A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of DNL104 in Healthy Subjects

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* Investigate the safety and tolerability of multiple ascending oral doses of DNL104 in healthy subjects* Characterize the pharmacokinetics (PK) of DNL104 in plasma and measure the trough concentrations of DNL104 in CSF* Explore the pharmacodynamics...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON45306

Source
ToetsingOnline

Brief title
Multiple Ascending Oral Doses of DNL104

Condition

- Neuromuscular disorders

Synonym
Amyotrophic Lateral Sclerosis (ALS)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Neurodegeneration, RIP1

Outcome measures

Primary outcome

-Safety and tolerability

*Treatment-emergent (serious) adverse events ((S)AEs).

*Concomitant medication

*Clinical laboratory tests

o Hematology

o Chemistry

o Coagulation

o Urinalysis

*Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

o Temperature (degrees Celsius)

o Respiratory rate (breaths per minute)

*Electrocardiogram (ECG)

o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF, QtcB

*Cardiac Holter

o Heart rate

o Arrhythmias (4 or more successive beats)

o Ectopy (up to three successive beats)

-Pharmacokinetic

*The area under the plasma concentration-time curve from zero to infinity(AUC0-inf);

*The maximum plasma concentration (Cmax);

*The area under the plasma concentration-time curve from zero to t of the last measured concentration above the limit of quantification (AUC0-last);

*The time to reach maximum plasma concentration (tmax);

*The terminal disposition rate constant (*z) with the respective half-life (t*).

*Other parameters, including Vz/F, CL/F, and other parameters as appropriate, as well as dose adjusted parameters, may be determined.

Secondary outcome

-Pharmacodynamic

*pS166-RIP1 kinase level in stimulated PBMCs

*Total RIP1 kinase protein level in stimulated PBMCs

*Cytokine levels in stimulated plasma (exploratory)

*Possible other relevant markers such as MLKL, pMLKL and other exploratory biomarkers

-Pharmacogenomic

A blood sample for DNA isolation will be collected from each subject pre-dose

on Day 1 for potential pharmacogenetic analysis of

genes that may affect the pharmacokinetics, pharmacodynamics, efficacy, or

safety of DNL104

NeuroCart tests:

Saccadic eye movements:

o saccadic reaction time (msec),

o saccadic peak velocity (deg/sec), and

o saccadic inaccuracy (%);

Smooth pursuit eye movements:

o percentage of time the eyes of the subjects are in smooth pursuit of the

target (%);

Body sway:

o antero-posterior sway (mm);

Adaptive tracking:

o average performance (%);

Study description

Background summary

Receptor-interacting protein kinase 1 (RIP1) is a serine/threonine kinase involved in the regulation of inflammation and cell death. In response to tumor necrosis factor (TNF)-alpha signaling, RIP1 is activated, and in turn regulates activation of downstream targets, including RIPK3, mixed-lineage kinase domain-like (MLKL) and NF-kB. This complex signaling cascade initiates a number of cellular processes, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death.

DNL104 is a novel, potent and selective RIP1 kinase inhibitor that has favorable pharmacokinetic properties and good penetration across the blood brain barrier, allowing target inhibition in the central nervous system. As such, it is a potential therapeutic candidate for neurodegenerative diseases where histopathology and / or genetics implicates cell death and inflammation, including amyotrophic lateral sclerosis (ALS), Alzheimer Disease (AD) and Parkinson Disease (PD).

Study objective

* Investigate the safety and tolerability of multiple ascending oral doses of DNL104 in healthy subjects
* Characterize the pharmacokinetics (PK) of DNL104 in plasma and measure the trough concentrations of DNL104 in CSF
* Explore the pharmacodynamics of DNL104 using an ex vivo stimulation assay to measure the inhibition of phosphorylation of the target protein and downstream markers that are directly impacted by RIP1 kinase inhibition
* Explore the pharmacodynamics of DNL104 in CSF

Study design

This is a Phase 1, multiple-ascending-dose, randomized, double-blind (subject and investigator), placebo-controlled, dose-ranging study in healthy subjects to evaluate the safety, tolerability, and PK of DNL104, a CNS-penetrant kinase inhibitor.

*Screening: Up to 32 days before dosing;
*In Clinic period: Days -2 to 13;
*Treatment and study assessments: Days 0 to 13
*Follow-up visit: 8-12 days after last dose.
*Group 2 and 3: Follow-up visit: 23-33 days after last dose.
Subjects will be admitted to the study unit on Day -2 and will be discharged approximately 60 hours after the last study drug administrationon day 10.

The dose level of DNL104 to be administered in each cohort was based on the pharmacokinetic and safety data obtained from the SAD and will be 50, 100 and 200 mg. Based on data from earlier MAD cohorts, these doses can be adjusted. Dosing will be trice daily. Available pharmacodynamics will also be evaluated between dose escalations.

Intervention

DNL104 or placebo

Study burden and risks

The burden for the participants includes the time investment for the briefing, screening, the occasions, and the follow-up visit. The occasion will consist of 13 days and 14 nights. Furthermore, subjects are asked to adhere to various lifestyle
regulations. Blood and urine will be collected during the screening, the occasion and the follow-up visit.

The starting dose was based on the safety, tolerability and PK of the SAD study with DNL104. The maximum dose to be tested in the MAD study will maintain the predicted 20-fold Cmax-based safety margin relative to the clinical signs observed in rats and dogs.
Dose escalation will be stopped in case of an unacceptable tolerability profile based on the nature, frequency, and intensity of observed AEs, labs and vital signs judged jointly by the investigator and the sponsor. In addition, the top dose for this study will not exceed the top dose of the SAD study.

There is no prior experience of administering multiple doses of DNL104 to humans. Therefore, the side effect profile in humans in currently unknown and very serious side effects are possible. A drug with the same mechanism of action (a RIP1 kinase inhibitor) has been tested
previously in humans with an adequate tolerability and safety profile (ClinicalTrials.gov Identifier: NCT02776033). Toxicology studies
of DNL104 show that doses equivalent to those to be tested in humans are very well tolerated in rats and dogs. The top dose to be
tested in humans will at Cmax have a >20-fold safety margin with respect to the Cmax exposure associated with acute, severe
clinical signs in rats. At exposures in animal studies that are higher than the exposures to be studied in humans, effects on the liver,
gall bladder and urinary bladder were observed, and the animals had mild decreases in blood pressure and resulting elevations in
heart rate. These are all effects that can be monitored in this first-in-human study. To minimize the risk of severe clinical signs, a
safety margin of >20-fold will always be maintained.

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. Healthy men or women between 18 and 55 years of age at screening (inclusive);
2. Subjects must be willing and able to give written informed consent, and must sign an ethics-committee-approved Informed Consent Form prior to any study-related procedures being performed;
3. Body mass index between 19 to 32 kg/m2 (inclusive) and a weight of at least 50 kg;
4. For males: When engaging in sexual activity with a woman of childbearing potential, both the subject and his female partner must use highly effective contraception, consisting of 2 forms of birth control (1 of which must be a male barrier method such as latex or polyurethane condoms) from screening, throughout the clinical study period, and for 90 days after the final study drug administration;
5. For males: The subject must not donate sperm from screening, throughout the clinical study period, and for 90 days after the final study drug administration;
6. For females: The subject must have been surgically sterilized (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; proper documentation required) at least 6 months before screening, or be postmenopausal (defined as 24 months without menses before screening, with an estradiol level of < 200 pmol/L and a follicle-stimulating hormone level of > 40 IU/L at screening);
7. Able to communicate with the investigator and study staff;
8. Willing and able to comply with the requirements of the study, scheduled visits, laboratory tests, and other study procedures;
9. Agrees to abide by study restrictions and agrees to remain in the study unit for the confinement period.

Exclusion criteria

1. History of clinically significant neurologic, psychiatric, endocrine, pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic, renal, metabolic, hematologic, immunologic, or allergic disease, or other major disorders;
2. Current significant medical or psychiatric condition, including suicidal ideation in the last 6 months (as assessed by the C-SSRS) or a lifetime suicide attempt;
3. Clinical laboratory test values outside the normal range at screening or baseline unless assessed by the investigator as clinically non-significant values;
4. Supine systolic blood pressure <90 or >140 mmHg, supine diastolic blood pressure <50 or >90 mmHg, pulse rate <40 or >110 bpm, or elevated body temperature at screening or baseline;
5. History of serious adverse reaction or serious hypersensitivity to any drug;
6. Evidence of clinically significant hepatic or renal impairment including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x the upper limit of normal (ULN), or bilirubin >1.2 x ULN, or GGT > 2.5 x ULN, or creatinine clearance (determined by MDRD) of <70 mL/min1,73m^2;
7. History of seizures;
8. History or presence of an abnormal ECG, including, but not limited to, complete left bundle branch block, second- or third-degree heart block, evidence of prior myocardial infarction, or any other abnormality that is clinically significant in the investigator*s opinion or precludes accurate interpretation and calculations of cardiac intervals (e.g., QT, QRS);
9. A QTcF value>450 msec or QRS >120 msec demonstrated in at least two ECGs recorded more than 30 min apart;
10. Hemoglobin level <7.5 mmol/L;
11. Any blood donation or other loss of blood greater than 500 mL within 3 months of screening or plasma donation within 2 weeks of screening;
12. Participation in any other investigational drug study within 90 days of first study drug administration, or previous participation in a study with DNL104.
13. Use of any prescription drug within 7 days or 5 half-lives (whichever is longer) of the first dose administration and anticipated use through the follow-up 1 visit;
14. Use of any over-the-counter medication (including vitamin/mineral supplements, and herbal medicines such as St. John's Wort) within 7 days of the first dose administration and anticipated use through the follow-up 1 visit;
15. Any surgical or medical condition possibly affecting drug absorption (e.g., gastrectomy);
16. Poor peripheral venous access;
17. Alcohol, caffeine, or grapefruit consumption within 48 h before dosing;
18. Average daily caffeine intake greater than 450 mg/ day (equivalent to 4 cups per day);
19. History of alcoholism, drug abuse, or drug addiction in the last 2 years;
20. Positive drug or alcohol test at screening;
21. Use of tobacco or nicotine products within the previous month before the first dose administration;
22. Positive serology for HIV, HBV, or HCV, by HIV1 and HIV2 antibodies, Hepatitis B antigen or Hepatitis C antibodies, respectively;
23. Subjects who are part of the clinical staff personnel or family members of the clinical site staff;

24. Any other issue which, in the opinion of the Investigator, will make the subject ineligible for study participation;
25. Subjects who are unwilling to agree to any food restrictions that may be required.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-01-2017
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	13-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	28-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	21-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-05-2017
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
EudraCT	EUCTR2016-003859-30-NL
CCMO	NL59310.056.16

Study results

Date completed:	21-04-2017
Results posted:	15-01-2018

First publication
15-01-2018

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File