

# Research study to investigate the safety, tolerability and effects of multiple doses of LTI-291 in healthy middle aged and older volunteers.

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• To evaluate the safety and tolerability of four oral dose levels of LTI-291 following multiple administrations in healthy middle-aged to elderly subjects. • To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of LTI-291...

<b>Ethische beoordeling</b>	Positief advies
<b>Status</b>	Werving gestopt
<b>Type aandoening</b>	-
<b>Onderzoekstype</b>	Interventie onderzoek

## Samenvatting

### ID

NL-OMON24313

### Bron

NTR

### Verkorte titel

Multiple Ascending Dose study of LTI-291

### Aandoening

GBA-Associated parkinsonism, movement disorder

### Ondersteuning

**Primaire sponsor:** • Lysosomal Therapeutics Incorporated

**Overige ondersteuning:** • Lysosomal Therapeutics Incorporated

### Onderzoeksproduct en/of interventie

## Uitkomstmaten

### Primaire uitkomstmaten

- Safety and tolerability endpoints<br>
- Pharmacokinetic endpoints<br>
- Pharmacodynamic safety biomarker endpoints

## Toelichting onderzoek

### Achtergrond van het onderzoek

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. 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, LTI-291 could be a potential treatment for patients with GBA-AP. All participants will be recruited in the Netherlands.

### Doel van het onderzoek

- To evaluate the safety and tolerability of four oral dose levels of LTI-291 following multiple administrations in healthy middle-aged to elderly subjects.
- To characterize the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of LTI-291 following multiple oral administrations in healthy middle-aged to elderly subjects.
- To evaluate the pharmacodynamics of LTI-291 following multiple oral administrations in healthy middle-aged to elderly subjects using NeuroCart assessments.
- To evaluate the pharmacodynamics of LTI-291 following multiple oral administrations in healthy middle-aged to elderly subjects using glycolipid biomarker assessments , plasma, isolated peripheral blood mononuclear cells (PBMCs), and in Cerebrospinal Fluid (CSF).

### Onderzoeksopzet

Study participation consists of a screening window of up to 21 days, a residence of 15 nights

spanning 15 days in-house, an outpatient visit and a follow up visit.

## Onderzoeksproduct en/of interventie

LTI-291 and placebo

## Contactpersonen

### Publiek

NA

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### Wetenschappelijk

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## Deelname eisen

### Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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, 50 to 75

years of age (inclusive) at screening.

3. Body mass index (BMI) between 18 and 32 kg/m<sup>2</sup>, 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 abstinence 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.

### **Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)**

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)). 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. Any contra-indication for undergoing a lumbar puncture procedure (e.g. anatomical variations or local skin infection).

4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.

5. 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.

6. 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.
7. Use of any medications (prescription or over-the-counter [OTC]) that are suspected to interfere or interact with the study medication, 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:
- a. Any known inducer or inhibitor of CYP3A4, CYP1A2 or CYP2D6;
  - b. Any drug known to inhibit blood coagulation.
8. 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.
9. Participation in an investigational drug or device study within 3 months prior to first dosing.
10. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent.
11. Positive test for drugs of abuse at screening or pre-dose.
12. Use of tobacco or nicotine products within 14 days before the first dose administration.
13. Demonstrates an excess in xanthine consumption (more than eight cups of coffee or equivalent per day)
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. 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.
16. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
17. 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.

## Onderzoeksopzet

### Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blinding:	Dubbelblind
Controle:	Placebo

### Deelname

Nederland	
Status:	Werving gestopt
(Verwachte) startdatum:	01-10-2017
Aantal proefpersonen:	40
Type:	Werkelijke startdatum

## Ethische beoordeling

Positief advies	
Datum:	14-09-2017
Soort:	Eerste indiening

## Registraties

### Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 44195  
Bron: ToetsingOnline  
Titel:

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

Register	ID
NTR-new	NL6516
NTR-old	NTR6705
CCMO	NL62048.056.17
OMON	NL-OMON44195

## Resultaten