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A biomarker study to assess day-to-day, within-day, and inter-individual variability in GCase enzyme activity and pathway biomarkers in healthy adults and patients with Parkinson's disease

Submission date
18/08/2023

Recruitment status
No longer recruiting

Registration date
31/08/2023

Overall study status
Completed

Last Edited
31/08/2023

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Beta-Glucocerebrosidase (GCase) is a lysosomal enzyme encoded by the glucosylceramidase beta 1 (GBA1) gene that is responsible for the 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 Bio, Inc. 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 goals of this cross-sectional phase 0 study are to verify the performance of the GCase activity assay at the Centre for Human Drug Research (CHDR) and to 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.

Who can participate?
Healthy adult participants and patients with Parkinson's disease aged from 50 to 100 years old

What does the study involve?
This is a non-interventional phase 0 study, consisting of 3 arms of 8 to 12 participants each: healthy adults (HV) and patients with Parkinson’s disease (PD) with and without heterozygous GBA1 mutations (GBA-PD and IPD, respectively). Intra-individual and inter-individual variability at multiple days and multiple timepoints throughout a single day will be evaluated.

What are the possible benefits and risks of participating?
This is a non-interventional biomarker study. No investigational drug will be administered to the participants. Therefore, participating will have no possible individual benefit. The data and analysis of this research will contribute to understanding Parkinson’s disease and future drug development, which can be seen as a collective benefit for participants of this study. 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.

Where is the study run from?
CHDR (The Netherlands)

When is the study starting and how long is it expected to run for?
April 2023 to October 2023

Who is funding the study?
Vanqua Bio, Inc. (USA)

Who is the main contact?
clintrials@chdr.nl

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)

NL84232-056-23

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CHDR2323

Study information

Scientific Title
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 and without heterozygous GBA1-mutations

Study objectives
GCase enzyme activity in lysosomal environment can be reliably and reproducibly measured in ex vivo patient samples, such as blood and cerebrospinal fluid.

Ethics approval required
Ethics approval required

Ethics approval(s)
submitted 30/05/2023, Ethics Assessment Foundation Biomedical Research Medical Ethics Review Committee (Stichting Beoordeling Ethiek Biomedisch Onderzoek Medisch Ethische ToetsingsCommissie) (Dr. Nassaulaan 10, Assen, 9410 HK, Netherlands; +31 592 405 871; info@stbebo.nl), ref: NL84232.056.23

Study design
Non-interventional phase 0 study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
This is a non-interventional phase 0 study, consisting of 3 arms of 8 to 12 participants each: healthy adults (HV) and patients with Parkinson’s disease (PD) with and without heterozygous GBA1 mutations (GBA-PD and IPD, respectively). Intra-individual and inter-individual variability at multiple days and multiple timepoints throughout a single day will be evaluated.

• For the screening visit subjects will be required to fast for at least 4 hours. For study visits on Day 1 and Day 8, participants will be required to fast for at least 2 hours. A meal will be provided after the 0h sampling. On Day 1 subjects will have to fast again 2 hours before the second blood sampling, which will be 4 hours after the first sample. Drinking water is allowed as required.

* Subjects will be assessed with a mini mental state examination to screen their cognitive function.

Intervention Type
Other

Primary outcome(s)
GCase activity and activation in healthy participants and patients with Parkinson’s disease with and without a GBA1 mutation measured in monocytes from whole blood samples using flow cytometry at multiple timepoints on day 1 and day 8

Key secondary outcome(s))
The following secondary outcome measures are assessed at multiple timepoints on day 1 and day 8 unless otherwise stated:
1. Sphingolipid pathway biomarker variability in healthy participants and patients with Parkinson’s disease with and without a GBA1 mutation measured using laboratory assays. The biomarkers and the medium the biomarkers are measured in are as follows: live cell GCase activity in whole blood, GCase activity in dried blood spots, GCase activation in whole blood, GluSphing in plasma and CSF, GluCer in plasma and CSF, ceramide in plasma and CSF, sphingomyelin in plasma and CSF, bis(monoacylglycerol)phosphate (BMP) in urine and CSF and serum amyloid alpha (SAA) in plasma and CSF.
2. Variability of additional exploratory biomarkers (to be determined).

Pharmacodynamic endpoints
1. GCase activity in dried blood spots (DBS) measured using fluorimetry
2. Live-cell GCase activity and GCase activation by VQ101 in whole blood measured using flow cytometry
3. GluSphing, GluCer, ceramide, sphingomyelin and SAA in plasma and CSF measured using LC-MS / MS
4. BMP in urine and CSF measured using laboratory assays at baseline
5. Variability in other exploratory biomarkers (to be determined) measured using laboratory assays

Completion date
15/10/2023

Eligibility

Key inclusion criteria
Group 1 (healthy volunteers)
1. Male or female 50-100 years of age at screening (inclusive)
2. BMI in the range of 18 – 32 kg/m2

Group 2 and 3 (patients with Parkinson’s disease with and without a GBA1 mutation)
3. Male or female 50-80 years of age at screening (inclusive)
4. BMI in the range of 18 – 32 kg/m2
5. Confirmed clinical diagnosis of Parkinson's disease by a neurologist, based on the presence of bradykinesia and either resting tremor and/or muscular rigidity in at least one limb
6. Hoehn and Yahr stage I-III, inclusive

7. GBA-PD group (2): confirmed presence of heterozygous GBA1 mutation via (historic) genotyping
8. IPD group (3): confirmed absence of GBA1 mutation via (historic) genotyping

Groups 1, 2 and 3
9. Able to speak, read, and understand study procedures in Dutch sufficiently to allow completion of all study assessments
10. Must understand and provide written informed consent prior to the initiation of any protocol-specific procedures
11. Willing and able to maintain stable doses and regimens for all medications, herbal treatments, medical marijuana, dietary supplements and caffeine intake from the screening visit through the last study visit
12. Willing and able to abstain from alcohol 24 hours prior to all study procedures at study Day 1 and Day 8
13. Women of childbearing potential must use a form of birth control (e.g., oral contraceptive, condom use, IUD, abstinence of heterosexual intercourse).

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 years

Upper age limit
100 years

Sex
All

Key exclusion criteria
Groups 1, 2 and 3
1. 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.
2. Recent participation (<90 days / 5x T1/2) in an interventional study
3. Any other clinically significant neuro-degenerative disorder
4. Recent blood loss or blood donation (>500mL whole blood) in the past 30 days
5. Recent infection with hospital admission (<1 month) or clinical evidence of infection at screening and study visits
6. Alcohol or drugs abuse in the past 12 months (a negative test for alcohol and drugs of abuse at screening and prior to the first blood sample collection will be required for inclusion)
7. Clinically abnormal findings in the resting ECG at screening as determined by the Investigator
8. Vital sign measurements must be within the following ranges during screening:
8.1. Body temperature, ≥35C to ≤38C

8.2. Systolic blood pressure, ≥90 to ≤160 mm Hg
8.3. Diastolic blood pressure, ≥40 to ≤95 mm Hg
8.4. Pulse rate, ≥40 to ≤100 bpm
9. Positive serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV) (positive hepatitis B core antibody [anti-HBc] with negative hepatitis B DNA is acceptable), or hepatitis C virus (HCV) (treated/resolved hepatitis C with negative polymerase chain reaction [PCR] RNA is allowed)
10. Any other issue that, in the opinion of the investigator, would make the participant ineligible for study participation
11. Previous exposure to gene therapy
12. For CSF sampling, any of the criteria below:
12.1. History of clinically significant hypersensitivity to local anesthetics that may be used for LP (e.g., lidocaine)
12.2. Criteria that would preclude an LP, such as a local infection at the site of the LP, <100× 103 /µl platelet count at screening or clinically significant coagulation abnormality or significant active bleeding, or treatment with an anticoagulant or treatment with more than two antiplatelet agents
12.3. History of clinically significant back pathology and/or back injury (e.g., degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with LP

Group 1
13. Clinical evidence or history of Parkinson's disease, parkinsonism or Gaucher disease
14. First-order relative with Parkinson's disease or Gaucher disease
15. Any history of unstable or poorly controlled psychiatric, endocrine, pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic, renal, metabolic, hematologic, immunologic, or allergic disease, or other major disorders. Well-controlled conditions are permitted if the investigator and Sponsor agree.

Group 2
16. Presence of clinical features suggestive of atypical Parkinsonian syndromes
17. Presence of homozygous or compound heterozygous GBA-1 mutation or PD-related risk variant

Date of first enrolment
13/07/2023

Date of final enrolment
27/09/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research (CHDR)
Zernikedreef 8
Leiden

Netherlands
2333 CL

Sponsor information

Organisation
Centre for Human Drug Research

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Industry

Funder Name
Vanqua Bio, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated during and/or analyzed during the current study will be available upon request from Omer Siddiqui, SiddiquiO@vanquabio.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes