A Phase 1/2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Single Dose and Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of DNL593 in Healthy Participants and Participants With Frontotemporal Dementia Followed by an Open-Label Extension

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This study has been transitioned to CTIS with ID 2023-508697-28-00 check the CTIS register for the current data. This Phase 1/2 study will enable clinical development of DNL593 in FTD-GRN. This is the first time DNL593 will be administered to humans...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53476

Source
ToetsingOnline

Brief title
DNLI-H-0001

Condition

- Other condition

Synonym
brain disease, dementia

Health condition

frontotemporale dementie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Frontotemporal dementia, FTD-GRN, granulin, neurodegenerative disease

Outcome measures

Primary outcome

Primary objective part B:

- To investigate the safety and tolerability of multiple doses of DNL593 in

participants with FTD-GRN

Primary endpoint:

- Incidence, severity, and seriousness of TEAEs during the 24-week double-blind

period

- Change from baseline in safety laboratory values, vital sign measurements,

ECG results, Columbia-Suicide Severity Rating Scale (C-SSRS), and physical and

neurological examination findings during the 24-week double-blind period

Primary objective part C:

- To investigate the safety and tolerability of multiple doses of DNL593 in participants with FTD-GRN up to 18 months

Primary endpoint:

- Incidence, severity, and seriousness of TEAEs during the OLE period
- Change from baseline in safety laboratory values, vital sign measurements, ECG results, C-SSRS, and physical/neurological examination findings during the OLE period

Secondary outcome

Secondary objective part B:

- To characterize the serum PK of DNL593 following multiple doses of DNL593 in participants with FTD-GRN
- To characterize the concentration of DNL593 in CSF following multiple doses of DNL593 in participants with FTD-GRN

Secondary endpoints:

- DNL593 serum PK parameters (when feasible):
  - o Cmax
  - o tmax
  - o Trough concentration (Ctrough)
  - o AUClast
  - o AUC from time 0 to the end of the dosing interval (AUC*)

o t1/2

o Accumulation ratio

- DNL593 CSF concentrations 24 hours postdose at Week 25

- DNL593 CSF:serum concentration ratio at Week 25

Secondary objective part C:

- To characterize the serum PK of DNL593 following multiple doses of DNL593 in participants with FTD-GRN

- To characterize the concentration of DNL593 in CSF following multiple doses of DNL593 in participants with FTD-GRN

Secondary endpoints:

- DNL593 serum PK parameters (when feasible):

o Cmax

o tmax

o Ctrough

o AUClast

o AUC*

o t1/2

o Accumulation ratio

- DNL593 concentration 24 hours postdose at multiple time points

- DNL593 CSF:serum concentration ratio at multiple time points

Study description

Background summary

FTD-GRN is caused by mutations in GRN, primarily resulting in haploinsufficiency and deficient levels of PGRN in CSF, blood, and tissues. PGRN is known to promote lysosomal function, in addition to having neurotrophic and anti-inflammatory effects. Patients with FTD-GRN have notable abnormalities in lysosomal, glial, and inflammation biomarkers. This includes an accumulation of lipofuscin in the brain and retina, and elevated expression of ionized calcium-binding adaptor molecule 1 (IBA1) and complement component 1q (C1Q), markers of microglial activation, in the frontal cortex. There is currently no effective therapy for FTD-GRN. There are no approved medications for FTD, and current therapy consists of off-label medication management for symptoms associated with FTD or behavioral and/or physical therapy with limited effects (Tsai and Boxer 2016). Because the impacts of FTD on both patient and caregiver health are profound, and disease progression is unrelenting until death, there is an unmet medical need for treatments that provide meaningful symptomatic benefit, improve survival, and/or delay progression of the disease.
Based on the proposed disease mechanism and data from in vitro and in vivo nonclinical models, increasing PGRN levels via a CNS-penetrant recombinant PGRN biologic such as DNL593 may be a successful therapeutic mechanism to correct the PGRN deficiency and thus treat FTD-GRN.

Study objective

This study has been transitioned to CTIS with ID 2023-508697-28-00 check the CTIS register for the current data.

This Phase 1/2 study will enable clinical development of DNL593 in FTD-GRN. This is the first time DNL593 will be administered to humans. The principal aim of this study is to obtain safety and tolerability data of DNL593, administered via IV infusion or SC injection or infusion, in healthy participants and participants with FTD-GRN. This information, together with the PK and PD data, will help establish the doses and dosage regimen suitable for efficacy studies and inform the design of future studies. The PD effect of DNL593 will be explored by measuring relevant biomarkers, including CSF biomarkers.

Study design

This is a Phase 1/2, multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, PK, and PD of single and multiple doses of DNL593 in two parts (Part A and Part B [for Part B, investigator, participants, and Sponsor medical monitor will remain blinded]) followed by an optional OLE period. Part A will evaluate the safety, tolerability, PK, and PD

of single doses of DNL593 in approximately 64 healthy male participants and healthy female participants of nonchildbearing potential. Part B will evaluate the safety, tolerability, PK, and PD of multiple doses of DNL593 over 24 weeks in up to 42 participants (minimum of 30 participants) with FTD-GRN. Part B will be followed by Part C, an optional OLE period for up to 18 months of treatment.

Intervention

Study Interventions, Dose, and Mode of Administration
• Study interventions: DNL593 and DNL593 placebo, both provided as a sterile lyophilisate. On the label, the drug product may be described as *lyophilisate* or *powder* per local requirements.
• Proposed doses for part B: Proposed doses for Part B: For Cohort B1, 9 mg/kg (based on most recently recorded weight) via IV infusion every 2 weeks (Q2W) for 3 months, followed by every 4 weeks (Q4W) for 3 months. For Cohort B2, no more than 2 × dose escalation from Part A or Cohort B1 via Q4W IV or SC administration. For Cohort B3, no more than 2 × dose escalation from Part A or from Cohort B1 or B2; route of administration and dosing interval will be selected based on emerging safety, PK, and PD data from previous cohorts.

Study burden and risks

Main procedures (BURDEN):
- B1: 9-10 ward visits and 3 hospitalisations
- B2: 6 ward visits and 3 hospitalisations. A hospitalisation consists of 2-3 study visits.
- B1 in OLE study (part C): 21 visits, incl. 7 overnight stays
- B2 in OLE study (part C): 21 visits, incl. 3 overnight stays
- ward visits last 4-8 hours.
- checks to be carried out (not during all visits):
- drug review
- Check to see if you can join the study.
- The investigator will take some blood from you.
- Urine test
- Physical examination.
- ECG
- A neurological exam
- CSF collection
- Brain MRI
- A neuropsychological test
- Speech and language test
- Short questions/questionnaires

ASSOCIATED RISKS:
While participating in this study, you may have side effects from the study drug. You may experience all, some, or no side effects, and the side effects

may vary in severity. The severity may be mild, moderate, severe, life threatening, or fatal.
Many side effects may go away shortly after the drug is stopped, but in some cases, side effects can last longer or be permanent.
No clinical studies with DNL593 have been conducted to date. Important potential risks have been identified based on established class effects and the nonclinical (studies done in animals) safety findings observed with DNL593 and they are

• Anemia, or low blood cells
• Immunogenicity (ability of a foreign substance to provoke an immune response in the body)
• Infusion related reactions (IRRs) are any signs or symptoms you may experience during drug infusion.

+ risks associated to the procedures (like collection of CSF, blood draws etc)
risks to (un)born child or pregnant women yet unknown.

BENEFIT:
protocol page 20:
FTD-GRN is a rare, uniformly fatal neurodegenerative disease caused by GRN mutations with no effective treatments towards the symptoms or progression of the disease. The mean age of onset of 61 years often affects people in the prime of life and results in substantial socioeconomic difficulties (Moore et al. 2020). Therefore, there is an unmet medical need for participants with FTD-GRN. Based on the disease mechanism and data from the nonclinical studies with DNL593, increasing PGRN levels via a CNS-penetrant recombinant PGRN biologic such as DNL593 may be a therapeutic mechanism to correct the PGRN deficiency and thus treat FTD-GRN.
This is the first clinical evaluation of DNL593, and clinical benefit has not yet been established. Participants with FTD-GRN in the current study may not receive any therapeutic benefit.

The treatment hypothesis of DNL593 is targeted towards the assumed cause of FTD-GRN, decreased PGRN levels due to the GRN mutation. Therefore, development of DNL593 is only possible within this specific population. The assessments included in this study are typical of standard neurological diagnosis for neurodegnerative disease (history, exam, MRI, lumbar puncture). As described above, there are currently no effective symptomatic or disease modifying therapies for FTD caused by GRN mutations. FTD-GRN is rapidly progressive, with substantial cognitive, behavioral and motor symtoms that greatly affect quality of life in the patient and his/her caregiver. Even in patients with advanced disease stage without cognitive or behavioral capacity for consent, it is possible that improvements in symptoms associated with FTD-GRN may lead to benefits in patient and/or caregiver quality of life.

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

Part B:
• Women of non-childbearing potential (surgically sterilized or post menopausal) or men, aged >=18 to <= 80 years. Women who are of childbearing potential but on highly effective, low user dependent contraceptive methods will be allowed.
• BMI of >= 18 to <= 32 kg/m²
• Have a Clinical Dementia Rating® plus National Alzheimer's Coordinating Center frontotemporal lobar degeneration global score >= 0.5
• Have confirmed granulin (GRN) mutation via genetic testing or historical records available for review by investigator
• When engaging in sex with a woman of child bearing potential, both the male participant and his female partner must use highly effective contraception

Part C
• All participants who completed Part B of this trial are eligible for an 18-month OLE if the participant has no unresolved clinically significant TEAEs, where continued dosing may represent a risk to participant safety.

Exclusion criteria

Part B
• Have any history of clinically significant neurologic, psychiatric, endocrine, pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic, renal, metabolic, hematologic, immunologic, or allergic disease, or other major disorders
• Have a history of malignancy, except fully resected basal cell carcinoma or other malignancies at low risk of recurrence
• Have a clinically significant history of stroke, cognitive impairment due to causes other than FTD, seizure within 5 years of screening, or head trauma with loss of consciousness within 2 years of screening
• Have a positive serum pregnancy test or are currently lactating or breastfeeding

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2023
Enrollment:	3

Type:	Anticipated

Ethics review

Approved WMO Date:	12-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2023
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
EU-CTR	CTIS2023-508697-28-00
EudraCT	EUCTR2021-005733-16-NL
ClinicalTrials.gov	NCT05262023
CCMO	NL81299.056.22