A Phase 0 biomarker study in patients with Parkinson*s Disease and healthy controls

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In preparation for future clinical studies using LRRK2 kinase inhibitors currently in development, the current study aims to characterize several potential pharmacodynamic markers of LRRK2 kinase inhibition and patient stratification. In particular...

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

Summary

ID

NL-OMON46465

Source
ToetsingOnline

Brief title
LRRK2 biomarkers in PD patients and controls

Condition

- Movement disorders (incl parkinsonism)

Synonym
movement disorder, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Denali Therapeutics Inc.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Biomarkers, LRRK2, Parkinson's Disease

Outcome measures

Primary outcome

- LRRK2 phosphorylation (pS935, total LRRK2 and pS935/Total LRRK2 ratio) in

1. PBMCs

2. Whole blood

3. Neutrophils

4. Urine exosomes

5. CSF exosomes

- Rab GTPase phosphorylation in

1. PBMCs

2. Whole blood

3. Neutrophils

4. Urine exosomes

5. CSF exosomes

- Lipidomic, metabolomic and/or proteomic analysis of

1. CSF

2. Urine and/or

3. Plasma

- CSF lysosomal enzyme activity

1. Cathepsin D,

2. Glucocerebrosidase

- CSF alpha-synuclein

1. Total

2. pS129 and/or

3. Oligomeric alpha-synuclein

- CSF and plasma cytokines (65-cytokine panel)

- Cellular analyses of fibroblast cultures, e.g. lysosome imaging,

immunohistochemistry for lysosome markers (LAMP1, LAMP2, etc), lysotracker,

LRRK2pS935 and pRab10 immunoassays, LC/MS analysis, protein turnover analysis,

and Lysosome enzyme activity assays.

- Potential other parameters related to LRRK2 that become available

Secondary outcome

NA

Study description

Background summary

Parkinson*s disease is the second most common neurodegenerative disease, affecting approximately 1*2% of individuals aged 65 or over (de Rijk et al. 1997; Blin et al. 2015), and the prevalence is projected to increase substantially as the population ages (Dorsey et al. 2007). Currently approved treatments improve motor symptoms but do not address the underlying cause of the disease. Over time, these symptomatic therapies lose effectiveness and are associated with increasing frequency and severity of adverse effects, such as dyskinesias and hallucinations. In addition, nonmotor symptoms, including depression, anxiety, sleep disorders, cognitive impairment, and dementia, are disabling and common features of Parkinson*s disease, but are poorly addressed by current therapies (Aarsland et al. 1996; Truong et al. 2008; Lyons and Pahwa 2011; Khoo et al. 2013; US FDA *Voice of the Patient* 2016). As such, Parkinson*s disease patients inevitably experience mounting disabilities over the years to decades that they live with the disease (Hely et al. 2005). Thus, there is a significant need for an effective disease-modifying therapy to prevent the progressive motor and nonmotor disabilities not addressed by current therapies.
LRRK2 mutations are an established cause of Parkinson*s disease, accounting for

approximately 4*5% of familial Parkinson*s disease (Healy et al. 2008; Chai et. al. 2013). Familial LRRK2 mutations are transmitted in an autosomal dominant pattern of inheritance with incomplete penetrance (Marder et al. 2015). In addition, variants within the LRRK2 gene are a genetic risk factor and account for 1*2% of sporadic Parkinson*s disease cases (Healy et. al. 2008; Chai et al. 2013; Hernandez et al. 2016). The majority of identified LRRK2 pathogenic mutations are located within the central catalytic domain of the protein, and these mutations increase kinase activity in in vitro assays (West et al. 2007; Sheng et al. 2012).

LRRK2 encodes a multidomain protein containing a GTPase domain, a kinase domain, and several potential protein-protein interaction domains. The majority of identified pathogenic mutations in LRRK2 are located within its catalytic domains, including the most common mutation associated with LRRK2-PD, G2019S. These mutations increase LRRK2 kinase activity, either through direct mutations within the kinase domain, or through indirect mechanisms. While the exact pathogenic mechanisms remain unknown, LRRK2 is believed to play a role in intracellular trafficking in the endo-lysosomal system (Henry et al. 2015; Cookson 2016), and LRRK2 mutations with increased kinase activity result in lysosomal dysfunction. Kinase activity is increased with LRRK2 mutations in vitro, and cellular data shows that 50% inhibition of G2019S mutant LRRK2 activity in cells reverses the lysosomal abnormalities. Evidence of this effect is further supported by data (on file with Denali Therapeutics Inc.) showing that expression of fluorescently tagged G2019S LRRK2 in H4 neuroglioma cells produces enlarged lysosomes, suggesting that increased LRRK2 kinase activity disrupts the lysosomal pathway. This effect is dependent on LRRK2 kinase activity, as treatment with LRRK2 kinase inhibitors related to DNL151 rescues the observed defects in lysosomal morphology. Hence, inhibiting increased LRRK2 kinase activity may mitigate LRRK2 mediated pathogenesis, including lysosomal dysfunction, supporting the therapeutic potential of DNL151 (Khan et al. 2005; Jaleel et al. 2007; West et al. 2007; Sheng et al. 2012; Steger et al. 2016).

The role of LRRK2 in intracellular trafficking in the endo-lysosomal system (Cookson 2016) is further supported by the fact that 1) expression of LRRK2 mutations with increased kinase activity results in altered lysosomal phenotype and function, and 2) expression of LRRK2 mutations with increased kinase activity (but not kinase-dead LRRK2 mutations) alters cell function and health in cellular and in vivo models. Alterations in both lysosomal function and cellular function associated with these LRRK2 mutations are reversed with LRRK2 kinase inhibitors (Henry et al. 2015; Lee et al. 2010).

LRRK2-driven Parkinson*s disease is characterized clinically by features consistent with idiopathic Parkinson*s disease. The pathological features of both forms of Parkinson*s disease are also similar, suggesting common pathogenic mechanisms. Lysosomal dysfunction may be a central mechanism for accumulation of intracellular proteins resulting in accumulation of *-synuclein and the formation of Lewy bodies, a cardinal pathological feature of idiopathic Parkinson*s disease (Dehay et al. 2013). The role of LRRK2 in *-synuclein accumulation and consequent pathology is suggested by in vitro and in vivo studies. Primary neuronal cultures expressing G2019S-LRRK2 develop *-synuclein

inclusions that can be reduced by LRRK2 inhibitor treatment. In vivo, infection of a transgenic G2019S-LRRK2 rat model of Parkinson*s disease with a virus overexpressing *-synuclein can induce dopaminergic neuron neurodegeneration, and this degeneration can be attenuated by LRRK2 inhibitor treatment (Daher et al. 2015; Volpicelli-Daley et al. 2016).
In summary, LRRK2 activity is linked to central mechanisms of Parkinson*s disease pathology through its role in lysosomal function, and LRRK2 kinase inhibitors, such as DNL201 (IND Number: 133665) represent a new class of therapeutics with potential to address the underlying biology of Parkinson*s disease.

Study objective

In preparation for future clinical studies using LRRK2 kinase inhibitors currently in development, the current study aims to characterize several potential pharmacodynamic markers of LRRK2 kinase inhibition and patient stratification. In particular, since LRRK2 is present in peripheral as well as central compartments, the present study will examine these markers in the blood and CSF compartments, and markers will be characterised in terms of both intra- and inter- subject variability. Patients with Parkinson*s disease with LRRK2 mutations, patients with PD without LRRK2 mutations, and healthy matched subjects will be studied to assess differences in biomarker-based phenotypes between the groups, as well as intra-subject variability and inter-subject variability within groups.

Study design

To investigate Day-to-day (intra-individual), and Inter-individual variability, a design with repeated measurements over two days has been selected. Participation comprises a total of up to 3-4 visits.

Study burden and risks

This study requires collection of skin, blood, CSF and urine samples. All collections will be performed in a state of the art clinical unit and medically supervised by qualified medical staff. The burden for the volunteer related to the study procedures will be kept to a minimum.
Genotyping the LRRK2 and GBA genes is a mandatory part of study participation if this has not already been done previously. Currently, confirmation of a LRRK2 or GBA mutation has no implications for PD treatment. Healthy Volunteers will undergo genotyping for Parkinson disease associated mutations in both genes, but will not be informed of the outcome of the genotyping.
If a PD patient does not wish to know their LRRK2 or GBA status, they cannot participate in the 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

Groups A and B
1. Confirmed clinical diagnosis of Parkinson*s disease by a qualified neurologist,
2. Hoehn and Yahr stage I-IV, inclusive,
3. Group A: Confirmed mutation in the Leucine-rich repeat kinase 2 (LRRK2) gene of the following types: G2019S, I2020T, R1441G, R1441C, R1441H, N1437H or Y1699C.
4. Group B: Confirmed wild type Leucine-rich repeat kinase 2 (LRRK2) gene.
5. Male or female of 30-85 years of age at screening (inclusive). Group A patients may be as young as 25 years of age with Investigatory and Sponsor agreement.
6. Body mass index (BMI) between 18 and 35 kg/m2 (inclusive), and with a minimum weight of 50 kg at screening.
7. Able to speak, read, and understand study procedures in Dutch sufficiently to allow completion of all study assessments.

8. Mentally competent as assessed by the screening physician and *if deemed necessary- by the treating neurologist
9. Must understand and provide written informed consent prior to the initiation of any protocol-specific procedures.
10. 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.
11. Willing and able to abstain from alcohol 48 hours prior to all study procedures at study visits 1 and 2.;Group C:
1. No clinical evidence or history of Parkinson disease
2. Male or female matched to a participant in Group A and/or Group B for gender, race, age (+/- 5 years) and BMI (+/- 3.5, with a minimum weight of 50 kg at screening).
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. Willing and able to maintain stable doses and regimens for all medications, herbal treatments, dietary supplements and caffeine intake from the screening visit through the last study visit.
6. Willing and able to abstain from alcohol 48 hours prior to all study procedures at study visits 1 and 2.

Exclusion criteria

Groups A * C
1. Self-reported substance or alcohol dependence (excluding caffeine), and/or participated in a substance or alcohol rehabilitation program to treat substance or alcohol dependence within the past 6 months
2. History or presence of clinically significant or unstable abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the investigator would jeopardize the safety of the participant or the validity of the study results
3. Positive urine drug screen, except for medical marijuana which is permitted
4. Positive breath alcohol test. Participants with a positive result may be rescheduled at the investigator*s discretion
5. Groups A and B: Parkinson disease associated mutations in the GBA gene, as determined by genetic testing or documented before screening.
6. Group C only: first order relative with Parkinson disease
7. Females who have a positive serum or urine pregnancy test
8. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening
9. Hemoglobin level <7.0 mmol/L (males) or <6.0 mmol/L (females)
10. Donation or loss of more than 500 mL whole blood within 30 days preceding entry into the treatment period
11. Difficulty with venous access or unsuitable or unwilling to undergo catheter insertion

12. 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 lumbar puncture
13. Significant coagulation abnormality (e.g. hemophilia, platelet count <100,000/microliter or clinically significant elevation in PT or PTT at screening), or has a medical condition requiring treatment with an anticoagulant (e.g. warfarin) or with two or more antiplatelet agents
14. Treatment with an investigational drug within 5 times the elimination half-life or within 30 days (whichever is longer) prior to Visit 1, or is currently enrolled in any research judged not to be scientifically or medically compatible with this study
15. Hospitalization during the 6 weeks prior to Visit 1
16. An employee of the sponsor or research site personnel directly affiliated with this study or their immediate family members defined as a spouse, parent, child or sibling, whether biological or legally adopted
17. Anyone who, in the opinion of the investigator or designee, is not considered to be suitable and is unlikely to comply with the study protocol for any reason
18. Current smoker or tobacco use within 6 months
19. Groups B and C only: presence of Type 2 diabetes based on medical history or screening laboratories, unless matched to a patient from Group A with Type 2 diabetes

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-01-2018
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO Date:	20-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-08-2018
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	NL63875.056.17