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A study of the variability of the protein LRRK2 and related proteins within one day, between different days, and between different healthy volunteers

Submission date
11/08/2023

Recruitment status
No longer recruiting

Registration date
15/08/2023

Overall study status
Completed

Last Edited
15/08/2023

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 of the study:
Parkinson's disease is a common brain disorder that mainly affects older people. Changes in a specific gene called LRRK2 can increase the risk of developing this disease. This gene plays a role in how cells in the brain work and communicate. People with certain changes in this gene have a higher chance of getting Parkinson's disease.
Scientists believe that when this gene doesn't work properly, it might cause problems in the brain cells and lead to the symptoms of Parkinson's disease. These symptoms include shaking, stiffness, and difficulty moving. One of the things this gene does is help with cleaning up waste products in brain cells. When the gene isn't working right, these waste products can build up and cause more problems.
Researchers are trying to find ways to fix or slow down the problems caused by this gene. They are studying how different treatments can help. Some treatments aim to make the gene work better, while others try to reduce the amount of this gene in the brain. They want to understand how effective these treatments are and how they can measure the changes they cause.
To do this, they are planning a study where they will collect samples from people over two weeks. These samples will help them see how the gene changes in the body over time. They will look at the levels of the gene, as well as other substances that are affected by it. One of the things they are interested in is a substance called Rab10, which can show how well the gene is working.
This study will help researchers learn more about how this gene affects Parkinson's disease and how different treatments might work. It will also help them find better ways to test these treatments and see if they are making a positive impact.

Who can participate?
Healthy volunteers between 18 and 70 years old.

What does the study involve?
This study wants to understand how a specific protein called LRRK2 and its related substances in

the blood and cerebrospinal fluid (the fluid around the brain) change. They are interested in these changes because they might help measure the effects of new medicines being developed for Parkinson's disease.
The study will collect samples from people over two weeks to see how these substances change over time. This information will help scientists develop new treatments for Parkinson's disease. They want to find treatments that can change how LRRK2 works and might help people with Parkinson's disease.
The study will look at how these substances vary in healthy people. They will measure them on different days and at different times of the same day. They will also compare these variations between different individuals.
Previous studies have shown that the levels of LRRK2 in the cerebrospinal fluid can tell us about changes in the brain. So, they will measure LRRK2 levels at two different times, 24 hours apart. This will help them understand how LRRK2 changes over time. They will also compare these changes between the cerebrospinal fluid and the blood.
To make sure their tests are accurate, they will use three different methods to measure LRRK2 in the cerebrospinal fluid. This will help them make sure that their tests are reliable and can be used in future studies to test new treatments.

What are the possible benefits and risks of participating?
This study won't give any new drugs to participants. Instead, it's focused on collecting information about certain markers in the body. These markers are found in the blood and in the fluid around the brain called cerebrospinal fluid.
To collect these markers, small amounts of blood and cerebrospinal fluid will be taken. These collections will happen in a very safe and modern place meant for research, and they will be overseen by trained medical professionals. Taking the blood and fluid samples is not risky, and the whole process will be made as easy as possible for the participants.

Where is the study run from?
The Centre for Human Drug Research (Netherlands)

When is the study starting and how long is it expected to run for?
June 2023 to Septmeber 2023

Who is funding the study?
Pharmaceutical company Arvinas Operations Inc. (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CHDR2329/ARV-NS-001, NL84388.056.23

Study information

Scientific Title
Longitudinal study to evaluate intra- and inter-individual variability of LRRK2 protein and related biomarkers in healthy participants

Study objectives
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, N551KR1398H-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-today, 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.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/06/2023, st. BEBO (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 592 405 871; info@stbebo.nl), ref: NL84388.056.23

Study design
Prospective single-centre biomarker study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
Other

Study type(s)
Screening

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Parkinson's Disease, Parkinsonism

Interventions
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 at the 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.

Approximately 8 participants will be enrolled in this study, to achieve 3 participants in Group A and 5 participants in Group B. Variability in LRRK2 will be assessed at multiple timepoints and multiple days as described below.

Participants will be screened up to 42 days before day 1 according to the inclusion/ exclusion criteria. The study will consist of 1 overnight stay on day 1-2 in the CHDR clinical unit. This stay includes 4 blood samples (on timepoints 0h, 4h, 8h and 24h for PBMC isolation) and either 1 (for Group A on timepoint 0h) or 2 (for Group B on timepoint 0h and 24h) CSF sampling timepoints. Participants will be discharged after a safety check (vital signs and assessments of potential adverse events). Thereafter, the study will continue with 3 outpatient visits for blood biomarker sampling on day 4, 8 and 15. The subsequent blood samples will be taken on time-matched timepoint related to the 0h timepoint on day 1. A follow-up contact for safety will be done via telephone 7 days (±1 day) after the last study visit on day 15. The end of study is defined as the date when the last participant, last follow-up occurs

Intervention Type
Other

Primary outcome measure
Evaluate longitudinal intraindividual and inter-individual variability of whole blood and/or PBMC biomarkers in healthy participants on Day 1: 0h, 4h, 8h. Day 2, 4, 8 and 15:
1. LRRK2 protein (pg/mL) in whole blood and PMBCs
2. Total protein (ug/mL) in PBMCs
3. LRRK2/total protein ratio in PBMCs
4. pS935 LRRK2, total LRRK2 and pS935 LRRK2/total LRRK2 peptide ratio in PBMCs
5. pRab10, Rab10 and pRab10/Rab10 peptide ratio in PBMCs

Secondary outcome measures
Evaluate longitudinal intraindividual and inter-individual variability of CSF LRRK2 and correlation of LRRK2 measurement in 3 different assays in healthy participants on Day 1 0h and Day 2 (Day 2 only for subjects in group B = 5)
1. LRRK2 protein (pg/mL) as measured by SISCAPA assay
2. LRRK2 protein (pg/mL) as measured by middomain SIMOA assay
3. LRRK2 protein (pg/mL) as measured by N-terminal SIMOA assay

Overall study start date
20/06/2023

Completion date
01/09/2023

Eligibility

Key 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

protocolspecific procedures.
5. Women of childbearing potential must use an effective form of contraception (e.g., oral contraceptive, condom use, IUD, abstinence of heterosexual intercourse) during the study.

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
8

Key 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.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated to confirm eligibility or judged to be clinically irrelevant for healthy participants.
3. 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).
4. Vital sign measurements outside the following ranges during screening:
- body temperature, >35C to ≤38C
- systolic blood pressure, >90 to ≤150 mm Hg
- diastolic blood pressure, >50 to ≤90 mm Hg
- pulse rate, >45 to ≤100 bpm
5. Abnormal findings in the resting ECG at screening defined as:
- QTcF> 450 or < 350 msec for men and QTcF> 470 or < 360 msec for women
- Notable resting bradycardia (HR < 40 bpm) or tachycardia (HR > 100 bpm)
- Other abnormal findings in the resting ECG as determined by the investigator
6. Females who have a positive serum or urine pregnancy test.
7. Female participant is pregnant, planning to become pregnant during the study conduct, or is breast feeding.
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.
9. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to day 1 of this study, or less than 5 half-lives, whichever is longer).
10. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 14 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent
11. Positive test for drugs of abuse at screening or at day 1.
12. Alcohol will not be allowed from at least 24 hours before screening or day 1.
13. 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.
14. Is demonstrating excess in caffeine consumption (more than eight cups of coffee or equivalent per day).
15. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
16. Loss or donation of blood over 500 mL within 3 months prior to screening or intention to donate blood or blood products during the study.
17. 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.
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, <100× 10^3/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.

Date of first enrolment
30/06/2023

Date of final enrolment
31/07/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
The Centre for Human Drug Research
Zernikedreef 8
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Sponsor information

Organisation
Arvinas (United States)

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Arvinas

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
01/09/2024

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date