Longitudinal Study to Evaluate Intra- and Inter-Individual Variability of LRRK2 Protein and Related Biomarkers in Healthy Participants

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Primary Objective- Evaluate longitudinal intra-individual and inter-individual variability of PBMC biomarkers in healthy participants:o LRRK2 protein (pg/mL)o total protein (ug/mL)o pS935 LRRK2/total LRRK2 peptide ratioo pRab10/Rab10 peptide ratio...

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

Summary

ID

NL-OMON53216

Source
ToetsingOnline

Brief title
Arvinas Biomarker Variability Study

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinsonism, Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Arvinas Operations, Inc

Source(s) of monetary or material Support: Pharmaceutical company

Intervention

Keyword: Biomarker, LRRK2 Protein, Variability

Outcome measures

Primary outcome

The endpoints include total LRRK2 protein, pS935 LRRK2 protein, and

pRab10/Rab10 levels measured in PBMCs.

Secondary outcome

• LRRK2 protein in CSF

Study description

Background summary

Parkinson*s disease (PD) is a common neurodegenerative disease, affecting approximately 1-2% of persons aged >= 65 years. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are an established risk factor for PD, linked to approximately 5% of familial PD and 1-2% of sporadic PD cases. While the exact pathophysiological mechanisms are not completely understood, the associated mutations cause an increase in LRRK2 kinase activity, which leads to lysosomal dysfunction. It is hypothesized that lysosomal dysfunction can be an important mechanism for accumulation of intracellular protein such as alpha-synuclein, which is a hallmark of PD pathophysiology. In recent years, multiple studies have aimed to inhibit LRRK2 kinase as a potential disease-modifying therapy for PD by restoring lysosomal function. As an alternative, human genetic data and results from preclinical studies suggest that reducing LRRK2 protein in the brain may be an effective approach for the treatment of PD. A non-coding variant within the LRRK2 locus, SNP rs76904798, increases LRRK2 expression in microglia and is associated with increased risk for developing PD; The protective LRRK2 haplotype, N551K-R1398H-K1423K, is associated with reduced LRRK2 levels; reduction of LRRK2 in brain is protective in mouse models of PD. To quantify the effect of these novel therapeutic interventions aimed at reducing LRRK2 protein levels, it is necessary to qualify methods that will allow measurement of total LRRK2 protein, phosphorylated LRRK2, and substrates of LRRK2. The latter includes a group of Rab guanosine triphosphates (GTPases) that regulate intracellular trafficking. One of the GTPases that will be

investigated in the present study is Rab10, which is phosphorylated by LRRK2 and may act as a key marker of LRRK2 downregulation.
This observational study is designed to evaluate the longitudinal variability of LRRK2 biomarkers in samples collected over 2 weeks to support the development of novel therapeutic interventions. Understanding the longitudinal variability of these biomarkers over this 2-week timeframe is key in the evaluation of novel LRRK2 therapeutics with a durable pharmacodynamic response. This study will assess variability in healthy participants of LRRK2 and pS935 LRRK2 protein levels and phosphorylation levels of the LRRK2 substrate Rab10 from day-to-day, within-day and between individuals. Additionally, preclinical data demonstrate that CSF LRRK2 can be used as surrogate biomarker for monitoring LRRK2 reductions in brain tissue. Therefore, LRRK2 protein levels will be measured at two timepoints 24 hours apart to evaluate longitudinal variability and to explore the correlation between CSF and Peripheral Blood Mononuclear Cells (PBMC)/whole blood LRRK2 levels. CSF will be collected for measurements in 3 different assays and to investigate the stability of LRRK2 in CSF over time and to confirm the robustness of the assay of CSF in a clinical trial setting.

Study objective

Primary Objective
- Evaluate longitudinal intra-individual and inter-individual variability of PBMC biomarkers in healthy participants:
o LRRK2 protein (pg/mL)
o total protein (ug/mL)
o pS935 LRRK2/total LRRK2 peptide ratio
o pRab10/Rab10 peptide ratio

Secondary Objective
- Evaluate longitudinal intra-individual and inter-individual variability of CSF LRRK2 and correlation of LRRK2 measurement in 3 different assays in healthy participants:
o LRRK2 protein (pg/mL) as measured by SISCAPA assay
o LRRK2 protein (pg/mL) as measured by mid-domain SIMOA assay
o LRRK2 protein (pg/mL) as measured by N-terminal SIMOA assay

Study design

This is a prospective, single-centre, methodology biomarker study in healthy participants. Randomisation is not applicable. Please see Part 3 of the Clinical Protocol.

Study burden and risks

This is a non-interventional biomarker study. No investigational drug will be administered. 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

1. 18 - 70 years of age at screening (inclusive).
2. BMI in the range of 18 - 30 kg/m2, inclusive at screening and with a minimum weight of 50 kg.

3. Able to speak, read, and understand study procedures in Dutch sufficiently to allow completion of all study assessments.
4. Must understand and provide written informed consent prior to the initiation of any protocol-specific procedures.
5. Women of childbearing potential must use a form of birth control (e.g., oral contraceptive, condom use, IUD, abstinence of heterosexual intercourse) during the study.

Exclusion criteria

1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the participant in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.

5. Abnormal findings in the resting ECG at screening defined as:
- QTcF longer than 450 or shorter than 350 msec for men and QTcF longer then 470 or shorter then 360 msec for women
- Notable resting bradycardia (HR under 40 bpm) or tachycardia (HR over 100 bpm)
- Other abnormal findings in the resting ECG as determined by the investigator

8. Use of any medications (prescription or over-the-counter [OTC] including herbal medication), within 14 days prior to the first blood collection on day 1, or less than 5 half-lives (whichever is longer), except for birth control, 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.

18. For CSF sampling, any of the criteria below:
- History of clinically significant hypersensitivity to local anaesthetics that may be used for LP (e.g., lidocaine).
- Criteria that would preclude an LP, such as a local infection at the site of the LP, less then 100x 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 2 antiplatelet agents.
- 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.

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):	05-07-2023
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO

Date:	22-06-2023
Application type:	First submission
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	NL84388.056.23