Phase 0 biomarker study: assessment of day-to-day, within-day and inter-individual variability in β-Glucocerebrosidase activity and pathway biomarkers in healthy adults and patients with Parkinson*s disease with heterozygous GBA1-mutations.

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Primary Objectives• Characterize day-to-day, within-day, intra-individual and inter-individual variability of GCase activity in healthy participants and patients with Parkinson*s disease with a GBA1 mutation.Secondary Objectives• Assess variability...

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

Summary

ID

NL-OMON56229

Source
ToetsingOnline

Brief title
GCase activity biomarker study

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: co-funding,Vanqua Bio Inc.

Intervention

Keyword: GBA1 mutations, Parkinson's disease, Pathway biomarkers

Outcome measures

Primary outcome

- Live Cell GCase activity in whole blood

- GCase activity in dried blood spots

Secondary outcome

- Selected lipids including but not limited to: Glusphing, GluCer, Ceramide,

Sphingomyelin and SAA in both plasma and CSF

Study description

Background summary

beta-Glucocerebrosidase (GCase) is a lysosomal enzyme encoded by the glucosylceramidase beta 1 (GBA1) gene that is responsible for hydrolysis of the sphingolipid glucosylceramide to ceramide and glucose. It has been well established that heterozygous mutations in GBA1 are a major risk factor for Parkinson*s disease (PD) and are present in 7-13% of PD cases. These mutations in GCase lead to reduced enzymatic activity in the lysosome which is associated with impaired lysosomal function. A consequence of this lysosomal dysfunction is the accumulation of misfolded alpha synuclein which is the hallmark of PD. PD patients with GBA1 mutations exhibit earlier onset of disease and have an increased risk of cognitive impairment but are otherwise indistinguishable from patients with idiopathic PD.
A significant challenge in the study of the GCase enzyme has been the measurement of enzymatic activity. While techniques to assess GCase activity exist, these methods assess GCase activity extracted from a cell lysate and do

not account for the physiology of the lysosomal environment that directly affects enzymatic function. Vanqua has developed an approach to assess in situ lysosomal GCase activity in monocytes from whole blood samples using flow cytometry. This technique will enable a real-time assessment of GCase activity. The primary goal of this cross-sectional phase 0 study is to verify the performance of GCase activity assay at CHDR and assess the day-to-day, within-day and inter-individual variability of the GCase activity assay in healthy volunteers and Parkinson*s disease patients. The secondary goal of this study is to assess plasma biomarkers in healthy volunteers and patients with GBA-PD. These markers include measurements of sphingolipids, measurements of lysosomal function, alpha synuclein, and analysis of plasma exosomes. Achieving these goals will establish a target engagement assay at CHDR for future clinical studies, and help guide future biomarker strategies for this program.

Study objective

Primary Objectives
• Characterize day-to-day, within-day, intra-individual and inter-individual variability of GCase activity in healthy participants and patients with Parkinson*s disease with a GBA1 mutation.

Secondary Objectives
• Assess variability of sphingolipid pathway biomarkers in healthy participants and patients with Parkinson*s disease with a GBA1 mutation. These biomarkers and the medium the biomarkers are measured in, are listed in table 1 of the protocol
• Assess variability of additional exploratory biomarkers (to be determined).

Study design

This is a non-interventional phase 0 study, consisting of 2 arms of 8 to 12 participants each: healthy adults (HV) and patients with Parkinson*s disease (PD) with heterozygous GBA1 mutations (GBA-PD). Intra-individual and inter-individual variability at multiple days and multiple timepoints throughout a single day will be evaluated.

Study burden and risks

This is a non-interventional biomarker study. No investigational drug will be administered to the participants. Sampling of the biomarkers will be done via blood sampling and CSF sampling. All collections will be performed in a state-of-the-art clinical research unit and will be medically supervised by qualified medical staff. The blood sampling and CSF sampling are considered low risk procedures and the burden for the participants related to the study procedures will be kept to a minimum.

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

- Male or female 50-80 years of age at screening (inclusive).
- BMI in the range of 18 - 32 kg/m2.
- for patients: Confirmed clinical diagnosis of Parkinson disease by a neurologist, based on presence of bradykinesia and either resting tremor and/or muscular rigidity in at least one limb.

Exclusion criteria

- Significant haematological abnormalities during screening such as anaemia (haemoglobin level <7.0 mmol/L (males) or <6.0 mmol/L (females)), leukopenia, or any other significant abnormalities in clinical laboratory test values. A

WBC distribution will be determined to ensure (near) normal WBC distribution as determined by the investigator.
- Recent participation (<90 days / 5x T1/2) in an interventional study.
- Any other clinically significant neuro-degenerative disorder.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2023
Enrollment:	20
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	18-07-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2023
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	NL84232.056.23