following biomarker assessments:
- Glucosylceramide (GluCer) in plasma, isolated peripheral blood mononuclear cells (PBMCs) and CSF
- Glucosylsphingosine (GluSph) in plasma and isolated peripheral blood mononuclear cells (PBMCs)
- Lactosylceramide (LacCer) in plasma, isolated peripheral blood mononuclear cells (PBMCs) and CSF
- Other exploratory biomarkers including other sphingolipids in the same metabolic pathway.

Study design

This will be a randomized, double-blind, placebo-controlled, multiple dose study in 40 Parkinson*s disease patients with a GBA1 mutation. The following dose levels will be investigated: 10 mg, 30 mg and 60 mg. 10 patients per dose level and 10 placebo patients in cohorts of 4 patients per cohort, 1 patient for each dose level of LTI-291 and 1 patient receiving placebo. Subjects will receive the compound once daily for 28 consecutive days.

Intervention

LTI-291 capsules (API-in-capsule) dosed at 10mg, 30mg or 60mg or matching capsules containing 15 mg of Avicel as placebo.

Study burden and risks

Based on a review of nonclinical safety findings (including daily oral administration of high LTI-291 doses to rats and dogs for 28 days), and clinical findings of the single and multiple dose studies of LTI-291 in humans,

this first-in-patient protocol is expected to be safe to initiate and conduct as designed. There is an acceptably-large margin between proposed clinical doses and exposures and animal-study NOAELs, and the planned protocol-specified clinical monitoring is expected to adequately ensure the safety of human subjects.

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. Signed informed consent prior to any study-mandated procedure.
2. Minimum age of 18 years.
3. Clinical diagnosis of Parkinson*s Disease at least 6 months prior to screening, confirmed by a neurologist.
4. A score of 1-4 on Hoehn & Yahr Scale.

5. Mutation(s) in glucocerebrosidase GBA1 gene.
6. 6. Mini Mental State Exam score >/<= 18 and assessed by the investigator or qualified designee as able to provide informed consent.
7. Body mass index (BMI) between 18 and 35 kg/m2, inclusive, and with a minimum weight of 45 kg at screening.
8. All females must be at least 2 years post-menopausal or surgically sterile or practice higly effective contraception until at least 90 days after their last dose of study treatment.
9. All males must practice effective contraception and abstain from sperm donation during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
10. Has the ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Any active or chronic disease or condition other than PD that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following medical history review, physical examination, vital signs (supine systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), and clinical laboratory parameters (hematology, blood chemistry, and urinalysis)). Minor deviations of laboratory values from the normal range may be accepted, if judged by the investigator to have no clinical relevance.
2. History of recent major surgery (within 60 days of screening) that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator.
3. Atypical or secondary parkinsonism by medical history or in the opinion of the investigator. Atypical parkinsonism includes, but not limited to a diagnoses of progressive supranuclear palsy, corticobasal syndrome and multiple system atrophy. Secondary parkinsonism includes drug-induced, post-infectious, post-traumatic and vascular parkinsonisms.
4. Patients that experience Freezing Of Gait (FOG) in the on-state of L-dopa treatment (paradoxical response), which might interfere with the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator.
5. Current (within last 30 days prior to start of clinical phase) use of a strong CYP3A4 modulator. Reference Appendix B for a list of prohibited CYP3A4 modulators.
6. Current use of any drug known to significantly inhibit blood coagulation in the opinion of the investigator.
7. Vaccination within 7 days prior to start of dosing.
8. Any contra-indication for undergoing a lumbar puncture procedure (e.g. anatomical variations or local skin infection).
9. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
10. Participation in an investigational drug or therapeutic device study within 3 months prior to first dosing, or within 6 months for a biologic investigational product.
11. Recent history (last 6 months) of abuse of addictive substances (alcohol, illegal

substances) or current use of more than 21 units of alcohol per week, drug abuse, or regular recreational user of sedatives, hypnotics, tranquillizers, or any other addictive agent.
12. Positive test for drugs of abuse at screening or pre-dose.
13. Women currently pregnant or breastfeeding.
14. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.
15. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.

Study design

Design

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):	29-12-2017
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LTI-291
Generic name:	n/a

Ethics review

Approved WMO

Date:	06-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-004086-27-NL
CCMO	NL62049.056.17