A First-in-Human Randomized, Placebo-controlled, Double-blind, Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Oral Doses of LTI-291 in Healthy Subjects

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- To evaluate the safety and tolerability of four different single oral doses of LTI-291 in healthy subjects.- To characterize the plasma pharmacokinetics (PK) of LTI-291 following single oral dosing in healthy subjects.- To evaluate the...

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

Summary

ID

NL-OMON44238

Source
ToetsingOnline

Brief title
Single Ascending Dose study of 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

- Pharmacokinetic endpoints

- Pharmacodynamic endpoints

Secondary outcome

-Wet biomarker measurements

-Genotyping

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 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 substrates 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 the enzyme via allosteric modulation, as with LTI-291, represents a novel, first-in-class potential treatment for patients with GBA-AP.

Study objective

- To evaluate the safety and tolerability of four different single oral doses of LTI-291 in healthy subjects.
- To characterize the plasma pharmacokinetics (PK) of LTI-291 following single oral dosing in healthy subjects.
- To evaluate the pharmacodynamics (PD) of LTI-291 following single oral dosing in healthy subjects using NeuroCart assessments.
- To evaluate the pharmacodynamics of LTI-291 following single oral dosing in healthy subjects using biomarker assessments (i.e. GluCer) in plasma and in isolated peripheral blood mononuclear cells (PBMCs).
- To Investigate the effect of high-caloric breakfast on PK and PD of LTI-291.

Study design

Randomized, double-blind, placebo-controlled, single ascending dose study in 40 healthy adults.The following dose levels will be investigated in ascending order: 3 mg, 10 mg, 30 mg and 90 mg. Each cohort will consist of 10 subjects where subjects are randomized to receive LTI-291 or placebo in an 8:2 ratio. The effect of food on PK and PD will be investigated in one cohort. In this cohort, subjects will return for a second visit for dosing (in the same 8:2 randomization) in the fed state after a wash-out of at least 1 week. Cohort 1 will be dosed using a sentinel approach

Intervention

LTI-291 capsules (API-in-capsule) dosed at 3 mg, 10 mg, 30 mg or 90 mg and 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), this single-dose protocol is expected to be reasonably 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 sentinel approach as well as protocol-specified clinical monitoring are 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. Healthy male or female subjects of non-childbearing potential (defined as postmenopausal with amenorrhea for at least 12 months) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy, 18 to 65 years of age (inclusive) at screening.
3. Body mass index (BMI) between 18 and 32 kg/m2, inclusive, and with a minimum weight of 50 kg at screening.
4. All males must practice effective contraception and abstain from sperm donation during the study and be willing and able to continue contraception and abstain from sperm donation for at least 90 days after their last dose of study treatment.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of 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 a detailed medical history, physical examination, vital signs (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. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis B antibodies, Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Systolic blood pressure (SBP) greater than 150 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 95 or less than 50 mm Hg at screening or baseline.
5. Abnormal findings in the resting ECG at screening defined as:
a. QTcF > 450 msec for males or > 470 msec for females;
b. Notable resting bradycardia (HR < 40 bpm) or tachycardia (HR > 100 bpm);
c. QRS > 120 msec;
d. Personal or family history of congenital long QT syndrome or sudden death;
e. ECG with QRS and/or T wave judged to be unfavorable for a consistently accurate QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
f. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator. No exceptions will be made for any known inducer or inhibitor of CYP3A4, CYP1A2 or CYP2D6.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
8. Participation in an investigational drug or device study within 3 months prior to first dosing.
9. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units of alcohol per week, drug abuse, or regular use of sedatives, hypnotics, tranquillizers, or any other addictive agent.
10. Positive test for drugs of abuse at screening or pre-dose.
11. Use of tobacco or nicotine products within 14 days before the first dose administration.
12. Demonstrates an excess in xanthine consumption (more than eight cups of coffee or equivalent per day).

13. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
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. If a woman: pregnant, or breast-feeding, or planning to become pregnant during the study.
16. 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.
17. Food Effect Cohort only: Subjects who are unwilling or unable to consume the required high fat test meal.

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:	Completed
Start date (anticipated):	24-07-2017
Enrollment:	40
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	30-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2017
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

ID: 23087

Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-002233-37-NL
CCMO	NL62047.056.17
OMON	NL-OMON23087