# Phase 0 biomarker assessment of day-to-day, within-day and interindividual variability in GBA pathway biomarkers in healthy adults and patients with Parkinson*s disease with and without heterozygous GBA1-mutations

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Primary Objectives* To investigate the intra-variability (day-to-day) of glucocerebrosidase pathway biomarkers in HV, PD-GBA+ and PD-GBA-Secondary Objectives* To investigate the intra-variability (within-day) of glucocerebrosidase pathway biomarkers...

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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-OMON52359

**Source**
ToetsingOnline

**Brief title**
GCase variability in GBA mutation

### Condition

- Movement disorders (incl parkinsonism)

**Synonym**
Parkinson□s disease; Parkinson□s disease with and without GBA mutation

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** BIAL R&D INVESTMENTS, S.A
**Source(s) of monetary or material Support:** BIAL R&D INVESTMENTS;S.A

## Intervention

**Keyword:** Biomarkers, GBA, heterozygous GBA1-mutations, Parkinson□s disease

## Outcome measures

### Primary outcome

Day-to-day variability (%CV) of:

* Glucocerebrosidase and galactocerebrosidase activity (in Dried blood spots)

* Acid ceramidase activity (in PBMCs)

* Glucosylsphingosine concentration (in granulocytes)

* Ceramide and dihydroceramide concentrations (in lymphocytes)

### Secondary outcome

Within-a-day variability (%CV) of:

* Glucocerebrosidase and galactocerebrosidase activity (in Dried blood spots)

* Acid ceramidase activity (in PBMCs)

* Glucosylsphingosine concentration (in granulocytes)

* Ceramide and dihydroceramide concentrations (in lymphocytes)

Between subject variability (%CV) of:

* Glucocerebrosidase and galactocerebrosidase activity (in Dried blood spots)

* GCase activity (in PBMCs)

* Acid ceramidase activity (in PBMCs)

* Glucosylsphingosine concentration (in granulocytes)

* Ceramide and dihydroceramide concentrations (in lymphocytes)

* Glucosylsphingosine, ceramide and dihydroceramide concentrations (in plasma)

* Glucosylceramide and lactosylceramide concentrations (in lymphocytes)

* Metabolic profile (in plasma)

* Metabolic flux through ceramide, dihydroceramide, glucosylceramide,

lactosylceramide, and sphingomyelin (in lymphocytes)

# Study description

**Background summary**

*-Glucocerebrosidase (GCase) is lysosomal enzyme that is encoded by the glucosylceramidase beta gene (GBA1). GCase metabolizes the sphingolipid glucosylceramide (GluCer) to ceramide (Cer) and glucose. Several studies have shown that heterozygous or homozygous GBA1 mutations that reduce enzymatic activity are associated with approximately a 20-fold increased risk of PD. Though the exact underlying mechanisms of the are not known, an increased deposition of alpha-synuclein is a hallmark of PD pathology. There is a bi-directional association between GCase and alpha-synuclein (aSyn), where a reduced activity of GCase increases deposition of aSyn, which then further reduces GCase activity. PD patients with GBA1 mutations are clinically indistinguishable from patients with idiopathic PD. However, in patients with GBA1 mutations the onset of symptoms is generally at an earlier age and cognitive impairment is more frequently seen than in idiopathic PD.

There is low variation in plasma GluCer for healthy volunteers, but the effect of disease state and GBA mutation status is not known. Variation of leukocyte sphingolipids has not been described in the literature. Plasma GluCer is elevated in PD with or without GBA mutation. In whole blood, GCase activity in PD with GBA mutation is lower than control. GCase activity in monocytes is lower in PD, with or without GBA mutation. Though baseline sphingolipid levels have been studied, the effect of disease state and GBA mutation status on flux through the sphingolipid pathway has not been examined.

This cross sectional, 3 arms phase 0 study is designed to assess the day-to-day, within-day and inter-individual variability of sphingolipid pathway biomarkers, including lysosomal enzyme activity, baseline sphingolipid levels,

and flux through the sphingolipid pathway, in healthy volunteers (HV) and Parkinson*s disease patients with a mutation in the GBA1 mutations gene (PD-GBA+) and without a mutation in the GBA1 gene (PD-GBA*) in preparation for future clinical studies with a GCase-activator or other lysosomal enzyme modulators.

**Study objective**

Primary Objectives
* To investigate the intra-variability (day-to-day) of glucocerebrosidase pathway biomarkers in HV, PD-GBA+ and PD-GBA-

Secondary Objectives
* To investigate the intra-variability (within-day) of glucocerebrosidase pathway biomarkers in HV, PD-GBA+ and PD-GBA-
* To investigate the inter-individual-variability (between subjects) of glucocerebrosidase pathway biomarkers in HV, PD-GBA+ and PD-GBA-
* To investigate the inter-individual variability (between subjects from cohort B only) of flux through spingolipid pathway biomarkers in HV, PD

**Study design**

This is a non-interventional, ex-vivo, phase 0 biomarker study, consisting of 2 cohorts: Cohort A will be used to evaluate intra-individual variability at multiple days and multiple timepoints throughout a single day. Cohort A will have 3 groups of 8 subjects each: healthy adults (HV) and patients with Parkinson*s disease (PD) with (PD-GBA+) and without (PD-GBA-) heterozygous GBA1 mutations. Cohort B will participate for a single inter-individual variability measurement for flux through the sphingolipid pathway. The 3 groups of cohort B will consist of 8 healthy adults (HV), 8 patients with Parkinson*s disease (PD) without GBA1 mutation and a up to a maximum of 8 subjects with Parkinson*s disease with GBA1 mutation (PD-GBA+) depending on recruitment.

**Study burden and risks**

This non-interventional biomarker study requires the collection of blood samples. All collections will be performed in a state of the art clinical research unit and medically supervised by qualified medical staff. This is considered a very low risk procedure and the burden for the volunteers related to the study procedures will be kept to a minimum. Only existing genotyping data is used and genotyping will not be performed for this 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

Cohort A
Group 1 (healthy volunteers)
1. Male or female 18 * 55 years of age at screening (inclusive)
2. BMI in the range of 18 * 32 kg/m2.

Cohort B
Group 1 (healthy volunteers)
1. Male or female 18 * 65 years of age at screening (inclusive)
2. BMI in the range of 18 * 32 kg/m2.

Cohort A and B

Group 2 and 3 (PD-GBA+ and PD-GBA-)
3. Confirmed clinical diagnosis of Parkinson disease by a qualified neurologist.
4. Hoehn and Yahr stage I-IV, inclusive
5. Male or female of 30-85 years of age at screening (inclusive)
6. BMI in the range of 18 * 32 kg/m2.
7. PD-GBA+ group (2): confirmed presence of GBA1 mutation via (historic) genotyping
8. PD-GBA- 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 visits 1, 2 and 3.
13. Women of childbearing potential must use a form of birth control (e.g. oral contraceptive, condom use, IUD, abstinence of hetero-sexual intercourse)

## Exclusion criteria

Group 1 and 2 and 3
1. Significant haematological abnormalities during screening such as anaemia, leukopenia, (haemoglobin level <7.0 mmol/L (males) or <6.0 mmol/L (females)), or any other significant abnormalities in clinical laboratory test values.
2. Recent participation (<90 days / 5x T1/2) in an interventional study for Parkinson disease
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)
6. Alcohol or drugs abuse in the past 12 months
7. Have no clinical or electrocardiographic signs of ischemic heart disease as determined by the Investigator with normal cardiac intervals appropriate for their gender. The Screening 12 lead ECG conduction intervals must be within gender specific normal range (e.g., QTcf female *470 msec QTcF males *450 msec, PR interval *220 msec).
8. Vital sign measurements must be within the following ranges during screening:
a. body temperature, >35C to *38C
b. systolic blood pressure, >90 to *160 mm Hg
c. diastolic blood pressure, >40 to *95 mm Hg
d. 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

Group 1
11. Clinical evidence or history of Parkinson disease, parkinsonism or Gaucher disease
12. First order relative with Parkinson disease or Gaucher disease
13. Any historyof 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 investigator and Sponsor agree.

# Study design

## Design

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| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Other |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 03-12-2021 |
| Enrollment: | 48 |
| Type: | Actual |

# Ethics review

Approved WMO

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| Date: | 23-11-2021 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 05-01-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 21-04-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# 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 | NL79102.100.21 |