Study to explore the use of glucocerebrosidase activity and other glycosphingolipids as potential biomarkers of GCase activation in healthy subjects and patients with Parkinson's Disease with and without a mutation in the GBA gene

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

Summary

ID

NL-OMON45713

Source
ToetsingOnline

Brief title
Biomarker study for GCase activity and enzyme levels

Condition

- Movement disorders (incl parkinsonism)

Synonym
movement disorders, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Centre for Human Drug Research,Clinical Research Organisation,Lysosomal Therapeutics Inc

Intervention

Keyword: Biomarker, GBA mutation, Healthy volunteers, Parkinson's Disease

Outcome measures

Primary outcome

1. GCase activity in whole-blood

2. GCase activity in isolated PBMCs

3. GCase protein in PBMCs

4. GluCer in PBMCs and plasm: performed at ABL laboratory using LTI-ABL-assay

- Potentially other substrates/products in the same metabolic pathway

Secondary outcome

N/A

Study description

Background summary

This phase 0 study will be serve to understand of variation in potential pharmacodynamics biomarkers (and methods of analysing these biomarkers) to be implemented in planned first-in-human single and multiple ascending dose studies with a novel GCase activator.

Study objective

To characterize the following markers in a given subject across multiple times of day, and across multiple days, to gain an understanding of intra-subject

variability.
- GCase activity in PBMCs and in whole-blood,
- GluCer in PBMCs and plasma
- Potentially other sphingolipids in the same pathway.
- GCase protein in PBMCs

Study design

A biomarker study in healthy adults and patients with PD with and without a GBA mutation. No investigational drug will be administered during this pre-study. Participants will be in-house on Day 1 and 23 (or before) for five blood draws (healthy volunteers only: the first in fasted state) and fixed breakfast, lunch and dinner. All subjects will return for a short visit on day 5 and 8 for blood donation only, between 9 and 10AM in fasted state. PD patients will return for two short visits on day 3 and 5. This design will allow assessment of within-day variability, day-to-day variability, and inter-individual variability of GCase activity, GCase protein and GluCer or other sphingolipids in healthy subjects and in PD patients with and without a GBA mutation.

Study burden and risks

This study requires collection of blood and urine samples. The burden for the volunteer related to the study procedures is limited. All collections will be performed in a state of the art clinical unit and medically supervised by qualified medical staff.

For the PD patients (Cohort 2 and 3) genotyping the GBA1 gene is a mandatory part of study participation. Patients that will be recruited will have participated in previous research in which genotyping of the GBA1 gene was performed and are already informed of their GBA status. Currently, confirmation of a GBA1 mutation has no implications for PD treatment. Patients will be informed on the presence of a mutation in their GBA1 gene, which is specified in the Informed Consent Document. If a patient does not wish to know their GBA1 status, they cannot participate in the study.

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

Group 1, Inclusion criteria;;1. Signed informed consent prior to any study-mandated procedure.
2. Healthy male and female volunteers, 18 to 70 years of age, of which 50% is *55 years of age, inclusive at screening. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical history and clinical laboratory parameters (hematology, blood chemistry and urinalysis).
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions. ;Group 2 & 3, Inclusion criteria;;1. Signed informed consent prior to any study-mandated procedure.
2. Diagnosis of PD at least 6 months prior to screening. The diagnosis requires: the presence of at least 2 of the 4 cardinal clinical manifestations of the disease, tremor, rigidity, bradykinesia, and disturbances of posture or gait.
3. A score of 1-4 on Hoehn & Yahr Scale.
4. Group 2: Confirmed mutation in the glucocerebrosidase (GBA1) gene.
5. Group 3: Confirmed wild type glucocerebrosidase (GBA1) gene.
6. Mini Mental State Exam score (MMSE) ><= 18 and assessed by treating neurologist as mentally competent.
7. Body mass index (BMI) between 18 and 35 kg/m2, inclusive, and with a minimum weight of 50 kg at screening.
8. Has the ability to communicate well with the Investigator in the Dutch language and willing

to comply with the study restrictions.

Exclusion criteria

Group 1, Exclusion criteria;;1. Any recent (within 7 days) infectious disease;
2. Positive Hepatitis B surface antigen (HBsAg), Hepatitis B antibodies, Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
3. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of screening, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1 g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator;
4. Participation in an investigational drug or device study within 3 months prior to first sampling.
5. 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;
6. Positive test for drugs of abuse at screening or pre-dose (in case of a positive test result, the test may be repeated once);
7. Alcohol will not be allowed from at least 24 hours before screening;
8. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit;
9. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day;
10. 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;
11. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study;
12. 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.;Group 2 & 3, Exclusion criteria;;1. Evidence of any active or chronic disease or condition other than PD 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 and clinical laboratory parameters (hematology, blood chemistry and urinalysis).
2. Positive Hepatitis B surface antigen (HBsAg), Hepatitis B antibodies, Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
3. History of recent major surgery (within 60 days of screening).
4. Atypical or secondary parkinsonism (in the judgment of the PI).
5. Any recent (within 7 days) infectious disease;
6. Participation in an investigational drug or device study within 3 months prior to first dosing.
7. 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 user of sedatives, hypnotics, tranquillizers, or any other addictive agent

8. Positive test for drugs of abuse at screening or pre-dose.
9. Alcohol will not be allowed from at least 24 hours before screening;
10. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit.
11. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day
12. 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.
13. 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: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-04-2017
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	03-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	04-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2017
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

No registrations found.

In other registers

Register	ID
CCMO	NL60806.056.17